APASL Oncology 2026 Tokyo

"Treatment Dynamics of Liver Tumors"

Abstracts

Oral Free Papers

Plenary Session
PS-1 10177

Plasma TWEAK as a Predictive Biomarker of Response to Tremelimumab plus Durvalumab in Advanced Hepatocellular Carcinoma

Takeru Hirao[1], Yuta Myojin[1], Akira Nishio[2], Yu Sato[1], Kazuma Daiku[1], Ryo Takahashi[1], Shuhei Yamamoto[1], Kazuki Maesaka[1], Kumiko Shirai[1], Kazuhiro Murai[1], Yuki Tahata[1], Yuki Makino[1], Yoshinobu Saito[1], Hayato Hikita[1], Takahiro Kodama[1]
[1]Department of Gastroenterology and Hepatology, Graduate School of Medicine, The University of Osaka, Suita, Japan, [2]Department of Gastroenterology, Japan Community Health care Organization Osaka Hospital, Osaka, Japan

Background: Combination immunotherapy with immune checkpoint inhibitors is standard for unresectable advanced hepatocellular carcinoma (HCC), yet response rates remain limited. Developing non-invasive blood biomarkers is essential for personalized treatment strategies.
Methods: Pretreatment plasma from 50 patients treated with durvalumab plus tremelimumab (Dur/Tre) was analyzed using Olink&reg (Discovery cohort), identifying TWEAK as a potential predictor of therapeutic response. TWEAK levels were validated by ELISA in an expanded Dur/Tre cohort (Validation cohort, n=76) and an atezolizumab plus bevacizumab (Atezo/Bev) cohort (n=134). Furthermore, immune profiles were characterized via CITE-seq on 38 paired PBMC samples from 19 advanced HCC patients.
Results: In the Discovery cohort, high plasma TWEAK levels correlated with prolonged PFS and OS. Olink&reg/ELISA correlation was strong (R2=0.7360). Validation confirmed high TWEAK as an independent favorable prognostic factor for PFS (p=0.0109) and OS (p=0.0048). CITE-seq of 316,530 cells from 38 PBMC samples identified 21 immune cell subtypes. TWEAK localized to CD8+T-cell and NK-cell clusters; GSEA revealed enhanced CD8+T-cell activation signatures in the high TWEAK group. In the Atezo/Bev cohort (n=134), patients with low TWEAK levels exhibited significantly better OS (p=0.0466). Comparing regimens, high TWEAK levels were associated with a trend toward better OS in the Dur/Tre group (p=0.0942), whereas low TWEAK levels were significantly associated with better OS in the Atezo/Bev group (p<0.0001).
Conclusions: Pretreatment plasma TWEAK is a promising predictive biomarker for Dur/Tre efficacy in advanced HCC. Furthermore, plasma TWEAK levels may serve as a useful indicator for optimizing treatment selection between Dur/Tre and Atezo/Bev combination therapies.

PS-2 10130

Surgical Benefit and Futility in Borderline Resectable Hepatocellular Carcinoma: A Multicenter Study

Norifumi Iseda[1], Shinji Itoh[1], Mizuki Ninomiya[2], Hiroto Kayashima[2], Takashi Motomura[1,2], Kengo Fukuzawa[3], Yoichi Yamashita[3], Kazutoyo Morita[4], Takeo Toshima[1], Tomoharu Yoshizumi[1]
[1]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[2]Department of Surgery, ASO Iizuka Hospital, [3]Department of Surgery, Japanese Oita Red Cross Hospital,
[4]Department of Surgery, Fukuoka City Hospital

Background: Hepatocellular carcinoma (HCC) is categorized as resectable (R), borderline resectable 1 (BR1), or borderline resectable 2 (BR2) according to the oncologic resectability classification (Expert Consensus 2023). However, optimal surgical indications and therapeutic limits for BR HCC remain unclear. This multicenter study aimed to identify BR HCC subgroups that may benefit from surgery and those with limited benefit.
Methods: Among 1,290 patients who underwent hepatectomy for primary HCC between 2016 and 2023 at 10 institutions, 1,109 patients with a minimum follow-up of 2 years were analyzed. Patients were classified as R, BR1, or BR2. Overall survival (OS) and recurrence-free survival (RFS) were evaluated according to resectability-related factors, including tumor size and number, vascular invasion, and extrahepatic metastasis. Biological risk was defined as alpha-fetoprotein (AFP) >12 ng/mL and des-γ-carboxy prothrombin (DCP) >150 mAU/mL.
Results: OS and RFS were significantly stratified among R, BR1, and BR2 groups (p<0.001). In BR1 patients (n=79), median survival time (MST) was 69 months with tumor size or number alone, 40 months with vascular invasion alone, and 30 months with combined factors. Low-risk patients (AFP <12 ng/mL and DCP <150 mAU/mL) showed unreached median OS. In BR2 patients (n=59), MST was 53.2 months for tumor size or number alone, 34 months for vascular invasion alone, 17.4 months for extrahepatic metastasis alone, and 5.6 months when all factors were present.
Conclusions: Surgery offers favorable outcomes in selected BR HCC patients with tumor burden-related factors alone, whereas benefit is limited in those with vascular invasion or extrahepatic spread.

Plenary Session
PS-3 10003

The First Application and Feasibility Assessment of 5G-enabled Remote Robot-assisted Hepatobiliary and Pancreatic Surgery in Patients with Malignant Tumors

Xingru Wang[1], Zhao Guodong[2], Guo Xianghong[3]
[1]Department of Hepatobiliary Surgery, Southwest Hospital, Army Medical University, [2]Department of General Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [3]Department of Surgery, Qujing Second Peoples Hospital of Yunnan Province

Background: Remote surgery has demonstrated potential via advanced network and satellite technologies, with previous robot-assisted laparoscopic surgery confirming feasibility at 4,670.2 km and 73 ms median delay. However, evidence for remote robot-assisted complex hepatobiliary surgery for resectable malignant tumors remains lacking, creating an urgent research gap.Materials and
Methods: This study first applied remote robotic surgery to 4 patients with liver, gallbladder, or pancreatic tumors using China's domestic MP2000 platform (Shenzhen Edge Medical). The primary surgeon operated 900 km from the site (1,035 km network distance), with 5G as primary and dedicated fiber as backup network. Network parameters were monitored, and local surgeons stood by for emergencies.
Results: All surgeries were successful. Average communication delay was 21 ms (end-to-end 100 ms) with no interruption/packet loss. Mean intra-cavity operation time was 240 min, intraoperative blood loss 100 mL, and all patients achieved R0 resection. No postoperative complications occurred; patients had stable physiology and intestinal function recovery within 24 h, with favorable short-term outcomes.
Conclusion: This study confirms the technical feasibility, safety, and short-term efficacy of remote robotic surgery for resectable hepatobiliary malignant tumors, filling the research gap. The approach (5G/backup networks, domestic platform, safety protocols) facilitates medical resource allocation, reduces urban-rural surgical disparities, and improves robotic utilization in county hospitals.

Video Session

VS-1 10073

Pitfalls in Posterior Sectionectomy and S7 Segmentectomy Focusing on the Running Pattern of the Right Posterior Inferior Portal Branch (P6a) and Portal Vein Branching Anatomy

Gakushi Kitamura, Yusuke Yamamoto, Ryo Morimura, Taisuke Imamura, Hidemasa Kubo, Rie Shibata, Atsushi Shiozaki
Division of Digestive Surgery, Department of Surgery Kyoto Prefectural University of Medicine, Kyoto, Japan

Background: Liver resection along right intersectional plane is demanding because of anatomical variations. Right posterior inferior portal branch (P6a) usually runs dorsal to right hepatic vein (RHV) (D-P6a) but often courses ventral (V-P6a). We aimed to clarify pitfalls in right posterior sectionectomy and segment VII (S7) segmentectomy.
Methods: Fifty-five patients with 3D imaging were classified into Dorsal/Ventral-P6a. RHV-inferior vena cava (IVC) angle, transection-plane angles, the presence of inferior right hepatic vein (IRHV), and the distance from liver surface to P7 root were measured. Posterior portal branching patterns were categorized into six types (Annals of Anatomy 252:152204) and stratified by the difficulty of Glissonean pedicle control from hilum.
Right posterior sectionectomy: Cases with early independent posterior branch were classified as Very Easy; with common posterior trunk as Easy; without either as Difficult; and those with IRHV, which makes dorsal approach difficult, as Very Difficult.
S7 segmentectomy: Cases with directly branched P7 from main portal vein were classified as Easy, and others as Difficult.
Results: V-P6a was 23 cases (42%) and associated with narrower transection-plane angle (141° vs 162°, $p < 0.01$), wider RHV-IVC angle (54° vs 44°, $p < 0.01$), and higher prevalence of IRHV (65% vs 34%, $p = 0.023$).
Right posterior sectionectomy:
V-P6a showed higher proportion of very difficult patterns (30.4% vs 3.1%, $p = 0.007$).
S7 segmentectomy:
In V-P6a, P7 was deeper (28 mm vs 25 mm, $p = 0.035$), and easy pattern was more frequent (43% vs 18%, $p = 0.04$).
Conclusion: Classification based on P6a may facilitate surgical planning.

VS-2 10074

Surgical Strategy for Laparoscopic Right Intersectional Plane Resection in Right Anterior/Posterior Sectionectomy and S7/S8 Segmentectomy, Based on the Courses of P6a and the Right Hepatic Vein

Yusuke Yamamoto, Ryo Morimura, Taisuke Imamura, Hidemasa Kubo, Rie Shibata, Gakushi Kitamura, Michihisa Moriguchi, Atsushi Shiozaki
Digestive Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan

Background: When the right posterior inferior portal branch (P6a) runs ventral to the right hepatic vein (RHV), variation along the right intersectional plane (RIS) can complicate laparoscopic right anterior sectionectomy (Lap-RAS), right posterior sectionectomy (Lap-RPS), and segmentectomies of segments VII (Lap-SS7) and VIII (Lap-SS8). We characterized the venous anatomy and propose procedure-specific strategies.
Methods: CT datasets from 55 hepatectomy patients were classified as Dorsal-P6a or Ventral-P6a; Ventral-P6a was subtyped as Long-RHV or Short-RHV by whether the RHV reached the S5-S6 interface. We evaluated the IVC-RHV angle, inferior RHV (IRHV) features, and S6-draining middle hepatic vein (MHV) branches.
Results: Ventral-P6a was present in 23/55 patients (42%): Long-RHV (n=15) and Short-RHV (n=8). The IVC-RHV angle widened stepwise (34.6° in Dorsal-P6a; 51.8° in Ventral-P6a/Long-RHV; 76.7° in Ventral-P6a/Short-RHV). An IRHV was universal in Ventral-P6a/Short-RHV and had the largest drainage territory; a larger axial IRHV angle was associated with a larger territory. MHV branches draining S6 were observed only in Ventral-P6a cases (39%) and occurred similarly in Long- and Short-RHV.
Video/Conclusions: The video demonstrates tailored RIS transection. Dorsal-P6a generally permits a flatter plane, whereas Ventral-P6a requires a steeply pitched plane. During Lap-RPS, S6-draining MHV branches should be identified and controlled; during Lap-RAS, early splitting of their confluence may risk congestion. In Ventral-P6a/Long-RHV, mid-course RHV division may be needed in Lap-RPS. In Ventral-P6a/Short-RHV, dorsal RHV exposure is difficult and a deep, dominant IRHV often favors preservation during Lap-SS7. Incorporating these patterns into preoperative planning may help maintain the intended RIS transection plane.

Video Session

VS-3 10004

Infrared Laser-guided Laparoscopic Portal Vein Drainage Area Anatomic Liver Resection Using ICG positive Staining

Xingru Wang[1], Cao Li[1], Hongguang Wang[2]
[1]Institute of Hepatobiliary Surgery of the Army, Southwest Hospital, Army Medical University, [2]Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Precise liver puncture and staining under ultrasound guidance during laparoscopic liver surgery remains a technical challenge. Currently, the success rate of puncture is only about 60%. Usually, the position of the puncture point is difficult to accurately locate, and the puncture depth is also difficult to precisely control. There is a lack of effective methods for precise puncture.
Methods: We described the method guidance of infrared laser-guided laparoscopic ICG positive staining portal vein drainage area anatomical hepatectomy in a patient with primary hepatocellular carcinoma, using "infrared laser-guided laparoscopic liver ultrasound puncture".
Results: All punctures were successful at the first attempt. The operation time was 130 minutes, the blood loss was 50 mL, and there were no complications. The patient was discharged 7 days after the operation. There were no complications during the 1-year follow-up.
Conclusions: Infrared laser-guided ultrasound technology can achieve three-dimensional precise puncture and accurately control the puncture position and depth. Combined with ICG positive staining, this technology can precisely locate and provide real-time navigation for the portal vein area.

VS-4 10077

Optimizing Specimen Extraction in Laparoscopic Resection of Giant Liver Tumors Using a Pfannenstiel Incision

Rie Shibata, Yusuke Yamamoto, Gakushi Kitamura, Hidemasa Kubo, Taisuke Imamura, Ryo Morimura, Michihisa Moriguchi, Atsushi Shiozaki
Division of Digestive Surgery, Department of Surgery, Kyoto Prefectural University of Medicine

Background: Although the advantages of minimally invasive surgery are well established, laparoscopic resection for giant liver tumors or anatomical hepatectomy often requires enlargement of the incision for specimen extraction, which may reduce the advantages of a minimally invasive approach. This study evaluated the clinical utility of the Pfannenstiel incision, a low transverse suprapubic incision, for specimen extraction in laparoscopic liver resection.
Methods: Between March and December 2025, nine patients who underwent laparoscopic liver resection for hepatic tumors with a maximum specimen diameter ≥120 mm at our institution and two affiliated centers were retrospectively analyzed. In all cases, specimens were extracted through a Pfannenstiel incision. The incision-to-specimen ratio, wound-related complications (surgical site infection, wound dehiscence, hypertrophic scarring, and incisional hernia), and postoperative length of hospital stay were assessed.
Results: Diagnoses included hepatocellular carcinoma (n = 3), intrahepatic cholangiocarcinoma (n = 2), metastatic liver tumor (n = 1), and hepatic hemangioma (n = 3). The median incision-to-specimen ratio was 0.42 (range, 0.30-0.68). In hemangioma cases, aspiration of tumor contents before extraction enabled further reduction of incision size. In addition, in primary liver malignancies, specimen extraction using a Pfannenstiel incision achieved favorable cosmetic outcomes without compromising oncologic integrity. No wound-related complications were observed. The median postoperative hospital stay was 7 days (range, 5-31 days).
Conclusion: The Pfannenstiel incision is a safe, oncologically feasible, and cosmetically advantageous option for specimen extraction in laparoscopic surgery for giant liver tumors, including HCC and iCCA. Operative videos will be presented to illustrate key technical points.

Video Session

VS-5 10143

Advanced Minimally Invasive Hepatectomy Through Standardized Hepatic Vein Control- Translating Laparoscopic Strategies to Robotic Surgery -

Taisuke Imamura, Ryo Morimura, Yusuke Yamamoto, Hidemasa Kubo, Rie Shibata, Gakushi Kitamura, Atsushi Shiozaki
Division of Digestive Surgery, Department of Surgery, Kyoto Prefectural University of Medicine

Background: Minimally invasive hepatectomy has become a standard procedure, with expanding indications toward technically demanding resections. In such procedures, control of the hepatic veins is a critical determinant of surgical safety. Hepatic vein control consists of two key components: (1) clear exposure of the hepatic veins and parenchymal transection using them as anatomical landmarks, and (2) a safe and planned approach to the hepatic vein roots at the inferior vena cava confluence.
Methods: We established laparoscopic techniques for hepatic vein control based on these two key components. Video presentations demonstrate parenchymal transection guided by case-specific hepatic vein anatomy and continuous exposure of the major hepatic vein roots using the Left-to-Right Vein Exposure technique. Based on this laparoscopic experience, we applied these concepts to robotic hepatectomy, and video presentations illustrate our current technical refinements, including strategic camera positioning, suction, and retraction.
Results: Laparoscopic video demonstrations show that systematic hepatic vein exposure enables stable parenchymal transection and safe access to hepatic vein roots. Robotic video demonstrations reveal that, despite constraints related to instrument number and the use of an angled endoscope, motion filtering, articulated instruments, and a stable camera platform allow precise dissection around the hepatic veins. Translating laparoscopically established concepts to the robotic approach resulted in consistent and reproducible hepatic vein control.
Conclusions: Standardization of the surgical concept of hepatic vein control, established in laparoscopic surgery, can be effectively translated into robotic hepatectomy. This approach has the potential to improve the safety and reproducibility of advanced minimally invasive hepatectomy.

VS-6 10069

Initial Experience with Robot-assisted Liver Resection Using the da Vinci SP System

Mei Nakamura, Tomoaki Sawano, Hiroko Okinaga, Riki Ninomiya, Masanao Kurata, Yasuji Seyama
Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital Department of Hepato-Biliary-Pancreatic Surgery

Background: At our institution, robot-assisted liver resection using a single-port surgical robot was introduced in December 2024, and 13 cases have been performed. We report the advantages, technical considerations, and short-term outcomes of liver resection using a single-port robotic system.
Methods: The da Vinci SP system was used for all procedures. A 3-4 cm skin incision was made according to the resection site, and an access port was placed. A 12-mm assistant port was inserted along the transection plane, allowing the use of CUSA.
Results: Between December 2024 and December 2025, 13 liver resections using the da Vinci SP system were performed. The procedures included partial liver resection in 9 patients, High-difficulty liver resection in 4. The primary diseases were liver cancer in 9 and liver metastasis in 4. During parenchymal transection, the console surgeon performed surgical field exposure, liver parenchymal transection using the crush-clamp technique, and vascular control, while the assistant dissected the liver parenchyma using CUSA. Both the surgeon and assistant were able to perform liver transection simultaneously. The median blood loss was 20 g (range, 0-600 g; blood loss > 50 g occurred only in left hepatectomy case). The postoperative course was uneventful in all patients, with a mean hospital stay of 6.3 days (range, 4-10 days).
Conclusion: Robot-assisted liver resection using a single-port surgical system was safely introduced at our institution. Effective collaboration between the console surgeon and the assistant using CUSA enabled efficient liver parenchymal transection.

Video Session
VS-7 10090

EUS-Guided Portal Vein Sampling as a Novel Liquid Biopsy Approach for Pancreatic Cancer

Hiroki Yamana, Hideki Kamada, Manabu Yamada, Daisuke Namima, Naoki Fujita, Kiyoyuki Kobayashi, Hideki Kobara
Department of Gastroenterology and Neurology, Faculty of Medicine, Kagawa University, Kagawa, Japan

Background: Liquid biopsy has gained increasing attention as a minimally invasive method for molecular cancer profiling. Endoscopic ultrasound-guided portal vein sampling (EUS-PVS) is considered especially useful. This is because it allows direct collection of portal vein blood rich in tumor-derived molecules before metabolic processing occurs in the liver. The portal vein is expected to contain circulating tumor DNA, microRNA, and circulating tumor cells at higher concentrations than peripheral blood. Pancreatobiliary tract cancer continue to have poor prognoses, necessitating highly sensitive diagnostic and prognostic evaluation tools. This study aimed to evaluate the feasibility and safety of EUS-PVS.
Methods: The left portal vein branch was punctured from the stomach using a 19G FNA needle. To minimize the risk of bleeding, the needle path was adjusted to traverse an adequate length of hepatic parenchyma. In this study, tumor markers in portal venous blood were measured and compared with those in peripheral blood. Safety was assessed based on procedure-related bleeding and intraperitoneal infection.
Results: EUS-PVS was performed in three patients, and portal venous blood collection was successful in all cases. No adverse events, including bleeding or infection, were observed. The procedure was completed within a short time, required no additional devices, and was technically straightforward.
Conclusion: EUS-PVS is a simple and safe technique that allows reliable acquisition of portal venous samples. While sufficient case numbers must be accumulated, examining ctDNA microRNA, and circulating tumor cells in the portal vein may further advance the diagnosis and treatment of pancreaticobiliary cancers in the future.

Oral Free Paper Session 1

FPS1-1 10053

Implementing Community-Based Hepatitis B Screening and Hepatocellular Carcinoma Screening in Resource-Limited Settings: A Qualitative Evaluation of Thailand's EZ Liver Network"

Passakorn Wanchaijiraboon[1], Puth Muangpaisarn[2], Somying Pumtong[3]
[1]Phrapokklao Cancer Center of Excellence, [2]Internal Medicine Unit, Phrapokklao Hospital,
[3]Faculty of Pharmacy, Mahidol University.

Background: Thailand has an estimated 2.2-3 million chronic HBV carriers, particularly among those born before the 1992 national vaccination program. Late-stage hepatocellular carcinoma (HCC) presentations remain common due to limited screening infrastructure. The EZ Liver Network was established in Chanthaburi Province, integrating HBV screening pathways with Lean-based referral coordination. This study evaluates the network's implementation and effectiveness.
Methods: Using Donabedian's structure-process-outcome framework, we conducted semi-structured interviews with 24 key stakeholders between January and April 2024. Participants were purposively selected from various healthcare levels, including village health volunteers, hospital physicians, provincial health officers, and national policymakers. Transcripts underwent content analysis with triangulation. Secondary data were obtained from participating hospitals.
Results: The network demonstrated strong provincial-level coordination, linking tertiary hospitals with community health centers. Clinical protocols were well-established with simplified referral criteria based on HBV viral load (more than 2,000 IU/ml). Between 2021-2023, 85 liver cancer patients received care: 22 early-stage (26%), 24 intermediate-stage (28%), and 39 late-stage (46%). Success factors included dedicated personnel, practical protocol adaptations, and strong inter-institutional relationships. Challenges involved workforce limitations, viral load testing reimbursement, and disconnected data systems.
Conclusions: The EZ Liver Network demonstrates that community-based HBV screening can improve care access and enable earlier HCC detection. For broader implementation, addressing workforce capacity, sustainable funding, and integrated information systems are essential. This model offers insights for hepatitis screening in resource-limited settings, supporting the WHO's 2030 elimination goals.

FPS1-2 10223

A Large-Center Comparison of Hepatocellular Carcinoma Characteristics in Hepatitis C Patients Treated with Direct-Acting Antivirals Versus Untreated Patients

Mohamed Abdel-Samiee[1], Mohamed Elgazzar[1], Tary Salman[1], Eman Abdelsameea[1], Mohamed Akl[1], Nabil Omar[1], Mohmoud Elsakhawy[2], Hazem Metwaly Omar[2], Ibrahim Abdelkader[3], Nermine Ehsan[4], Dina Elazab[4], Mohamed Mohamady[4], Shrif Abas[1], Mohamed ElKassas[5], Ahmed Elsherif[4]
[1]Department of Hepatology and Gastroenterology, National Liver Institute, Menoufia University, Shebin El-Kom, [2]Diagnostic Medical Imaging and Intervention Radiology Department, National Liver Institute, Menoufia University, Menoufia, [3]Hepatobiliary and Liver Transplant Surgery, National Liver Institute, Menoufia University, Menoufia, [4]Pathology Department, National Liver Institute, Menoufia University, Menoufia, [5]Endemic Medicine Department, Faculty of Medicine, Helwan University, Cairo

Background: Hepatocellular carcinoma (HCC) represents the leading cause of cancer-related morbidity in Egypt. HCC developing after treatment with direct-acting antivirals (DAAs) for hepatitis-C virus (HCV) infection may exhibit distinct biological characteristics and clinical behavior compared with HCC occurring in patients without prior DAA exposure. We aimed to compare the epidemiological profile, clinical presentation, laboratory, radiological findings, and tumor behavior of HCC cases developing after DAA therapy with those of DAA-naive HCC patients.
Methods: Patients with HCV-related HCC were classified into two groups: Group I included 2036 patients who developed HCC following DAA, Group II comprised 6338 patients with HCC not received DAAs. All patients underwent comprehensive clinical evaluation, laboratory investigations, and radiological assessment. Tumor staging was performed using BCLC staging system.
Results: Patients in Group II exhibited more advanced liver disease, as reflected by higher Child-Pugh classes, FIB-4, and MELD scores compared with Group I (P 0.001). In contrast, HCC cases in the post-DAA group demonstrated more aggressive tumor features, including a higher multiple hepatic focal lesions frequency (P 0.033), significantly elevated alpha-fetoprotein (P 0.012), increased portal vein invasion (P 0.001), greater incidence of extrahepatic metastasis (P 0.001), and a higher prevalence of infiltrative tumor patterns (P 0.002).
Conclusion: HCC developing after DAA therapy appears to exhibit more aggressive biological behavior compared with HCC in DAA-naives, despite relatively better underlying liver function. These findings underscore the importance of strict and continuous HCC surveillance in cirrhotic patients following DAA in accordance with international guidelines to facilitate early detection and timely management.

Oral Free Paper Session 1

FPS1-3 10107

Reduced Performance of Alpha-fetoprotein in Sustained Virological Response-related and Non-viral Early Hepatocellular Carcinoma: Complementary Value of PIVKA-II

Yuji Ikeda[1], Shunsuke Sato[1], Keisuke Hamamura[2], Hiroki Nago[1], Masahiro Yamaguchi[1], Rihwa Om[1], Yuichiro Terai[1], Yuji Kita[1], Sho Sato[1], Ayato Murata[1], Yuji Shimada[1], Tatsuki Oyaizu[2], Takuya Genda[1]
[1]Juntendo University Shizuoka Hospital, Shizuoka, Japan, [2]Shizuoka City Shizuoka Hospital, Shizuoka, Japan

Background/Aims: Alpha-fetoprotein (AFP) is widely used for hepatocellular carcinoma (HCC) detection, but its performance may vary by etiology, particularly in sustained virological response (SVR)-related and non-viral HCC (NBNC). We evaluated etiology-specific positivity of AFP and protein induced by vitamin K absence or antagonist-II (PIVKA-II) and the incremental detection achieved by their combination in early-stage HCC.
Methods: This retrospective two-center study included consecutive adults with newly diagnosed, treatment-naive HCC in Japan (2007-2023). Among 1,415 patients, 15 with missing AFP and PIVKA-II were excluded (final n=1,400). PIVKA-II was unavailable in 32 warfarin users (available n=1,368). Positivity was defined as AFP >=10 ng/mL and PIVKA-II >=40 mAU/mL. Early-stage HCC was defined by BCLC 0/A and UICC T1a; either-positive indicated AFP and/or PIVKA-II positivity.
Results: In the overall cohort, AFP and PIVKA-II positivity increased with advancing stage (P<0.001 for both BCLC and UICC T categories). In BCLC 0/A, AFP positivity was higher in HCV (64.6%) than in SVR (39.0%) and NBNC (39.7%), whereas PIVKA-II positivity showed smaller etiologic differences (HBV 40.6%, HCV 47.8%, SVR 40.8%, NBNC 58.4%). In BCLC 0/A, either-positive rates improved detection, particularly in SVR (59.2% vs AFP 38.2%) and NBNC (70.6% vs AFP 40.1%), with substantial PIVKA-II-only yield (SVR 21.1%; NBNC 30.5%). Similar patterns were observed for UICC T1a, including PIVKA-II-only contribution in NBNC (24.4%).
Conclusions: AFP performance is reduced in early SVR-related and NBNC HCC, whereas PIVKA-II provides complementary value. Dual-marker assessment improves early-stage HCC detection in emerging etiologic populations.

FPS1-4 10131

Clinical Characteristics and Surveillance Impact on Non-Viral Hepatocellular Carcinoma: A 20-Year Observational Study

Katsuya Nagaoka, Yoko Yoshimaru, Takahiro Mizuta, Toshinori Toyota, Satoshi Narahara, Hiroki Inada, Sotaro Kurano, Kentaro Tanaka, Takayuki Tokunaga, Etsuko Iio, Takehisa Watanabe, Hiroko Setoyama, Haruki Uojima, Yasuhito Tanaka
Department of Gastroenterology and Hepatology, Graduate School of Medical Sciences, Kumamoto University

Background: As the etiology of hepatocellular carcinoma (HCC) shifts from viral hepatitis toward non-B, non-C (NBNC) causes, understanding the efficacy of surveillance in real-world clinical settings is vital. This study evaluated how regular surveillance and healthcare settings influence clinical outcomes across different etiologies.
Methods: We retrospectively analyzed 1,143 patients with first-onset HCC between 2003 and 2023. Patients were categorized by etiology: HBV (n=182), HCV (n=555), and NBNC (n=375). Regular surveillance was defined as undergoing imaging at least annually. We compared early-stage diagnosis (BCLC 0/A), curative treatment rates, and overall survival (OS) between surveilled and non-surveilled groups, as well as between specialized and non-specialized institutions.
Results: Overall, 58.8% of patients underwent regular surveillance. The surveilled group showed significantly higher rates of early detection (79.8% vs. 36.9%) and curative intervention (52.8% vs. 21.6%) compared to the non-surveilled group (both p<0.001), leading to superior 5-year OS (67.0% vs. 38.6%, p<0.001). Surveillance adherence was notably lower in NBNC patients (37.9%) compared to HCV (75.7%) and HBV (50.5%) patients. Furthermore, patients managed at specialized liver centers achieved higher early diagnosis (85.0% vs. 66.7%, p<0.001) and curative treatment rates (59.3% vs. 36.8%, p<0.001).
Conclusion: Periodic surveillance is essential for improving HCC prognosis; however, a significant gap persists in the growing NBNC population. Essential strategies to mitigate the poor outcomes currently associated with NBNC-HCC include strengthening the transition from primary care to specialized hepatology centers and implementing etiology-specific protocols that integrate imaging with biomarkers like AFP.

Oral Free Paper Session 1

FPS1-5 10118

Integrative Clinical and Molecular Risk Score for Prevention of HBV-related HCC

Hiroyuki Suzuki[1], Hiroaki Kanzaki[1], Naoto Fujiwara[2], Courtney Katz[1], Ece J. Dinc[1], Hsiao-Ling Huang[3], Ming-Chin Yu[3], Tsung-Han Wu[4], Sen-Yung Hsieh[3], Yujin Hoshida[1]
[1]Division of Digestive and Liver Diseases, Department of Internal Medicine, University of Texas Southwestern Medical Center, TX, U.S., [2]Department of Gastroenterology and Hepatology, Mie University, Tsu, Mie, Japan
[3]Chang Gung Memorial Hospital, Taiwan 4New Taipei Municipal TuCheng Hospital, Tucheng, Taiwan

Background: Patients with HBV-related chronic liver disease remain at risk even with the use of antiviral therapies. Clinical variable-based scores such as PAGE-B score have been proposed for hepatocellular carcinoma (HCC) risk precision in those patients. However, there is still room for improvement to refine risk stratification and early detection of HBV-related HCC.
Methods: We defined and validated multi-omic molecular signatures (transcriptome including viral-host fusion transcripts, single nucleotide polymorphisms [SNPs] in coding regions, somatic DNA mutational signature, and somatic DNA mutations with predicted functional consequence) associated with time to incident HCC development and validated their outcome association in total of 111 patients with HBV-related cirrhosis (median follow-up 9.3 years; IQR 3.4-12.3).
Results: In the derivation set including 81 HBV cirrhosis patients, we defined a 95-gene transcriptomic signature, which was associated with fibrogenic molecular pathways among several others. In addition, DNA mutational signatures related to reactive oxygen species-induced DNA damage were associated with HCC risk. Spatial mapping of these signatures on liver tissue samples is currently underway. No~marginal association was observed for SNPs previously reported for HCC risk association. These HCC risk-associated molecular signatures were integrated with PAGE-B score, and evaluated in independent validation sets, a case-control series (n=30). The integrative score was associated with HCC risk (Firth-adjusted OR, 30.6; 95% CI, 1.4-671).
Conclusions: An integrative clinical and molecular risk score for HBV-related HCC showed promising performance in our preliminary validation studies, which warrants further validation. The score may serve as a companion biomarker for the candidate chemopreventive agents.

FPS1-6 10120

Serum Biomarker-based Score to Evaluate HCC Risk in HCV-cured Patients

Hiroaki Kanzaki[1], Courtney Katz[1], Chung-Feng Huang[2], Ming-Lun Yeh[2], Ming-Lung Yu[2,3,4], Atsushi Ono[5], Masataka Tsuge[5], Shiro Oka[5], Kazuaki Chayama[6], Yuki Hayata[7], Satoshi Kawamura[7], Shigeyuki Kurosaki[7], Ryosuke Tateishi[7], Yoshikuni Kawaguchi[8], Kiyoshi Hasegawa[8], Hitomi Sezaki[9], Masahiro Kobayashi[9], Hiromitsu Kumada[9], Naoto Fujiwara[10], Yujin Hoshida[1]
[1]Division of Digestive and Liver Diseases, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, USA. [2]Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, College of Medicine and Center for Liquid Biopsy and Cohort Research, Kaohsiung Medical University, Kaohsiung, Taiwan, [3]School of Medicine and Doctoral Program of Clinical and Experimental Medicine, College of Medicine and Center of Excellence for Metabolic Associated Fatty Liver Disease, National Sun Yat-sen University, Kaohsiung, Taiwan, [4]Division of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [5]Department of Gastroenterology and Metabolism, Graduate School of Biomedical & Health Sciences, Hiroshima University, Hiroshima, Japan, [6]Collaborative Research Laboratory of Medical Innovation, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan, [7]Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [8]Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [9]Department of Hepatology, Toranomon Hospital, Tokyo, Japan, [10]Department of Gastroenterology and Hepatology, Graduate School of Medicine, Mie University, Mie, Japan

Background: Despite successful antiviral therapy, patients cured of hepatitis C virus (HCV) infection remain at risk for hepatocellular carcinoma (HCC). We previously developed an etiology-agnostic prognostic liver secretome signature (PLSec-AFP). This study aimed to develop an HCV cure-specific prognostic liver secretome signature (PLSec-HCVcure) and to evaluate whether its integration with PLSec-AFP improves HCC risk stratification after HCV cure.
Methods: PLS-HCVcure was developed using liver transcriptome data from 85 HCC-treated patients and validated in 39 HCC-naive patients. The transcriptome signature was translated into candidate serum proteins using a computational pipeline. Secretome signatures were optimized in two cohorts: optimization set 1 included 146 HCC-treated patients, and optimization set 2 included 121 HCC-naive patients with cirrhosis. The finalized secretome signature, PLSec-HCVcure, was validated in an independent cohort of 116 HCC-naive cirrhosis patients. Finally, integration with PLSec-AFP was evaluated.
Results: PLS-HCVcure was defined as a 170-gene signature and was associated with HCC recurrence in HCC-treated patients (adjusted HR 35.9) and with HCC incidence in HCC-naive patients (adjusted HR 10.6). A secretome-based signature, PLSec-HCVcure, consisting of three proteins (lactadherin, osteopontin, and antileukoproteinase), was validated in HCC-naive cirrhosis patients (subdistribution HR 5.1). Integration of PLSec-HCVcure with PLSec-AFP stratified patients into three risk groups; compared with the low-risk group, HCC risk was higher in the intermediate-risk group (subdistribution HR 3.0) and highest in the high-risk group (subdistribution HR 14.5).
Conclusion: These results indicate that HCC risk stratification is feasible after HCV cure.

Oral Free Paper Session 2

FPS2-1 10123

Hepatocellular Carcinoma Stage, Treatment Patterns, and Survival Outcomes in a Contemporary Multicentre International Cohort

Yin Min Hwang[1], N Apoorva Sasikumar[1], Caleb Wei Hao Ng[2], Darren Jun Hao Tan[2], Beom Kyung Kim[3,4], Nobuharu Tamaki[5], Karn Wijarnpreecha[6,7], Sung Won Lee[8], Ken Liu[9,10], Gang Chen[11], Takumi Kawaguchi[12], Anand V Kulkarni[13], Hirokazu Takahashi[14,15], Nicholas Syn[1], Daniel Q Huang[1,2,16], Cheng Han Ng[2]
[1]National University of Singapore, Singapore, [2]National University Hospital, Singapore, [3]Yonsei University College of Medicine, Republic of Korea, [4]Severance Hospital, Republic of Korea, [5]Musashino Red Cross Hospital, Japan, [6]University of Arizona College of Medicine, USA, [7]Banner University Medical Center, USA, [8]Catholic University of Korea, Republic of Korea [9]University of Sydney, Australia [10]Royal Prince Alfred Hospital, Australia [11]The First Affiliated Hospital of Wenzhou Medical University, China, [12]Kurume University School of Medicine, Japan, [13]Asian Institute of Gastroenterology, India [14]Saga University, Japan [15]Saga University Hospital, Japan, [16]National University Health System, Singapore

Background: Hepatocellular carcinoma (HCC) is a major cause of cancer–related mortality worldwide. Despite substantial changes in HCC aetiology and management, their impact on Barcelona Clinic Liver Cancer (BCLC) stage at diagnosis, treatment patterns, and survival is not well defined.
Methods: We conducted a large, retrospective, multicentre cohort study including 2,887 adults with HCC diagnosed across 10 tertiary liver centres in Asia, Oceania, and North America. Survival outcomes were compared using restricted mean survival time (RMST).
Results: The median (IQR) age at diagnosis was 64 (57–73) years, 75.8% of participants were male, and 83.1% were Asian. The proportion of hepatitis C virus–related HCC declined over time (13.46% from 2015–2024 vs 28.82% from 2005–2014, p≤0.001), while metabolic dysfunction–associated steatohepatitis–related HCC increased (27.19% vs 24.75%, p=0.001). The distribution of BCLC stage 0/A, B, and C at diagnosis was 62.66%, 18.43%, and 18.91%, respectively, with no significant temporal change (p=0.122). Overall, 49% of patients received curative–intent therapy, 36.9% non–curative therapy, and 14.0% supportive care. Curative treatments were administered less frequently over time (57.8% from 2005–2014 vs 46.3% from 2015–2024, p<0.001). Survival improved, with 1–, 3–, and 5–year survival increasing from 90.7%, 77.7%, and 68.4% (2005–2014) to 90.7%, 81.0%, and 74.7% (2015–2024; p<0.001).
Conclusions: Despite improved HCC survival, there has been no corresponding increase in early–stage diagnosis, and the use of curative therapies has declined. Enhanced strategies for early detection and timely intervention remain urgently warranted.

FPS2-2 10091

Development and Validation of a Deep Learning Model to Prognosticate Hepatocellular Carcinoma

Juequn Zhou[1], Ryan Yanzhe Lim[1], Vigneshwaran Selvakumar[2], Nicholas Syn[3,4], Gang Chen[5,6], Man Yee Ng[1], Li Jie[7,8], Beom Kyung Kim[9,10], Karn Wijarnpreecha[11,12], Hirokazu Takahashi[13,14], Daniel Q Huang[1,15,16]
[1]Yong Loo Lin School of Medicine, National University of Singapore, [2]Lee Kong Chian School of Medicine, Nanyang Technological University, [3]National University of Singapore, Department of Biomedical Informatics, Yong Loo Lin School of Medicine, [4]National University of Singapore, Department of Pathology, Yong Loo Lin School of Medicine, [5]Department of Hepatobiliary Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, [6]Zhejiang-Germany Interdisciplinary Joint Laboratory of Hepatobiliary-Pancreatic Tumor and Bioengineering, The First Affiliated Hospital of Wenzhou Medical University, [7]Department of Infectious Diseases, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, [8]Institute of Viruses and Infectious Diseases, Nanjing University, [9]Department of Internal Medicine, Yonsei University College of Medicine, [10]Yonsei Liver Center, Severance Hospital, [11]Division of Gastroenterology and Hepatology, Department of Medicine, University of Arizona College of Medicine, [12]Department of Internal Medicine, Banner University Medical Center, [13]Liver Center, Saga University Hospital, [14]Division of Metabolism and Endocrinology, Department of Medicine, Faculty of Medicine, Saga University, [15]Division of Gastroenterology and Hepatology, Department of Medicine, National University Hospital, [16]National University Centre for Organ Transplantation, National University Health System

Background: Prognostic models for hepatocellular carcinoma (HCC) may have limited accuracy. We aimed to construct and validate a novel prognostic model for HCC that incorporates biomarkers for liver function and tumor characteristics.
Methods: Consecutive participants with HCC from four international tertiary institutions in Asia and the U.S. comprised the derivation (n = 627) and validation (n = 270) cohorts. The Liver Cancer Risk predictioN (LCRN) Index was constructed utilizing a deep feed-forward neural network based on the Cox proportional hazards framework. The discriminative performance of the LCRN Index was evaluated using Harrell's concordance index (C-index) and compared to the albumin bilirubin grade (ALBI) and Barcelona Clinic for Liver Cancer (BCLC) staging. Model calibration was assessed using the integrated Brier score and Arjas plots.
Results: The median (IQR) age was 66.0 (58.0 - 73.0) years, median (IQR) body mass index was 23.9 (22.1 - 25.9) kg/m2 and 78% were male. The LCRN Index comprised type 2 diabetes mellitus, ascites, hepatic encephalopathy, albumin, bilirubin, AFP and diameter of largest tumor nodule. In the validation cohort, the LCRN Index (1-year area under the receiver operating curve [AUC]: 0.86; 3-year AUC 0.80; 5-year AUC 0.76) outperformed the ALBI grade and BCLC stage for prognosticating HCC. The LCRN Index demonstrated better calibration compared to the ALBI grade and BCLC stage.
Conclusion: If further validated, the LCRN Index may be a useful tool for prognosticating HCC.

Oral Free Paper Session 2

FPS2-3 10122

Young Onset Hepatocellular Carcinoma Presents at Advanced Stage with Limited Treatment Options

Amruthavarshini Nagabhushana[1], Ashish Singh[2], Ravish Sanghi Raju[3], Thomas Samuel Ram[4], Anuradha C[5], Shyamkumar N K[5], Anu Eapen[5], Santhosh E Kumar[1], Ashish Goel[1]

[1]Department of Hepatology, Christian Medical College, Vellore, Tamil Nadu, India, [2]Department of Medical Oncology, Christian Medical College, Vellore, Tamil Nadu, India, [3]Department of Hepatopancreatobiliary Surgery, Christian Medical College, Vellore, Tamil Nadu, India, [4]Department of Radiation Oncology, Christian Medical College, Vellore, Tamil Nadu, India, [5]Department of Radiology, Christian Medical College, Vellore, Tamil Nadu, India

Background: Impact of presentation age in hepatocellular carcinoma (HCC) is not well studied. We aimed to assess the clinical profile of young onset HCC.

Methods: We retrospectively analyzed patients with LI-RADS-5 HCC discussed in multi-disciplinary team (MDT) meetings between October-2023 to October-2025. All patients with young-onset HCC (aged ≤40 years group) were compared to randomly selected equal number of HCC patients with age >40 years.

Results: Of 703 patients with HCC during the study period, 90 patients were aged ≤40 years {age (median, range): 35,19-40 years, M:77; Hepatitis B (HBV): 73%} were compared to 90 patients aged >40 years {age: 57,44-75 years, M: 76, HBV: 38%, Metabolic: 47%}. Underlying cirrhosis was less common in years (66% v/s 96%, p<0.01).Tumors in ≤40 years group were more advanced- vascular invasion: 46(51%), metastasis: 19(21%), within Milan criteria: 16(18%); as compared to >40 years group- vascular invasion: 30(33%), p<0.05; metastasis: 9(10%), p<0.05; within Milan criteria: 42(47%), p<0.01. Advanced BCLC stages were more common in ≤40 years group stage C+D: 50(55%) v/s 36(40%), p<0.05.Age remained a significant predictor (aHR: 2.14, 95% CI: 0.9-4.6; p-value: 0.055) of tumor being beyond Milan criteria after adjusting for etiology (HBV) and mode of detection (surveillance v/s initial presentation).MDT offered curative/ loco-regional treatment less commonly in ≤40 years group:27(30%) as compared to >40 years group: 46 (51%), p<0.05.

Conclusion: Despite the absence of underlying cirrhosis, significantly more advanced disease was noted in HCC patients aged ≤40 years. This limited their loco-regional/curative treatment options.

FPS2-4 10136

Environmental Exposure to Cadmium, Lead, and Mercury as a Public Health Risk Factor for Hepatocellular Carcinoma

Ankush Kumar, Pardeep Kumar

Department of Biochemistry, Shakuntla Hospital and Research Center, Delhi, India

Background: Environmental exposure to heavy metals such as cadmium (Cd), lead (Pb), and mercury (Hg) represents a growing public health concern, particularly in regions with industrial pollution, contaminated water sources, and occupational hazards. This study assessed the association between Cd, Pb, and Hg exposure and hepatocellular carcinoma (HCC), emphasizing environmental risk assessment and population-level health implications.

Methods: A case control analysis was conducted involving 118 patients with confirmed HCC and 89 non malignant controls. Concentrations of Cd, Pb, and Hg were measured in blood and liver tissue samples to estimate environmental body burden. Complementary experimental studies were performed in Wistar rats exposed orally to these metals at environmentally relevant doses, and in human cancer cell lines exposed to comparable concentrations. Oxidative stress indices, apoptotic signaling pathways, and tissue accumulation patterns were evaluated.

Results: HCC patients demonstrated significantly higher concentrations of Cd, Pb, and Hg in blood and liver tissues compared with controls, with cancer risk increasing across higher exposure quartiles. Animal studies confirmed rapid hepatic accumulation following exposure, supporting biological plausibility. Cellular experiments showed increased oxidative stress and impairment of intrinsic apoptotic pathways following metal exposure. Together, these findings indicate a dose-related association between environmental heavy metal exposure and hepatocellular carcinogenesis.

Conclusions: This integrated evidence highlights cadmium, lead, and mercury as modifiable environmental risk factors for hepatocellular carcinoma. From a public health perspective, strengthening environmental monitoring, reducing industrial emissions, improving water quality, and implementing targeted screening in high-risk populations may contribute to liver cancer prevention.

Oral Free Paper Session 2
FPS2-5　10151

Feasibility and Safety of Hepatic Rehabilitation in HCC Patients with Decompensated Cirrhosis

Takumi Kawaguchi[1], Ryuki Hashida[2,3], Dan Nakano[1], Kouki Nakamura[3], Masahide Fujiyoshi[1], Shunji Koya[3], Tsubasa Tsutsumi[1], Keisuke Amano[1], Hiroo Matsuse[3]
[1]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan
[2]Department of Orthopedics, Kurume University School of Medicine, Kurume, Japan
[3]Division of Rehabilitation, Kurume University Hospital, Kurume, Japan

Background: Hepatic rehabilitation (HR) is pivotal for improving physical function and quality of life in HCC patients who frequently suffer from frailty. However, its usefulness and safety remain unclear in patients with decompensated cirrhosis. We aimed to investigate the feasibility and safety of HR on liver reserve and physical function in cirrhotic patients with Child-Pugh class B/C.
Methods: This study included 118 HCC patients with cirrhosis who underwent HR (Child-Pugh class A, n=73; Child-Pugh class B/C, n=45). HR involved aerobic and resistance exercises. We evaluated changes in Child-Pugh score and class, and physical function (Barthel Index, handgrip strength, five-times chair stand test [CS-5], liver frailty index [LFI]) before and after HR.
Results: At baseline, physical function was similar between the Child-Pugh class A and B/C groups (LFI A 4.2 vs B/C 4.3, p=0.5570), despite the Child-Pugh class B/C group having significantly worse liver function. The Child-Pugh class B/C group showed no increased risk of adverse events such as falls and death. Change in physical function scores (ΔBarthel index, Δhandgrip strength, ΔCS-5, ΔLFI) showed no significant difference between the two groups. Regarding liver reserve, the Child-Pugh class B/C group showed a significantly better outcome in Child-Pugh class change (worsening/unchanged/improved: class A 33/40/0, class B/C 7/35/3; p=0.0007).
Conclusions: HR can be safely implemented in HCC patients with decompensated cirrhosis, similar to those with compensated cirrhosis. The intervention effectively maintained physical function without increasing the risk of adverse events or worsening liver function, supporting its integration into multidisciplinary HCC care.

Oral Free Paper Session 3

FPS3-1 10011

Aging-Driven Immunosuppressive Remodeling of the Tumor Microenvironment in Gallbladder Cancer: Insights from Single-Cell Transcriptomics

Lei Kong, Shengxin Gu, Mingyang Wang, Xiaoling Song, Jun Gu
Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Aging significantly influences cancer progression by altering the tumor microenvironment (TME). In gallbladder cancer (GBC), age-related changes in the TME may impact tumor initiation, immune evasion, and metastasis. While aging has been shown to promote an immunosuppressive TME in other cancers, its effects in GBC are not well understood. This study aims to investigate age-dependent alterations in the GBC TME using single-cell transcriptomics.
Methods: We performed single-cell RNA sequencing on tumor samples from two GBC cohorts: younger patients (<60 years, n=5) and older patients (>70 years, n=5). By analyzing cell-cell communication, transcription factor activity, and pseudotime trajectories, we identified age-related changes in cellular subpopulations and molecular characteristics within the TME.
Results: Aging significantly alters both immune and stromal components of the GBC TME. In the older cohort, we observed an increased prevalence of immunosuppressive populations, including regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs). Tregs exhibited enhanced suppressive function, while TAMs shifted towards a pro-tumor M2 phenotype. Aging also expanded exhausted CD8+ T cells, diminishing anti-tumor immunity. Stromal fibroblasts in older patients upregulated genes involved in extracellular matrix (ECM) remodeling, fostering a fibrotic, tumor-promoting environment. Endothelial cells displayed altered vascular characteristics. Transcription factor analysis revealed increased NF-kB and STAT3 activity, while pseudotime analysis suggested aging drives differentiation shifts toward tumor-supportive phenotypes.
Conclusions: Aging induces significant alterations in the GBC TME, promoting an immunosuppressive and tumor-enhancing environment. These findings emphasize the need for age-specific therapeutic strategies targeting TME changes, particularly in elderly GBC patients.

FPS3-2 10144

KLF5 Mediates a Galectin1-FBP1-RAS/ERK Cascade to Drive Proliferation and Migration in Intrahepatic Cholangiocarcinoma

Xing Yu, Yu Tian, Ke Zhang, Huahong Duan, Ruiqi He, Junyu Lin, Chuyi Bai, Hao Li
School of Basic Medical Sciences, Hunan Normal University Health Science Center, Changsha, China

Background: Intrahepatic cholangiocarcinoma(ICC), the second most common primary liver cancer following hepatocellular carcinoma, exhibits aggressive behavior and poor prognosis. Galectin1(Gal1), a carbohydrate binding protein implicated in tumor progression, has an unclear role in ICC. This study aimed to elucidate the underlying mechanisms of Gal1 in ICC progression.
Methods: RT-qPCR and immunohistochemical analyses showed elevated Gal1 expression in ICC tissues, which was significantly linked to poor prognosis. In line with this finding, Gal1 knockdown markedly suppressed ICC cell proliferation and migration both in vitro and in vivo. Further, ChIP seq and Enhancer-reporter assays determined Kruppel-like-factor 5(KLF5), directly binds to regulatory elements of the Gal1 locus, leading to activation of Gal1.
Results: Mechanistically, KLF5 mediated Gal1 induction enhances epithelial mesenchymal transition and resistance to chemotherapeutic agents. Moreover, transcriptome sequencing of Gal1 knockdown ICC cells revealed that Gal1 may exert its oncogenic function by suppressing fructose-1,6-bisphosphatase 1(FBP1), and activating the RAS/ERK signaling pathway. Consistently, FBP1 expression was markedly reduced in ICC clinical samples; its overexpression suppressed ICC cell proliferation and migration, whereas FBP1 silencing partially reversed the inhibitory effects observed in Gal1 deficient cells. In addition, KLF5 dependent Gal1 depletion upregulated FBP1, leading to the inactivation of the RAS/ERK pathway and attenuation of ICC progression.
Conclusion: Collectively, our findings demonstrate that KLF5 mediated Gal1 expression promotes ICC proliferation and migration through FBP1 suppression and subsequent activation of RAS/ERK signaling, highlighting Gal1 as a potential therapeutic target and providing new insights into ICC molecular pathogenesis.

Oral Free Paper Session 3

FPS3-3 10167

Lactylation of PPP1CA at K305 Promotes Lymph Node Metastasis in Intrahepatic Cholangiocarcinoma by Sustaining TGF-β Signaling

Yuheng Hu, Jun Li
Department of Hepatobiliary and Pancreatic Surgery, Tenth People's Hospital of Tongji University, School of Medicine, Tongji University, Shanghai, China

Background: Lymph node (LN) metastasis is a critical prognostic factor for intrahepatic cholangiocarcinoma (ICC). While lactate-mediated protein lactylation (Kla) is a newly discovered post-translational modification, its role in ICC metastasis remains poorly defined.
Methods: Single-cell and bulk RNA sequencing were used to profile the metabolic landscape of metastatic ICC. Pan-Kla IP-MS was performed to identify lactylated proteins. Site-directed mutagenesis, in vitro phosphatase assays, and footpad-to-popliteal LN metastasis mouse models were utilized to investigate the functional significance of the identified modification.
Results: Increased glycolysis and lactate production, driven by the transcription factor BHLHE40, significantly correlated with ICC LN metastasis. Lactate was found to activate the TGF-β pathway. Mechanistically, IP-MS identified PPP1CA, a catalytic subunit of protein phosphatase 1, as a target for lactylation at K26 and K305. Functional screening revealed that K305 lactylation (K305la) is the primary modification that inhibits PPP1CA's phosphatase activity. This inhibition prevents p-SMAD3 dephosphorylation, leading to sustained TGF-β signaling and enhanced cell invasion. Abolishing lactylation via the K305R mutation restored PPP1CA activity and significantly reduced LN metastasis in vivo. Furthermore, combined inhibition of lactate and TGF-β receptors showed synergistic anti-tumor effects.
Conclusions: We identified a novel "metabolic-epigenetic" axis where lactate-induced PPP1CA-K305la acts as a molecular switch that impairs the "brake" of the TGF-β pathway. Targeting this axis offers a potential therapeutic strategy for LN-metastatic ICC.

FPS3-4 10202

Epigenetic Silencing of PTEN as a Prognostic and Translational Biomarker in Periampullary Adenocarcinoma

Asgar Ali, Sundeep Singh Saluja, Sadhana Sharma
[1]Department of Biochemistry, All India Institute of Medical Sciences Patna, [2]Department of Gastrointestinal Surgery, GB Pant Hospital, New Delhi, India

Background: Periampullary adenocarcinoma (PAC) is a biologically heterogeneous malignancy lacking robust molecular prognostic markers. Although PTEN alterations have been described in gastrointestinal cancers, the prognostic impact of epigenetic PTEN silencing across the periampullary spectrum has not been systematically evaluated.
Materials and Methods: In this retrospective cohort study, 101 resected PAC cases were analyzed for PTEN gene alterations. Mutational analysis was performed using Sanger sequencing, promoter methylation by methylation-specific PCR, protein expression by immunohistochemistry, and apoptosis by TUNEL assay.
Results: PTEN promoter hypermethylation was detected in 54.4% of periampullary tumors and was significantly associated with advanced T stage (p=0.017), lymph node positivity (p=0.004), perineural invasion (p=0.001), and tumor recurrence (p=0.001). Loss of PTEN protein expression occurred in 52% of cases and was associated with poor overall survival, with the worst outcomes observed in patients harboring both PTEN hypermethylation and low expression. Ampullary tumors demonstrated superior survival compared with duodenal, bile duct, and pancreatic head cancers (p=0.001). Early-stage disease showed improved survival (p=0.001). Adjuvant chemoradiotherapy improved survival (p=0.010), while PTEN apoptosis negativity was associated with better outcomes.
Conclusion: This is the first study to demonstrate that epigenetic silencing of PTEN, rather than genetic mutation, is a key prognostic driver in periampullary adenocarcinoma. Assessment of PTEN promoter methylation and protein expression may serve as clinically actionable biomarkers for risk stratification and postoperative decision-making. These findings support the integration of PTEN-based molecular profiling to identify high-risk patients who may benefit from intensified surveillance or PI3K/AKT-targeted therapeutic strategies.

Oral Free Paper Session 3

FPS3-5 10184

Prognostic Impact of Adipose Tissue Volume in Unresectable Biliary Tract Cancer Treated with Gemcitabine, Cisplatin, and Immunotherapy

Tsuyoshi Takeda, Takashi Sasaki, Yoichiro Sato, Tatsuki Hirai, Yuri Maegawa, Jun Hamada, Takafumi Mie, Takaaki Furukawa, Yukari Suzuki, Takeshi Okamoto, Masato Ozaka, Naoki Sasahira
Department of Hepato-Biliary-Pancreatic Medicine, Cancer Institute Hospital of Japanese Foundation for Cancer Research

Background: The obesity paradox, in which obese patients experience improved outcomes following immune checkpoint inhibitor (ICI) therapy, has been reported in several malignancies. However, the prognostic impact of body composition in unresectable biliary tract cancer (uBTC) remains unclear. This study evaluated the efficacy of gemcitabine, cisplatin, and ICI (GC+ICI) according to adipose tissue index (ATI) in patients with uBTC.
Methods: We retrospectively analyzed patients with uBTC who received first-line GC+ICI between 2023 and 2024. Total, visceral, and subcutaneous ATI were measured using pretreatment computed tomography images and were dichotomized into low and high groups based on sex-specific median values. Clinical outcomes were compared between ATI groups.
Results: Sixty-eight patients were included. Primary tumor sites were intrahepatic bile duct in 18, extrahepatic bile duct in 28, gallbladder in 17, and ampulla of Vater in 5. Patients with high ATI had a lower prevalence of sarcopenia. Objective response rates and disease control rates did not significantly differ between groups. Among adipose tissue components, high subcutaneous ATI was strongly associated with improved progression-free survival (PFS) (9.4 months vs 3.5 months, p&It;0.001) and overall survival (OS) (20.5 months vs 7.7 months, p&It;0.001). In multivariable analysis, high subcutaneous ATI remained an independent predictor of prolonged PFS and OS.
Conclusions: In patients with uBTC treated with GC+ICI, high subcutaneous adipose tissue was associated with favorable survival outcomes. These findings suggest a potential association between body composition and clinical outcomes in uBTC treated with immunotherapy.

FPS3-6 10172

Feasibility and Safety of Endoscopic Ultrasound-guided Tissue Acquisition for Biliary Lesions

Keito Nakagawa, Saburo Matsubara, Risa Sunada, Tomohiro Arai, Noriko Murakami, Morito Ikeda, Naosuke Kuraoka
Department of Gastroenterology and Hepatology Saitama Medical Center, Saitama Medical University

Introduction: Pathological diagnosis of biliary lesions is usually performed via a transpapillary approach; however, its diagnostic yield is insufficient. Endoscopic ultrasound-guided tissue acquisition (EUS-TA) presents an alternative, but evidence remains limited.
Aims & Methods: In this study, we evaluated the feasibility and safety of EUS-TA for biliary lesions, including the bile duct, gallbladder, and ampullary region. A retrospective analysis was conducted on 68 patients with 71 biliary lesions who underwent EUS-TA at our institution between April 2017 and December 2024. Final diagnoses were established based on surgical specimens or clinical follow-up in non-surgical cases.
Results: The median age was 75 years (range: 50-90), and 43 patients (63.2%) were male. Lesions comprised 26 bile duct (malignant/benign, 17/9), 31 gallbladder (22/9), and 14 ampullary lesions (10/4); overall, 49 lesions were malignant and 22 were benign. Bile duct and ampullary lesions were cases where transpapillary diagnosis was inconclusive. Gallbladder lesions had distinct masses or wall thickening. The overall diagnostic yield (sensitivity/specificity/accuracy) for differentiating between benign and malignant lesions was 92.3%/100%/94.4%, respectively. In bile duct lesions, sensitivity/specificity/accuracy were 78.9%/100%/84.6%, respectively. In gallbladder and ampullary lesions, diagnostic yield was 100%. Adverse events occurred in 2/71 (2.8%): obstructive jaundice and pancreatitis; one required transpapillary biliary drainage. Surgery was performed in 21 patients (29.6%), with no cases of peritoneal dissemination observed.
Conclusion: EUS-TA demonstrates high diagnostic yield and safety for biliary lesions, offering a viable alternative when transpapillary approaches fail to differentiate benign from malignant pathology.

Oral Free Paper Session 4

FPS4-1 10094

MicroRNA-199a-5p Disrupts Unfolded Protein Response-mediated Stress Adaptation in Hepatocellular Carcinoma Cells

Chaiyaboot Ariyachet, Thammachanok Boonto
Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Background: Hepatocellular carcinoma (HCC) cells often hijack adaptive mechanisms to survive intrinsic and extrinsic stressors. We aimed to identify key tumor-suppressive microRNAs (miRNAs) that regulate these survival pathways in HCC.
Methods: We analyzed miRNA profiling from nine curated datasets in the dbDEMC database. Functional effects of miR-199a-5p were assessed in JHH-4 and SNU-449 cells. Mechanisms were elucidated via RNA-seq, overrepresentation analysis (ORA), gene set enrichment analysis (GSEA), and endoplasmic reticulum (ER) stress-specific fluorescent reporters (ATF4/XBP1). Direct targets were validated using dual-luciferase assays and western blotting.
Results: Bioinformatic analysis identified miR-199a-5p as the only miRNA consistently downregulated across all nine datasets, with low expression correlating with poor patient prognosis. Overexpression of miR-199a-5p significantly impaired HCC cell proliferation, migration, and colony formation. RNA-seq, ORA, and GSEA revealed the unfolded protein response (UPR) as the primary pathway suppressed by miR-199a-5p. Specifically, miR-199a-5p-overexpressing cells failed to activate ATF4 and XBP1 reporters upon ER stress induction. This impaired adaptation led to a significant accumulation of proteotoxic aggregates, as confirmed by thioflavin assays. Mechanistically, we identified HSPA5 and ERN1 as direct targets of miR-199a-5p; dual-luciferase assays and western blots confirmed that miR-199a-5p directly binds to their 5' untranslated regions (UTRs) to suppress protein expression.
Conclusions: miR-199a-5p acts as a potent tumor suppressor by disabling the UPR-mediated stress rheostat. By targeting HSPA5 and ERN1, miR-199a-5p sensitizes HCC cells to proteotoxic stress. Restoring miR-199a-5p expression represents a promising therapeutic strategy to enhance the efficacy of stress-inducing HCC oncology treatments.

FPS4-2 10108

Dynamic Regulation of Membrane Fluidity Drives Tumor Evolution and Attenuates TNF α-Mediated Apoptosis in Hepatocellular Carcinoma

Boqiang Liu, Liang Shi, Yi Wang
Zhejiang Provincial Key Laboratory of Laparoscopic Technology, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China

Background: Membrane fluidity is a fundamental biophysical property of cells and is essential for maintaining normal physiological functions, including molecular transport and signal transduction. While tightly regulated under physiological conditions, whether and how alterations in membrane fluidity contribute to tumor progression remain largely unknown. Here, we sought to systematically investigate the role of membrane fluidity in hepatocellular carcinoma (HCC) evolution.
Methods: Clinical HCC tissues and matched non-tumorous liver tissues were collected to establish a patient cohort for membrane fluidity analysis. In parallel, a murine HCC tumor evolution model and in vitro HCC cell models were established. Membrane fluidity was quantitatively assessed across clinical samples, tumor evolutionary stages, and cellular conditions. High-throughput transcriptomic sequencing was integrated to identify downstream signaling pathways associated with altered membrane fluidity, followed by functional validation experiments.
Results: Analysis of the HCC patient cohort revealed a significant increase in membrane fluidity in tumor tissues compared with adjacent non-tumorous liver tissues (Fig. A-C). In the murine tumor evolution model, membrane fluidity progressively increased during HCC evolution (Fig. D). Transcriptomic profiling identified significant alterations in the TNFα signaling pathway associated with changes in membrane fluidity (Fig. E-I). Functional assays further confirmed that experimentally reducing membrane fluidity enhanced TNFα-induced apoptosis in HCC cells (Fig. J-K).
Conclusion: These findings reveal membrane biophysics as an underappreciated driver of tumor evolution and suggest that targeting membrane fluidity or its associated TNF signaling axis may represent a novel therapeutic strategy for HCC.

Oral Free Paper Session 4

FPS4-3 10162

AARS1 Promotes Tumor Progression and Immune Evasion through ATF6 Lactylation-driven Tryptophan Metabolism in Hepatocellular Carcinoma

Yiming Wang, Hao Wang, Fan Li, Ming Ni, Ling Lu
Nanjing Medical University

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death, and many patients derive limited benefit from systemic and immunotherapies due to an immunosuppressive tumor microenvironment. Regulatory T cells (Tregs) are central to this state, but how tumor-intrinsic programs generate stable Treg-promoting signals in HCC is unclear. Alanyl-tRNA synthetase 1 (AARS1) was identified as a lactate-sensitive protein lactyltransferase, yet its clinical relevance in HCC and role in immune evasion are unknown. TDO2-driven tryptophan-kynurenine metabolism promotes Treg accumulation, but its upstream regulation by tumor lactylation has not been defined. This study investigates how AARS1 links glycolysis, ATF6 lactylation, TDO2 signaling and Treg-mediated immunosuppression, and whether targeting this axis is therapeutically beneficial.
Methods: Single-cell and spatial RNA-seq were used to map AARS1 expression. HCC was induced in mice with hepatocyte-specific Aars1, Atf6 or Tdo2 gain- or loss-of-function using DEN/CCl4 and Myc/Ras. Tumor glycolysis was assessed by micro-PET/CT and ECAR. AARS1 lactyltransferase activity was measured by PPi/AMP production and ATF6 K424 lactylation. Immune cells were profiled by flow cytometry and CyTOF.
Results: AARS1 was upregulated in HCC and associated with glycolysis, Treg accumulation and poor prognosis. AARS1 lactylated ATF6 K424 to drive TDO2-kynurenine signaling and Treg expansion, which in turn enhanced glycolysis. Beta-alanine inhibition of AARS1 broke this loop, restrained HCC growth and improved anti-PD-1 response.
Conclusion: AARS1 is a lactylation-dependent hub coupling tumor glycolysis to the ATF6-TDO2-kynurenine axis and Treg-mediated immunosuppression. Disrupting this pathway with beta-alanine remodels the microenvironment, limits HCC progression and enhances anti-PD-1 efficacy.

FPS4-4 10178

Dfna5-dependent Hepatocyte Death Promotes Inflammatory TNF Signaling in Kupffer Cells to Drive Hepatocarcinogenesis

Tomoya Hamabe, Yoshinobu Saito, Yoichi Sasaki, Kazuhiro Murai, Hayato Hikita, Takahiro Kodama
Department of Gastroenterology and Hepatology, The University of Osaka, Graduate School of Medicine

Background: Hepatocyte death is a key driver of chronic liver disease (CLD) progression and hepatocarcinogenesis. We previously demonstrated that persistent hepatocyte apoptosis promotes hepatocellular carcinoma (HCC). Dfna5 (Gasdermin E), a pore-forming protein activated by caspase cleavage, induces membrane rupture and release of pro-inflammatory intracellular contents. However, the role of Dfna5-mediated hepatocyte death in liver inflammation and HCC development remains unclear.
Methods: DFNA5 was silenced in AML12 hepatocytes using siRNA, and intrinsic apoptosis was induced with ABT-737. Alb-Cre Mcl-1 fl/fl (Mcl-1 L-KO) mice were crossed with Dfna5 fl/fl mice to generate Mcl-1/Dfna5 L-KO mice. Bulk mRNA sequencing was performed to identify Dfna5-dependent inflammatory pathways. Kupffer cells were depleted using clodronate liposomes. Clinical relevance was assessed using TCGA-LIHC survival data.
Results: ABT-737 induced caspase-3/7 activation and Dfna5 cleavage in vitro. DFNA5 knockdown did not affect caspase activation but significantly reduced LDH release, indicating suppression of secondary necrosis. In Mcl-1 L-KO mice, Dfna5 deletion markedly reduced hepatic Tnfa expression without altering serum ALT levels or caspase activity. mRNA-seq revealed significant suppression of TNF/NF-κB related pathways, validated by reduced expression of Tnf, Ccl2, and Cxcl2. Kupffer cell depletion abolished hepatic Tnfa expression, identifying Kupffer cells as the primary TNFα source. HCC developed in all Mcl-1 L-KO mice but was significantly reduced in Mcl-1/Tnfα double-KO mice. High DFNA5 expression was associated with poorer survival in TCGA-LIHC.
Conclusion: Dfna5 promotes secondary necrosis of apoptotic hepatocytes, thereby inducing Kupffer cell-derived TNF/NF-κB signaling that contributes to hepatocarcinogenesis. Targeting the Dfna5-TNF/NF-κB axis may represent a novel therapeutic strategy for inflammation-associated liver cancer.

Oral Free Paper Session 5

FPS5-1 10100

Natural Killer Cell Drives Liver Cancer Evolution Through Cholesterol Metabolism Reprogramming

Liang Shi, Boqiang Liu, Xingrou Guan, Hanyuan Chen
Zhejiang Provincial Key Laboratory of Laparoscopic Technology, Sir Run Run Shaw Hospital, Zhejiang University

Background: Tumor cells acquire survival advantages and evade therapy through continuous evolution. The liver, enriched in natural killer (NK) cells, presents a unique immune microenvironment. Although cholesterol metabolism is linked to liver precancerous lesions and hepatocellular carcinoma (HCC), its role in tumor evolution under immune pressure remains unclear.
Methods: Single-cell and single-nucleus RNA sequencing were performed on in vitro evolution models and patient tissue samples. A Support Vector Machine classifier, trained on in vitro data, was used to quantify NK-resistant (G2-R-like) tumor cells in patient epithelia. A genome-wide CRISPR/Cas9 knockout screen identified tumor-intrinsic regulators under NK cell-induced selective pressure. Therapeutic efficacy was evaluated using Hepa1-6 P4 tumors in Rag1-/-, NCG, and hLAG3-humanized C57BL/6 mouse models.
Results: Prolonged NK cell co-culture generated resistant liver cancer cells with enhanced cytotoxic resistance and activation of oncogenic pathways. This in vitro evolution model was validated in clinical cohorts. CRISPR screening identified rapid cholesterol metabolic reprogramming as a key adaptation, with liver X receptors (LXRs) as central regulators. The LXR agonist GW3965 restored NK cell sensitivity and promoted cholesterol efflux in vitro. In NK-R patients, infiltrating NK and CD8+ T cells were functionally suppressed, exhibiting elevated LAG-3 and FGL-1 expression. Combination therapy targeting LAG-3 and activating LXRs (with GW3965) synergistically halted tumor progression and enhanced the durability of immune checkpoint blockade in murine models.
Conclusion: Early NK cell-mediated immunosurveillance drives the metabolic and immunoevasive evolution of liver cancer. Targeting this axis through combined immunometabolic therapy represents a promising strategy to counteract tumor evolution and improve treatment outcomes.

FPS5-2 10147

A Fe-Curcumin-based Strategy to Reinvigorate CAR-T Cells by Reversing Exhaustion and Senescence in Liver Cancer

Yuchan Xue, Songbo Zhao, Qiang Zhu
Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China

Background: Chimeric antigen receptor-T (CAR-T) therapy has demonstrated remarkable efficacy in hematological malignancies. However, its effectiveness against hepatocellular carcinoma (HCC) remains limited by T cell exhaustion, senescence, and the immunosuppressive tumor microenvironment (TME). Curcumin, a natural anti-tumor compound, exhibits limited efficacy as a monotherapy. This study innovatively constructs an Fe-curcumin (FC) nanoplatform confer a superior "memory-persistence" phenotype upon CAR-T cells, thereby aiming to overcome these critical barriers in HCC treatment.
Methods: We developed ROS-scavenging Fe-curcumin nanoparticles for co-delivery with CAR-T cells. Their impacts on CAR-T cell apoptosis, proliferation, exhaustion, and memory phenotypes were profiled via flow cytometry and RNA-seq. In vivo antitumor efficacy and TME modulation were assessed in murine models using MRI and immunohistochemistry.
Results: The FC nanoparticles effectively induced tumor cell apoptosis without exerting cytotoxicity on T cells or CAR-T cells. Furthermore, they alleviated CAR-T cell senescence and exhaustion by suppressing the p53 signaling pathway, thereby enhancing cytotoxicity and proliferative capacity. RNA-Seq and flow cytometry confirmed an upregulated memory phenotype alongside downregulated exhaustion markers in FC-treated CAR-T cells. In vivo, the FC/CAR-T combination demonstrated a significant suppression of tumor growth and an extension of survival. The nanoparticles also remodelled the TME by alleviating hypoxia and acidosis, and enhancing endogenous T/NK cell infiltration.
Conclusion: This study demonstrates that FC reinvigorate CAR-T cells by mitigating exhaustion and senescence via p53 pathway inhibition, while concurrently remodeling the immunosuppressive TME. Our findings provide a novel and potent combinatorial strategy to overcome the key limitations of CAR-T therapy in solid tumors.

Oral Free Paper Session 5
FPS5-3 10119

Reverse-engineering Strategy Identified DDR1 as HCC Chemoprevention Target Post HCV Cure

Hiroaki Kanzaki[1], Courtney Katz[1], Hiroyuki Suzuki[1], Ece J Dinc[1], Naoto Fujiwara[2], Yujin Hoshida[1]
[1]Division of Digestive and Liver Diseases, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, U.S.
[2]Department of Gastroenterology and Hepatology, Graduate School of Medicine, Mie University, Mie, Japan

Background: We previously reported an etiology-agnostic HCC risk signature (PLS) and an etiology-specific HCC risk signature (PLS-HCVcure). These signatures can be utilized for reverse-engineering exploration of chemoprevention for post-SVR HCC.
Methods: To identify candidate chemopreventive agents, we performed in silico screening of compounds using PLS and PLS-HCV cure. In vitro validation was conducted using a PLS-inducible cell-based (cPLS) model. In vivo testing was performed in the DEN+CCl4 mouse model. Clinical relevance of candidate compound/target were assessed by spatial transcriptomic profiling.
Results: In silico compound screening identified a DDR1 inhibitor, 7rh, as a top candidate. In the cPLS model, 7rh favorably modulated PLS in a dose-dependent manner. In the DEN+CCl4 mouse model, administration of 7rh significantly reduced tumor burden and favorably modulated HCC risk signatures. 7rh treatment suppressed molecular pathways related to inflammation, apoptosis, necroptosis, DNA damage repair, and cell cycle regulation, as well as a subset of carcinogenesis-related hepatocyte signatures. In liver tissues from patients who achieved a sustained virological response (SVR), spatial transcriptomic profiling identified a hepatocyte subpopulation with activated DDR1 signaling. This subpopulation exhibited activation of HCC risk signatures observed in the in vivo model, as well as activation of a subset of carcinogenesis-related hepatocyte signatures.
Conclusion: These findings support pharmacological DDR1 inhibition as a promising chemopreventive strategy in HCV-cured patients with advanced fibrosis.

Oral Free Paper Session 6

FPS6-1 10038

Clinical Characteristics of Combination Immunotherapy in Elderly Patients with Unresectable Hepatocellular Carcinoma

Chikako Nagao[1], Korenobu Hayama[1], Michika Kitamura[1], Kenta Suzuki[1], Kaori Koyano[1], Yuta Hasegawa[1], Tomomi Okubo[2], Taeang Arai[1,2], Norio Itokawa[2], Masanori Atsukawa[1]

[1]1Division of Gastroenterology and Hepatology, Nippon medical school, Tokyo, Japan,

[2]Division of Gastroenterology and Hepatology, Nippon medical school,

[3]Division of Gastroenterology and Hepatology, Nippon medical school Chiba Hokusoh Hospital

Background and Aims: Combination immunotherapy has been established as treatment for unresectable hepatocellular carcinoma (uHCC). In real-world clinical practice, its use in elderly patients has increased; however, safety and efficacy in this population remain insufficiently clarified. Thus, this study aimed to evaluate the safety and treatment outcomes of combination immunotherapy in elderly patients with uHCC.

Methods: We retrospectively analyzed 121 patients with uHCC treated with immune checkpoint inhibitor–based combination therapy (atezolizumab plus bevacizumab or durvalumab plus tremelimumab) between October 2020 and May 2025. Patients were stratified into two groups according to age: <75 years and ≥75 years.

Results: The median age was 74 (range 34–89) years, with 96 men and 25 women. Child–Pugh class A/B was observed in 110/11 patients, and mALBI grades 1/2a/2b were 35/32/50, respectively. Immune–related adverse events occurred in 25 patients, with a significantly higher incidence in patients aged <75 years. Among 82 patients evaluable by mRECIST, the objective response rate was 42.3% and the disease control rate was 76.0%. Median progression–free survival and overall survival were 183 and 585 days, respectively. Treatment efficacy was comparable between patients aged <75 and ≥75 years. However, non–liver–related causes of death, including pneumonia and sepsis, were significantly more frequent in the ≥75 years group.

Conclusions: Combination immunotherapy provides comparable efficacy and safety in elderly patients with adequate performance status and hepatic functional reserve. Nevertheless, careful systemic management is essential in elderly patients because of the higher incidence of non–liver–related mortality.

FPS6-2 10064

Prognostic Value of Combined Child–Pugh Score and Modified Albumin–bilirubin Grade in Unresectable Hepatocellular Carcinoma Treated with Atezolizumab plus Bevacizumab

Tomonao Taira, Tomoyuki Satake, Go Igarashi, Kanae Inoue, Taro Shibuki, Masataka Amisaki, Mitsuhito Sasaki, Hideaki Takahashi, Hiroshi Imaoka, Shuichi Mitsunaga, Masafumi Ikeda

Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Atezolizumab plus bevacizumab (AB) is established as first–line therapy for unresectable hepatocellular carcinoma (uHCC) in patients with Child–Pugh (CP) class A. However, the liver function of patients classified as CP class A is heterogeneous, and the prognostic value of further stratification using the modified albumin–bilirubin (mALBI) grade remains unclear.

Methods: We retrospectively analyzed 123 patients with uHCC who received AB as first–line therapy at our institution. Patients with CP class A were stratified into four groups according to CP score and mALBI grade: group 1 (CP score 5/mALBI grade 1–2a), group 2 (5/2b), group 3 (6/1–2a), and group 4 (6/2b). Overall survival (OS) and progression–free survival (PFS) were evaluated using Kaplan–Meier analysis and Cox proportional hazards models.

Results: The median age was 72 years, 78.0% had an ECOG PS of 0, and 51.2% had BCLC stage C disease. The median OS was not reached in group 1, whereas it was 31.2/20.6/13.6 months in groups 2/3/4, respectively. Among these, only group 4 showed a statistically significant difference compared with group 1 ($p=0.005$). In multivariable analysis, group 4 was independently associated with poorer OS compared with group 1 ($p=0.007$). For PFS, groups 2 and 4 showed significantly shorter PFS than group 1 ($p=0.010$ and 0.002), whereas group 3 did not ($p=0.469$). Treatment–related adverse events of grade ≥3 were comparable across all groups.

Conclusions: mALBI grade stratification revealed prognostic heterogeneity within CP class A, identifying CP score 6/mALBI grade 2b as a poor prognosis subgroup.

Oral Free Paper Session 6

FPS6-3 10106

Association of Lenvatinib Pharmacokinetics with mALBI in Hepatocellular Carcinoma and Evaluation of Efficacy and Safety

Yumi Otoyama, Takahiro Fuji, Erika Nomura, Yoko Nakajima, Ikuya Sugiura, Yuki Ichikawa, Yu Shimozuma, Manabu Uchikoshi, Masashi Sakaki, Hitoshi Yoshida
Division of Gastroenterology, Department of Medicine, Showa Medical University, Tokyo, Japan

Background: The dose of lenvatinib (LEN) for hepatocellular carcinoma (HCC) is determined based on body weight and Child-Pugh classification. Because LEN is highly bound to albumin, impaired liver function or hypoalbuminemia may increase the unbound drug concentration, potentially affecting efficacy and safety. This prospective study evaluated the pharmacokinetics of LEN and investigated the impact of hepatic reserve on treatment outcomes and safety.
Methods: Forty-one HCC patients treated with LEN were enrolled. By measuring plasma LEN concentrations before treatment and at multiple time points after initiation, unbound area under the concentration-time curve per dose (AUCu/dose) was calculated. We examined the association between AUCu/dose and hepatic reserve capacity, as well as the associations between hepatic reserve capacity, AUCu/dose, progression-free survival (PFS), and adverse events.
Results: AUCu/dose significantly correlated with modified albumin-bilirubin (mALBI) grade (P = 0.007). Grade ≥2 adverse events were more frequent in patients with higher AUCu/dose and mALBI grade ≥2b (P = 0.033 and P = 0.036, respectively). Relative dose intensity (RDI) was significantly lower in patients with higher AUCu/dose and mALBI grade ≥2b (P = 0.023 and P = 0.006) and was significantly associated with both PFS and adverse events (P = 0.012 and P = 0.002).
Discussion and Conclusion: Elevated AUCu/dose due to mALBI grade ≥2b was associated with increased adverse events, leading to reduction in RDI. Furthermore, reduced RDI was significantly associated with shorter PFS, suggesting that mALBI is a useful indicator to predict the therapeutic efficacy and safety based on pharmacokinetics.

FPS6-4 10139

Regional Lymph Node Metastasis in Hepatocellular Carcinoma Treated with Immune-based Systemic Therapy: Prognostic Significance and Implications for Clinical Staging

Qian Chen, Zhi-Cheng Jin, Gao-Jun Teng
Center of Interventional Radiology & Vascular Surgery, Department of Radiology, Zhongda Hospital, Medical School, Southeast University, Nanjing, China

Background: We aimed to determine the prognostic significance of regional lymph node metastasis (LNM) in hepatocellular carcinoma (HCC) and evaluate its potential to refine established staging systems.
Methods: This nationwide, multicenter cohort included 3167 patients with unresectable HCC who received first-line immune-based systemic therapy across 45 tertiary hospitals from January 2018 to June 2024. Overall survival (OS) for regional LNM (N1M0), distant metastasis (N0M1), and macrovascular invasion (MaVI) groups was estimated using the Kaplan-Meier method and compared by log-rank test, with stabilized inverse probability of treatment weighting (sIPTW) applied to reduce baseline imbalances. The prognostic performance of the BCLC, HKLC, and CNLC systems was evaluated before and after separating N1 from extrahepatic spread using C-index, Akaike information criterion (AIC), and likelihood ratio tests (LRT).
Results: Regional LNM occurred in 203 (6.4%) patients. After sIPTW, the median OS for N1M0 group was 32.2 months (95% CI, 24.9-NR), significantly longer than the N0M1 group (20.5 months; aHR 0.51 [0.34-0.77]; p=0.001) and the MaVI group (21.1 months; aHR 0.53 [0.36-0.77]; p&It;0.001). Weighted 1-, 2-, and 3-year OS rates for N1M0 were 92.2%, 62.5%, and 41.8%, compared with 86.3%, 44.5%, and 21.9% for N0M1 and 76.1%, 43.0%, and 23.6% for MaVI. Subclassifying N1 improved prognostic discrimination across all staging systems, as indicated by higher C-indexes, lower AIC values, and significant LRT χ^2 statistics (all p&It;0.001).
Conclusion: Regional LNM represents a prognostically distinct entity and merits consideration as a separate category from other extrahepatic metastases in future HCC staging systems.

Oral Free Paper Session 7

FPS7-1 10097

Should Transarterial Chemoembolization Be Applied with Systemic Therapy for Hepatocellular Carcinoma with Hepatic Vein and/or Inferior Vena Cava Tumor Thrombus? : A Multicenter Study

Long-Wang Lin
Zhongda Hospital, Medical School, Southeast University, Nanjing, China

Background: To evaluate whether TACE should be applied with systemic therapy for HCC with HVTT/IVCTT, in a first-line therapy setting.
Methods: This multi-center retrospective cohort study included HCC patients with HVTT/IVCTT treated between June 2018 and March 2024. Patients received either systemic therapy plus TACE (Group A) or systemic therapy alone (Group B). Propensity score matching (PSM) was utilized to balance the baseline characteristics. Four sensitivity analysis including inverse probability of treatment weighting (IPTW) was performed. The primary outcomes were overall survival (OS) and progression-free survival (PFS).
Results: A total of 972 HCC patients with HVTT/IVCTT (696 in Group A and 276 in Group B) were included. The median follow-up time was 32.1 (95% CI: 30.4-33.8) months. After PSM, Group A demonstrated a significantly longer median OS compared to Group B (20.9 vs. 14.3 months; HR=0.65, 95% CI: 0.54-0.77, P&It;0.0001). Group A achieved a significantly longer median PFS compared to Group B (10.7 vs. 7.3 months; HR=0.67, 95% CI: 0.57-0.79, P&It;0.0001, per RECIST v1.1 criteria). Additionally, Group A exhibited a significantly higher objective response rate per RECIST v1.1 (45.3% vs. 28.8%, P&It;0.001) and per mRECIST criteria (53.6% vs. 36.3%, P&It;0.001). Grade more than 3 treatment-related adverse events occurred in 238 patients in Group A (34.2%) and 87 patients in Group B (31.5%).
Conclusions: TACE in combination with systemic therapy shows improved survival benefit and manageable safety profiles compared systemic therapy alone. These results support the use of TACE alongside first-line systemic therapy for HCC patients with HVTT/IVCTT.

FPS7-2 10160

Real-World Outcomes of Sequential Transarterial Chemoembolization followed by Atezolizumab-Bevacizumab in Patients with Advanced Hepatocellular Carcinoma

Soe Thiha Maung[1,3], Sung Won Chung[2], Jonggi Choi[2], Roongruedee Chaiteerakij[1]
[1]Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, [2]Asan Medical Center, Seoul, Korea.
[3]Ma Har Myaing Hospital, Yangon, Myanmar

Background: Transarterial chemoembolization (TACE) is standard for unresectable hepatocellular carcinoma (HCC), but repeated sessions may cause liver dysfunction and refractoriness. Atezolizumab plus bevacizumab (Atezo-Bev) is a promising post-TACE therapy. This study evaluates survival and predictors of response to Atezo-Bev after TACE.
Methods: This retrospective study included patients with advanced and unresectable HCC who received TACE followed by Atezo-Bev. Kaplan Meier analysis and Cox regression were used to assess survival outcomes.
Results: Among 154 patients (median age 61.8years; 82.5%male), 76.0% BCLC stage B and 77.3% were TACE-refractory. Median number of TACE and Atezo-Bev cycles was 4 and 6, respectively. The 2-year OS rate was 62.7%. In TACE-refractory patients, median OS was 31.7 months. On multivariable Cox regression, independent predictors of worse OS included INR (HR 180.28, 95%CI: 1.45-6361.72,p=0.001) and PIVKAII (HR 1.58, 95%CI 1.10-2.28,p=0.014). In the TACE-refractoriness, INR (HR 310.73, 95%CI 7.93-12179.11,p=0.002) and PIVKAII (HR 1.63, 95%CI 1.13-2.37,p=0.010) remained significant. Median PFS was 4.9 months overall and 4.7 months in TACE-refractory cases. Multivariable predictors of shorter PFS included elevated INR (HR 24.03, 95%CI 3.80-151.81,p=0.001), higher number of prior TACE sessions (HR 1.07, 95%CI 1.02-1.13,p=0.004), and AST (HR 1.00, 95%CI 1.00-1.01,p=0.040), which were consistent in the TACE-refractory subgroup. Patients with INR>1.08 or PIVKAII>178 mAU/mL and TACE refractoriness showed significantly worse OS (p=0.013 and p<0.001) and PFS (p=0.007 and p=0.016).
Conclusion: Hepatic function at Atezo-Bev initiation is more prognostic than TACE refractoriness. Repeated TACE may elevate INR and impair liver reserve, compromising Atezo-Bev efficacy. Early transition before decompensation may improve outcomes.

Oral Free Paper Session 7
FPS7-3 10183

Efficacy of Combined Three-Dimensional Conformal Radiotherapy and Hepatic Arterial Infusion Chemotherapy for Unresectable Hepatocellular Carcinoma with Major Vascular Invasion

Joji Tani, Hiroki Tai, Rie Yano, Mai Nakahara, Kyoko Oura, Tomoko Tadokoro, Asahiro Morishita, Hideki Kobara
Department of Gastroenterology and Neurology, Kagawa University Faculty of Medicine

Background: Advanced hepatocellular carcinoma (HCC) with major vascular invasion (Vp3/4, Vv3) carries extremely poor prognosis. Our institution employs combined hepatic arterial infusion chemotherapy (HAIC) using New FP regimen and three-dimensional conformal radiotherapy (3DCRT) for these unresectable cases.
Methods: Among 1,021 HCC patients (2007-2023), we analyzed 51 with major vascular invasion receiving New FP-HAIC plus 3DCRT (50 Gy to tumor thrombus). We evaluated treatment response, survival, adverse events, and feasibility of sequential therapies.
Results: Patient characteristics included median age 69 years, Vp3-4/Vv3=45/6, stage III/IVa/IVb=11/32/8, Child-Pugh 5/6/7=14/18/19. Treatment achieved high efficacy against tumor thrombus (response rate 82.4%; TE4/3/2/1=20/22/6/3). Overall response rate was 64.7% (CR/PR/SD/PD=5/28/10/8) with disease control rate 84.3%. No significant liver function deterioration occurred at three months. Sequential treatments included surgical resection (n=3) and molecular targeted agents (sorafenib: 19, lenvatinib: 4, atezolizumab+bevacizumab: 4). Grade3 adverse events (radiation gastritis with bleeding: 3, HBV reactivation: 1) were successfully managed. Median survival was 12.9 months overall - 7.2 months with initial treatment alone versus 28.9 months with sequential therapy. Multivariate analysis identified tumor thrombus response (p=0.0026, HR:0.126) and sequential therapy (p=0.0029, HR:0.253) as independent prognostic factors.
Conclusion: Combined HAIC with New FP and 3DCRT demonstrates excellent tolerability and efficacy for unresectable HCC with major vascular invasion. Early vascular invasion control restores hepatic blood flow, preserving liver function and enabling subsequent therapies, potentially improving long-term survival.

Oral Free Paper Session 8

FPS8-1 10111

Prognostic Impact of the Oncological Resectability Criteria in Patients Undergoing Liver Resection for Hepatocellular Carcinoma

Hayato Abe, Yukiyasu Okamura, Osamu Aramaki, Nao Yoshida, Yusuke Mitsuka, Shu Inagaki, Masataka Shindate
Division of Digestive Surgery, Department of Surgery, Nihon University School of Medicine, Tokyo, Japan

Background: The borderline resectable hepatocellular carcinoma (BR–HCC) criteria were introduced in 2023. We aimed to evaluate outcomes of liver resection (LR) based on the BR-HCC criteria.
Methods: We retrospectively analyzed 638 patients who underwent LR as initial treatment for primary HCC between 2014 and 2023. Patients treated with LR were classified according to the BR–HCC criteria into resectable (R), borderline resectable 1 (BR1), or borderline resectable 2 (BR2). Associations between clinicopathological factors and survival outcomes were assessed.
Results: According to the criteria, 528 patients were categorized as R, 59 as BR1, and 51 as BR2 in LR group. Median overall survival (OS) time of LR group was as follows: R, not reached; BR1, 88.4 months; BR2, 36.2 months, while median recurrence-free survival (RFS) time of LR group was as follows: R, 51.7 months; BR1, 20.8 months; BR2, 4.8 months. The classification was significantly correlated with OS (BR1 [vs. R]: HR 2.01 P=0.009; BR2 [vs. R]: 3.56, P<0.001) and RFS (BR1 [vs. R]:HR 1.87 P=0.002; BR2 [vs. R]:HR4.18 P<0.001) in LR group. Multivariate analyses identified BR-HCC (BR1 or BR2), impaired liver function (ALBI score), and treatment era as independent prognostic factors for OS. Treatment during 2018–2023 was independently associated with improved outcomes, underscoring the impact of systemic chemotherapy.
Conclusion: The resectability classification based on the oncological criteria showed acceptable prognosticating ability in patients undergoing LR for HCC. Optimal outcomes are likely to require integration of systemic chemotherapy across the entire treatment course.

FPS8-2 10078

Surgical Outcomes and Treatment Strategies for Solitary Giant Hepatocellular Carcinoma

Atomu Suzuki[1], Hidenori Takahashi[1], Yukio Tokumitsu[1], Yoshitaro Shindo[1], Hiroto Matsui[1], Masao Nakajima[1], Yuta Kimura[1], Shinobu Tomochika[1], Michihisa Iida[1], Tatsuya Ioka[2], Hiroaki Nagano[1]
[1]Department of Gastroenterological, Breast and Endocrine Surgery, Yamaguchi University Graduate School of Medicine, [2]Department of Oncology Center, Yamaguchi University Hospital

Background: The BR-HCC Expert Consensus defines solitary hepatocellular carcinoma (HCC) without macrovascular invasion as resectable (R) regardless of tumor size; however, whether resection alone achieves satisfactory outcomes in giant solitary HCC remains unclear. We evaluated surgical outcomes stratified by oncologic resectability and focused on solitary giant HCC.
Methods: We retrospectively reviewed 248 patients who underwent initial hepatectomy for HCC between 2005 and 2021, excluding cases with macrovascular invasion and distant metastasis. Patients were classified according to the HCC oncologic resectability classification (R/BR1/BR2). Overall survival (OS) and clinicopathological variables were compared. In the R cohort, outcomes were further compared according to tumor size.
Results: The cohort comprised R (n=215), BR1 (n=14), and BR2 (n=19). Age and Child-Pugh class did not differ among groups, whereas median maximum tumor diameter (2.9/3.5/7.0cm) and tumor number (1/2/4) increased significantly from R to BR2. Anatomical resection was more frequent in BR than in R (p<0.05). Median OS was significantly longer in R than in BR1/BR2 (59.0 vs. 37.2/44.2 months; p<0.05). Within R, median OS declined with increasing tumor size (<3 cm: 63.2; 3-<5 cm: 68.2; 5-<10 cm: 56.9; >10 cm: 23.3 months; trend p=0.203). Patients with tumors>10 cm had significantly worse OS than those with tumors <10 cm (p<0.05), and OS for >10 cm tumors was comparable to BR1.
Conclusion: Solitary HCC >10 cm demonstrates outcomes similar to BR1 despite being classified as R. Hepatectomy should be positioned within a multimodal strategy to improve prognosis in solitary huge HCC.

Oral Free Paper Session 8
FPS8-3 10146

Association between Prophylactic Antibiotics and Post-ablation Infections in Hepatocellular Carcinoma Patients: A Retrospective Multicenter Cohort Study

Ting Luo, Jie Yu, Ping Liang
Chinese PLA General Hospital, Beijing, China

Background: The role of prophylactic antibiotics in preventing infections following hepatocellular carcinoma (HCC) ablation remains unclear. We aimed to clarify whether prophylactic antibiotics reduce infection rates after HCC ablation and to identify patient subgroups who might benefit.
Materials and Methods: This retrospective, multicenter cohort study included HCC patients who underwent percutaneous thermal ablation between May 2018 and April 2024, classified into prophylactic antibiotic (PA) and non-prophylactic antibiotic (non-PA) groups. The primary outcome was infection, categorized as severe or non-severe, while secondary outcomes included duration of hospitalization, costs, and fever. Propensity Score Matching (PSM) and Overlap Weighting (OW) were employed to control for baseline differences, and the Firth's penalized likelihood method was applied to all logistic regression analysis.
Results: A total of 2446 patients (mean age 60.4, SD 10.6 years; 520 women) from six centers were included. Comparing the PA and nPA groups, the PA group showed lower overall infection rates than the nPA group (4.1% vs. 6.6%, P=0.024 in primary cohort), which was comparable after adjustment (P = 0.1 after PSM and P = 0.32 after OW). Logistic regression analysis revealed that BCLC B, high glucose level, and history of biliary surgery were significant independent risk factors of infection in both PSM and OW cohort.
Conclusion: Routine prophylactic antibiotic use is not necessary in percutaneous HCC ablation; however, it may be considered for selected patients.

Oral Free Paper Session 9

FPS9-1 10076

PIVKA-II Monitoring to Predict Response to The First Transarterial Chemoembolization (TACE) in Intermediate-Stage Hepatocellular Carcinoma

Chitchai Rattananukrom[1], Napapong Nitiwaranggoon[1], Anucha Ahooja[2], Tanita Sutthichaimongkol[1]
[1]Division of Gastroenterology and Hepatology, Department of Medicine, Khon Kaen University, Khon Kaen, Thailand, [2]Department of Radiology, Khon Kaen University, Khon Kaen, Thailand

Background: Hepatocellular carcinoma (HCC) is a major cause of cancer-related mortality, with transarterial chemoembolization (TACE) being the standard for intermediate-stage disease. Early prediction of treatment response is crucial. Protein induced by vitamin K absence-II (PIVKA-II) is a potential biomarker, but its role in predicting complete response (CR) to the first TACE is unclear. This study aimed to determine the optimal cut-off and diagnostic performance of PIVKA-II percentage reduction (PIVKA-II response) at 2 weeks post-TACE in predicting CR at 8 weeks.
Method: We conducted a prospective diagnostic accuracy study with 57 intermediate-stage HCC patients undergoing first TACE. Serum PIVKA-II was measured at baseline, 2, and 8 weeks post-TACE. Radiologic response at 8 weeks used mRECIST. AUROC analyzed PIVKA-II response predictability at 2 and 8 weeks.
Result: At 8 weeks, 26% achieved CR. Median PIVKA-II response at 2 weeks was significantly greater in CR (98%) versus partial response (79%), stable disease (71%), and progressive disease (65%) groups ($p = 0.04$). An AUROC of 0.74 indicated that a PIVKA-II reduction $\geq$ 83.8% at 2 weeks predicted CR with 80.0% sensitivity, 64.3% specificity, 44.4% PPV, 90.0% NPV, and 68.4% overall accuracy.
Conclusion: Early reduction in serum PIVKA-II levels after first TACE correlates with radiologic response, particularly CR. With an AUROC of 0.74, a PIVKA-II response at 2 weeks shows promise as an early surrogate marker for predicting CR, which could facilitate timely therapeutic decisions and improve clinical outcomes.

FPS9-2 10158

Role of Transjugular Intrahepatic Portosystemic Shunt (TIPS) in Refractory Gastrointestinal Bleeding inHepatocellular Carcinoma Patients with Portal Vein Thrombosis: A Prospective Cohort Study

Atteyat Semeya
Hepatogastroenterology department, Benha teaching Hospital, Gothi, Egypt

Background and Aims: Portal vein thrombosis (PVT) in hepatocellular carcinoma (HCC) patients with refractory variceal bleeding represents a therapeutic challenge. TIPS has been traditionally contraindicated but may offer life-saving intervention in selected cases. This study evaluates TIPS feasibility, safety, and efficacy in this population.
Methods: Prospective cohort study of HCC patients with PVT and refractory variceal bleeding undergoing TIPS (Child-Pugh A-B, MELD less than or equal to 18) from January-December 2024 at Benha Teaching Hospital. Primary outcomes: technical success (gradient reduction to less than 12 mmHg), clinical success (bleeding control at 6 weeks), and 30-day mortality. Secondary outcomes: rebleeding rates, survival, TIPS patency, and hepatic encephalopathy at 12 months.
Results: Sixty patients enrolled. Technical success: 80% (88% partial PVT, 68% complete PVT). Clinical success: 72%. 30-day mortality: 11%. Rebleeding: 24% at 6 months, 33% at 12 months (median 7 months). TIPS patency: 78%. New/worsening hepatic encephalopathy: 36% (severe 11%). Overall survival: 65% at 6 months, 55% at 12 months. Predictors of technical success: partial PVT, shorter thrombosis duration, operator experience. Independent predictors of clinical success: Child-Pugh score less than or equal to 7, post-TIPS gradient less than 10 mmHg.
Conclusions: TIPS is feasible in selected HCC-PVT patients with refractory bleeding, offering effective bleeding control with acceptable safety. Careful patient selection based on liver function and tumor burden is crucial. Results support TIPS consideration in this challenging population with limited alternatives.

Oral Free Paper Session 10

FPS10-1 10029

Development of Novel Deep Multimodal Representation Learning-based Model for the Differentiation of Liver Tumors on B-Mode Ultrasound Images

Masaya Sato[1,2], Tamaki Kobayashi[1], Takashi Tanaka[3], Takuma Nakatsuka[2], Hiroaki Goto[1], Tomomi Iwai[1], Ryosuke Tateishi[2], Kazuhiko Koike[2], Yutaka Yatomi[1]
[1]Department of Clinical Laboratory Medicine, Graduate School of Medicine, The University of Tokyo,
[2]Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, [3]Groovenauts, Inc

Background and Aim: Recently, multimodal representation learning for images and other information such as numbers or language has gained much attention. The aim of the current study was to analyze the diagnostic performance of deep multimodal representation model-based integration of tumor image, patient background, and blood biomarkers for the differentiation of liver tumors observed using B-mode ultrasonography (US).
Method: First, we applied supervised learning with a convolutional neural network (CNN) to 972 liver nodules in the training and development sets to develop a predictive model using segmented B-mode tumor images. Additionally, we also applied a deep multimodal representation model to integrate information about patient background or blood biomarkers to B-mode images. We then investigated the performance of the models in an independent test set of 108 liver nodules.
Results: Using only the segmented B-mode images, the diagnostic accuracy and area under the curve (AUC) values were 68.52% and 0.721, respectively. As the information about patient background and blood biomarkers was integrated, the diagnostic performance increased in a stepwise manner. The diagnostic accuracy and AUC value of the multimodal DL model (which integrated B-mode tumor image, patient age, sex, AST, ALT, platelet count, and albumin data) reached 96.30% and 0.994, respectively.
Conclusion: Integration of patient background and blood biomarkers in addition to US image using multimodal representation learning outperformed the CNN model using US images. We expect that the deep multimodal representation model could be a feasible and acceptable tool for the definitive diagnosis of liver tumors using B-mode US.

FPS10-2 10204

Dissociation between Multiphasic CT-Defined Tumor Burden and Endoscopic Portal Hypertension Severity in Cirrhotic and Non-Cirrhotic Hepatocellular Carcinoma

Aldisa Puspitasari, Dela Intan Permatasari, Adinda Amalia, Kemal Fariz Kalista
Division of Hepatobiliary, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia,
Dr. Cipto Mangunkusumo General National Hospital, Jakarta, Indonesia

Background: Hepatocellular carcinoma (HCC) is frequently complicated by portal hypertension. Tumor burden assessed by computed tomography (CT) is often presumed to exacerbate portal hypertension; however, its relationship with endoscopic portal hypertension severity, particularly in cirrhotic versus non-cirrhotic HCC, remains poorly defined.
Methods: We retrospectively reviewed 128 patients with HCC who underwent screening esophagogastroduodenoscopy (EGD) and had not received HCC-specific therapy at a tertiary referral center between November 2024 and November 2025. HCC was diagnosed radiologically and/or histologically according to European Association for the Study of the Liver (EASL) guidelines. Cirrhosis was determined using liver stiffness measurement by transient elastography. Tumor burden was assessed using the up-to-seven criteria based on multiphasic CT. Portal hypertension severity was evaluated using the Endoscopic Portal Hypertension Severity Score (range, 0–6).
Results: Of the 128 patients, 96 (75.0%) had cirrhosis and 32 (25.0%) were non-cirrhotic. Tumor burden was classified as high (beyond up-to-seven) in 104 patients (81.3%). Endoscopic portal hypertension severity scores were significantly higher in cirrhotic than in non-cirrhotic patients ($p < 0.001$). In contrast, tumor burden showed no significant correlation with portal hypertension severity score (Spearman $\rho = -0.10$, $p = 0.244$), and this finding remained consistent after stratification by cirrhosis status. In ordinal logistic regression analysis, cirrhosis was independently associated with greater portal hypertension severity (adjusted OR = 11.4, $p < 0.001$), whereas CT-defined tumor burden was not ($p = 0.258$).
Conclusions: Endoscopic portal hypertension severity in HCC predominantly reflects underlying cirrhotic liver disease rather than CT-defined tumor burden.

Oral Free Paper Session 10
FPS10-3 10210

Stereotactic Body Radiotherapy Enhances the Efficacy of Nivolumab in Advanced Hepatocellular Carcinoma: A Comparative Cohort Analysis

Phool Chand, Vinod Arora, Deepti Sharma, Satender Pal Singh, Ankit Bhardwaj, Shiv Kumar Sarin
Department of hepatology ILBS, Institute of Liver and Biliary Sciences (ILBS), New Delhi, India

Background: Outcomes with immune checkpoint inhibitor monotherapy remain suboptimal in advanced hepatocellular carcinoma. Stereotactic body radiotherapy may enhance antitumor immunity through immunogenic cell death and abscopal effects. We evaluated whether adding stereotactic body radiotherapy to nivolumab improves tumor response and survival compared with nivolumab alone.
Methods: In this retrospective cohort study conducted between 2018 and 2025, 420 patients with advanced hepatocellular carcinoma treated with nivolumab were screened, of whom 34 were excluded due to incomplete follow up, early discontinuation, missing imaging, or protocol deviations. The final analysis included 384 patients comprising stereotactic body radiotherapy plus nivolumab (n=64) and nivolumab alone (n=320). Nivolumab was initiated two weeks after radiotherapy, delivered at 30 to 40 Gy in 5 to 8 fractions with a median dose of 35 Gy in 6 fractions. Tumor response was assessed using modified RECIST at 6 and 12 months.
Results: Despite higher baseline tumor burden in the combination group ($p<0.001$), liver function was better preserved with lower bilirubin, MELD, MELD-Na, and more favourable ALBI scores (all $p<0.001$). At 6 months, objective response rate (62.5 percent vs 25.9 percent, $p<0.001$) and disease control rate (75.0 percent vs 45.0 percent, $p<0.001$) were higher with combination therapy. Median progression free survival (10.0 vs 4.5 months, $p<0.001$) and overall survival (20.4 vs 10.1 months, $p<0.001$) were longer. Immune related hepatitis occurred only with nivolumab monotherapy ($p=0.005$).
Conclusion: Stereotactic body radiotherapy combined with nivolumab improves tumor response and survival without excess hepatotoxicity and warrants prospective evaluation in advanced hepatocellular carcinoma.

Late Breaker Session 1

LBS1-1 10248

HLA-DR+ Tumor Cells Mimic Antigen-presenting Cells to Mediate Immunosuppression in HBV-related Hepatocellular Carcinoma

Wenjing Yuan[1,2], Ling Lan[1,2], Zixu Wang[1,2], Junqing Chang[3], Yuman Chen[4], Yuhan Lou[5], Zhuoran Chen[6], Yan Guo[1,2]

[1]People's Hospital of Zhengzhou University, [2]Henan Provincial People's Hospital, [3]Gushi County People's Hospital, [4]The First Affiliated Hospital of Nanyang Medical College, [5]The First Affiliated Hospital of Henan University, [6]Henan No.3 Provincial People's Hospital

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide, with hepatitis B virus (HBV) as a major driver. Despite the pivotal role of viral infections in shaping the tumor microenvironment (TME), the mechanistic differences among HBV-, hepatitis C virus (HCV)-, and non-B non-C (NBNC)-associated HCC remain poorly understood. By integrating the largest publicly available single-cell RNA sequencing (scRNA-seq) dataset of HCC (160 samples from 124 patients) with multi-scale protein-level validation using multiplex immunofluorescence and tissue microarrays (198 HCC specimens), we identified HLA-DR+ tumor cells as a distinctive feature of HBV+HCC. These tumor cells uniquely express MHC class II molecules, typically restricted to antigen-presenting cells, and correlate with immune checkpoint activation and PD-L1 expression, potentially contributing to an immunosuppressive microenvironment specific to HBV+HCC. Trajectory analysis revealed distinct CD8+ T-cell differentiation pathways in HBV+HCC, characterized by enhanced exhaustion and stem-like phenotypes. Notably, HLA-DR+ tumor cells not only recruited CD8+ T cells but also promoted their exhaustion, reinforcing the suppressive TME. Clinically, high proportions of HLA-DR+ tumor cells predicted poor survival outcomes, particularly when combined with elevated PD-L1 expression, and HLA-DR+ tumor cells may be a potential predictive biomarker for immunotherapy efficacy in HCC. Collectively, our findings establish HLA-DR+ tumor cells as a defining characteristic of HBV+HCC, providing novel insights into the unique immunosuppressive mechanisms in this context and potential therapeutic targets for immunotherapy.

LBS1-2 10236

High Ammonia Promotes EHHADH-dependent Pyrimidine Degradation to Induce Inflammatory Cell Death in HCC

Jinhui Wei, Chuanzhao Zhang, Baohua Hou, Shanzhou Huang
Guangdong Cardiovascular Institute, Guangzhou, China

Background: Metabolic reprogramming is a hallmark of hepatocellular carcinoma (HCC). While low-level ammonia promotes tumor growth, high-level ammonia induces toxicity. We aimed to identify targets mediating ammonia-induced HCC cell death to develop novel therapeutic strategies.
Methods: Using a transgenic HCC mouse model and multi-omics (metabolomics, transcriptomics, proteomics), we investigated the role of the ammonia-induced gene EHHADH. Mechanisms were validated via metabolic flux analysis, enzymatic assays for DPYD activity, and single-cell RNA sequencing. Therapeutic efficacy was evaluated using an EHHADH agonist combined with anti-PD-1 therapy.
Results: High ammonia significantly inhibited HCC growth by inducing GSDME-dependent inflammatory cell death. Mechanistically, ammonia caused polyunsaturated fatty acid (PUFA) accumulation, activating PPARA to transcriptionally upregulate EHHADH. Elevated EHHADH increased peroxisomal ROS and disrupted the mitochondrial TCA cycle, leading to cytosolic Acetyl-CoA accumulation. This triggered DPYD acetylation, accelerating pyrimidine catabolism and causing nucleotide depletion and replication stress, which ultimately drove pyroptosis. This inflammatory cell death significantly increased phagocyte and CD8+ T cell infiltration, synergistically enhancing anti-PD-1 efficacy.
Conclusions: This study identifies a novel "Metabolic-Immune" axis where ammonia exploits the PPARA-EHHADH pathway to drive pyrimidine catabolism and replication stress. Targeting EHHADH-mediated pyroptosis represents a promising strategy to suppress tumor growth and sensitize HCC to immune checkpoint blockade.

Late Breaker Session 1

LBS1-3 10239

Sarcomatoid Transformation is Associated with Immunosuppressive Remodeling in Hepatocellular Carcinoma

Ryo Morisue[1,2,3], Motohiro Kojima[1,4,5], Shinji Kohsaka[6], Toshihiro Suzuki[7], Jun Akiba[8], Shun-ichi Ariizumi[9], Keiichi Okano[10], Naoto Gotohda[2], Shumpei Ishikawa[1,11]

[1]Division of Pathology, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center, Chiba, Japan, [2]Department of Hepatobiliary and Pancreatic Surgery, National Cancer Center Hospital East, Chiba, Japan, [3]Department of Surgery, Osaka International Cancer Institute, Osaka, Japan, [4]Department of Pathology and Clinical Laboratories, National Cancer Center Hospital East, Chiba, Japan, [5]Division of Surgical Pathology, Department of Pathology, Kyoto Prefectural University of Medicine, Kyoto, Japan, [6]Division of Cellular Signaling, National Cancer Center Research Institute, Tokyo, Japan, [7]Division of Cancer Immunotherapy, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center, Chiba, Japan, [8]Department of Pathology, Kurume University School of Medicine, Fukuoka, Japan, [9]Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, Tokyo, Japan, [10]Department of Gastrointestinal Surgery, Faculty of Medicine, Kagawa University, Kagawa, Japan, [11]Department of Preventive Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Background: Sarcomatoid hepatocellular carcinoma (HCC) is a rare and highly aggressive subtype with poor clinical outcomes. Its biological basis and immune tumor microenvironment (TME) remain incompletely understood.

Methods: We performed whole-transcriptomic profiling of paired sarcomatous (Sa) and carcinomatous (C) components macrodissected from formalin-fixed, paraffin-embedded specimens of surgically resected sarcomatoid HCCs collected between 1997 and 2020. Immune cell composition within the intratumoral TME was inferred using CIBERSORTx, and paired comparisons between Sa and C components were conducted.

Results: A total of 36 patients with 38 tumors were identified. Transcriptomic profiling (32 Sa and 24 C samples) revealed that the Sa component was characterized by enrichment of epithelial-mesenchymal transition ($Q < 0.001$), cell-cycle-associated programs, including G2M checkpoint ($Q < 0.001$) and E2F targets ($Q < 0.001$), and TGF-ß signaling ($Q = 0.03$), together with suppression of hepatocytic metabolic pathways. Compared with 66 ordinary HCC, sarcomatoid HCC exhibited significantly increased CD204+ M2 macrophages and PD-1+CD8+ T cells, and tumor PD-L1 expression ($Q < 0.001$, respectively). Among immune populations, M2-like macrophages were the dominant contributors to the sarcomatoid immune TME, followed by resting memory CD4+ T cells and CD8+ T cells. Paired analysis revealed significantly higher abundance of M2-like macrophages ($P = 0.04$), activated natural killer cells ($P = 0.02$), and activated mast cells ($P = 0.03$) in Sa compared with C, whereas activated dendritic cells were significantly reduced ($P = 0.02$).

Conclusions: Sarcomatoid transformation in HCC is associated with mesenchymal differentiation and macrophage-dominant immunosuppressive remodeling of the tumor microenvironment, which may contribute to its aggressive clinical behavior.

LBS1-4 10254

Bile-based Liquid Biopsy for Diagnosis and Therapeutic Stratification of Biliary Strictures

Hiroshi Ohyama[1,2], Yosuke Hirotsu[2], Masao Omata[2,3]

[1]Department of Gastroenterology, Graduate School of Medicine, Chiba University, Chiba, Japan, [2]Genome Analysis Center, Yamanashi Central Hospital, [3]University of Tokyo

Background: Differentiating benign from malignant biliary strictures remains difficult because conventional histological and cytological approaches during endoscopic retrograde cholangiopancreatography (ERCP) have limited sensitivity. Bile is a disease-specific liquid specimen that may reflect tumor-derived genomic alterations and provide translational diagnostic value.

Aim: To assess the diagnostic and translational utility of bile-based liquid biopsy in patients with biliary strictures.

Methods: Seventy-seven patients with biliary strictures who underwent ERCP between April 2018 and March 2021 were retrospectively analyzed. Based on histopathology and clinical follow-up, 48 patients were classified as malignant (cholangiocarcinoma, n=38; gallbladder cancer, n=10) and 29 as benign. DNA extracted from bile samples was analyzed using targeted next-generation sequencing, and oncogenic mutation detection was regarded as evidence of malignancy.

Results: Median bile DNA concentrations were not significantly different between benign and malignant groups (993 ng/mL vs. 554 ng/mL, P=0.458). Diagnostic sensitivity was 27% for bile cytology and 60% for bile-based genomic analysis, increasing to 67% when combined (P=0.046). Actionable genetic alterations were detected in 8 of 48 malignant cases (17%). Among benign cases with oncogenic mutations, 4 patients developed radiologic progression and were subsequently diagnosed with malignancy during follow-up.

Conclusions: Bile-based liquid biopsy improves diagnostic accuracy for indeterminate biliary strictures and enables detection of actionable genomic alterations, supporting its translational potential for early diagnosis and precision oncology.

Late Breaker Session 2

LBS2-1 10246

Large Language Models Underperform Multidisciplinary Teams for Hepatocellular Carcinoma Treatment Decisions Despite Escalating Prompting Strategies: A Prospective Study

Amith Vishwanath[1], Santhosh E Kumar[2], Amruthavarshini Nagabhushana[2], Ashis Kumar Chowdhary[2], Stephan Benny[2], Anisha Mariam Koshy[3], Joy John Mammen[4], Arun Zachariah[5], Ashish Singh6, Thomas Samuel Ram[7], Shyamkumar Nidugala Keshava[8], Santhosh Babu KB[8], Ravish Sanghi Raju[9], Anuradha Chandramohan[10], Anu Eapen[10], Mahasampath Gowri.S[11], Ashish Goel[2]

[1]Department of Medical Gastroenterology, Christian Medical College Vellore, India, [2]Department of Hepatology, Christian Medical College Vellore, India, [3]Biomedical Informatics Unit, Christian Medical College Vellore, India, [4]Department of Transfusion Medicine, Christian Medical College Vellore, India, [5]Education Technology Unit, Christian Medical College Vellore, India, [6]Department of Medical Oncology, Christian Medical College Vellore, India, [7]Department of Radiation Oncology, Christian Medical College Vellore, India, [8]Department of Interventional Radiology, Christian Medical College Vellore, India, [9]Department of Hepato-Pancreato-Biliary Surgery, Christian Medical College Vellore, India, [10]Department of Radiodiagnosis, Christian Medical College Vellore, India, [11]Department of Biostatistics, Christian Medical College Vellore, India

Background & Aims: Large language models (LLM) remain unvalidated for complex clinical decision-making in prospective settings. This study compared locally deployed open-source LLM's performance to multidisciplinary team (MDT) decisions for hepatocellular carcinoma (HCC) treatment recommendations.

Methods: We conducted a prospective observational study including hepatocellular carcinoma patients from MDTs (May-October 2025) at a quaternary care center in India. Four locally deployed models (Phi-4 14.7B parameters, Gemma-3 9B, Llama-3.1 9B, Mistral-Small 7B) were evaluated using four prompting strategies: basic prompts without guidance, step-by-step reasoning instructions, retrieval-augmented generation (EASL 2025 guidelines), and advanced agentic retrieval with multiple queries. The primary outcome was normalized discounted cumulative gain at position 3 (NDCG@3), a scale that compared the recommendation and its order. Secondary outcomes included categorical agreement patterns and performance stratification by Barcelona Clinic Liver Cancer stage.

Results: We evaluated 92 HCC patients across 20 MDT meetings, with patients in BCLC stages 0/A (32.6%), B (16.3%), C (40.2%), and D (7.6%). Phi-4 with retrieval-augmented generation achieved the highest NDCG@3 of 0.50±0.40, significantly outperforming other models ($p<0.001$). Best -performing configuration (Phi-4 with retrieval-augmented generation) showed 23.9% perfect matches with multidisciplinary team decisions, 44.6% partial matches, and 31.5% complete failures. More advanced prompting strategies significantly improved performance ($p <0.001$). Test-retest reliability was excellent, confirming technical reproducibility.

Conclusions: Locally deployed LLMs do not perform as well as MDT team for HCC treatment planning, with only 23.9% achieving perfect alignment. The striking discrepancy between early-stage disease and advanced-stage competence reveals fundamental limitations in clinical reasoning for nuanced decisions.

LBS2-2 10272

Causal Machine Learning-Guided Personalized Immunochemotherapy Strategies in Intrahepatic Cholangiocarcinoma

Jun-Hao Mei[1], Kai Zhang[2], Ying Zhang[1], Zhen Li[3], Nai-Jian Ge[4], Xue Han[1], Rong Liu[5], Gao-Jun Teng[1], Jian Lu[1]

[1]Center of Interventional Radiology & Vascular Surgery, Zhongda Hospital, Medical School, Southeast University, Nanjing, China, [2]Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [3]Department of Interventional Radiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, [4]Department of Intervention, Third Affiliated Hospital of Naval Medical University, Shanghai, China, [5]Faculty of Hepato-Biliary-Pancreatic Surgery, The First Medical Center of Chinese People's Liberation Army (PLA) General Hospital, Institute of Hepatobiliary Surgery of Chinese PLA, Beijing, China

Background: Immunochemotherapy (IO-chemo) is first-line standard care for advanced intrahepatic cholangiocarcinoma (iCCA), but benefit varies greatly among individuals. We aimed to develop a system for identifying high-benefit populations through individualized treatment effect (ITE) estimation.

Methods: This multi-cohort study included iCCA patients receiving IO-chemo or chemotherapy. The discovery cohort (2018-2022, three centers; n=1485) was used to develop a causal machine-learning model (CMICC) for heterogeneous treatment effect estimation. An independent external validation cohort (2017-2023, seven centers; n=562) was employed for validation. Target trial emulation ensured unbiased average treatment effect estimation. Patients were stratified into high-benefit, no-to-moderate-benefit, and negative-benefit groups based on predicted ITE. Counterfactual analyses compared overall survival between model-guided and actual treatment selection. Model performance was evaluated using Qini and TOC curves; interpretability was assessed via SHAP.

Results: The CMICC model incorporated 17 of 55 multidimensional variables. In the high-benefit group, IO-chemo significantly improved survival versus chemotherapy (HR 0.39, 95% CI 0.30-0.52; $P<0.001$), with 24.1-31.2% mortality reduction at 12-36 months. No significant benefit was observed in the no-to-moderate-benefit group (HR 0.91, 95% CI 0.70-1.18; $P=0.488$). IO-chemo was harmful in the negative-benefit group (HR 1.91, 95% CI 1.47-2.48; $P<0.001$). Counterfactual analysis demonstrated CMICC-guided treatment improved survival compared with actual treatment (HR 0.53 and 0.62 for respective comparisons; both $P<0.001$), confirmed in external validation.

Conclusion: The CMICC model effectively stratifies iCCA patients by IO-chemo benefit and may improve survival through individualized treatment decisions.

Late Breaker Session 2

LBS2-3 10232

NEO-ERA-01: A Phase II Study of Neoadjuvant HAIC (GEMOX) plus Adebrelimab and Lenvatinib in High-risk Resectable Intrahepatic Cholangiocarcinoma

Jianhua Rao[1], Yuan Cheng[2], Yongquan Chi[1], Long Zhang[1], Tao Wang[3], Shengjie Jin[4], Bin Zhang[5], Jinguo Xia[1], Jing Huang[6], Xuan Xiao[7], Feipeng Zhu[8], Yong Yang[6], Ye Fan[1], Xiaoxing Mu[1], Wei Xu[1], Haipeng Jiang[1], Dousheng Bai[4], Wentao Wang[3], Ling Lu[1,5], Feng Cheng[1]

[1]Hepatobiliary Center, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China, [2]Department of Medical Oncology, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China, [3]Department of Liver Surgery and Liver Transplantation Center, West China Hospital of Sichuan University, Chengdu, China, [4]Department of Hepatobiliary Surgery, Northern Jiangsu People's Hospital Affliated to Yangzhou University, Yangzhou, China, [5]Department of General Surgery, Affiliated Hospital of Xuzhou Medical University, Xuzhou, China, [6]Department of Hepatopancreatobiliary Surgery, Ningbo Medical Center Lihuili Hospital, Ningbo, China, [7]Department of Pathology, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China 8Department of Radiology, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China

Background: Postoperative recurrence limits survival in patients with resectable intrahepatic cholangiocarcinoma (ICC).

Methods: This multicenter, single-arm, phase II trial enrolled patients with resectable high-risk ICC (tumor size >5 cm, multiple tumors, major vascular invasion, or lymph node involvement). Patients received 2-4 cycles of HAIC-GEMOX (oxaliplatin 85 mg/m2 and gemcitabine 800 mg/m2, Day 1), adebrelimab (1200 mg, Day 3), and lenvatinib (8 mg, Days 5-21) every 3 weeks, followed by resection. The primary endpoint was treatment completion; secondary endpoints included safety, R0 resection, objective response rate (ORR), event-free survival (EFS), overall survival (OS), major pathological response (MPR; ≤ 50% residual viable tumor).

Results: As of January 15, 2026, 31 patients (median age 58 years; 58% male) were enrolled from four centers in China. 27 patients completed neoadjuvant therapy (mean 2.5 cycles) and surgery; one remained on treatment, and three did not undergo surgery due to disease progression, adverse events, or chronic heart failure. Imaging evaluation was available for 30 patients. ORR and disease control rate were 43.3% and 93.3% (CR 3.3%, PR 40.0%, SD 50.0%, PD 6.7%). Among 27 resected, 25 (92.6%) achieved MPR, including two pCRs. R0 resection rate was 96.3%. Median largest tumor size was 5.9 cm, and 44.4% had lymph node involvement. Grade 3 treatment-related adverse events occurred in 35.5% of patients, with no grade 4/5 events or treatment-related mortality. EFS and OS are immature.

Conclusion: Neoadjuvant HAIC combined with adebrelimab and lenvatinib demonstrated encouraging pathological responses with acceptable safety in high-risk resectable ICC.

LBS2-4 10250

Stage-dependent Liver Stiffness Resolution after HCV SVR: A Longitudinal 8-year Follow-up Study

Shuntaro Obi[1,2], Yoshiki Asahina[2], Tomoyoshi Murata[2], Shoudai Toyama[2], Hiroyuki Amano[2], Hiroshi Ashizawa[2], Shinya Takaoka[2], Yushi Imai[2], Yukiko Asakawa[2], Hitoshi Mochizuki[2,3], Sumio Hirose[2], Yuichiro Kojima[2], Masao Omata[2,4]

[1]Department of Internal Medicine, Teikyo University Chiba Medical Center, Chiba, Japan, [2]Department of Gastroenterology, Yamanashi Central Hospital, Yamanashi,Japan, 3Genome Analysis Center, Yamanashi Central Hospital, Yamanashi, Japan, 4The University of Tokyo, Tokyo, Japan

Background: Although liver stiffness regression after sustained virologic response (SVR) is well recognized, its long term, stage dependent course remains unclear. We prospectively evaluated longitudinal stiffness changes after HCV eradication.

Methods: We prospectively followed 492 patients who achieved SVR with direct-acting antivirals between 2013 and 2023. Liver stiffness was repeatedly measured using Fibro-Scan. Patients were stratified by baseline stiffness: <4 kPa (n=22), 4-<8 kPa (n=222), 8-<12 kPa (n=102), and >12 kPa (n=146). Stiffness trajectories and hepatocellular carcinoma (HCC) incidence were analyzed.

Results: Among 492 patients (median follow-up 6.1 years, maximum 10.4 years), stiffness trajectories differed by baseline stage. Patients with low baseline stiffness (<8 kPa) showed minimal change and maintained stable values with low HCC incidence. Patients with advanced stiffness (>8 kPa) exhibited marked early improvement within 2-3 years after SVR, followed by a plateau after approximately 5 years with persistently elevated stiffness. Despite regression, HCC occurred predominantly in patients with high baseline stiffness, reaching 24% (35/146) in those with baseline stiffness >12 kPa.

Conclusion: Liver stiffness resolution after SVR is stage dependent. In advanced fibrosis or cirrhosis, early improvement plateaus without normalization, and HCC risk persists, supporting continued surveillance after SVR.

Late Breaker Session 3

LBS3-1 10241

Efficacy and Safety of Postoperative Adjuvant Donafenib Therapy in Patients with High-risk Recurrence after Radical Resection of Hepatocellular Carcinoma: A Multicenter Retrospective Study

Jianhua Rao[1], Yongquan Chi[1], Jizhou Wang[2], Long Zhang[1], Xinhua Zhu[3], Hongwei Zhang[4], Shaochuang Wang[5], Xin Wei[6], Yonghua Xu[7], Feng Zhang[1], Xuehao Wang[1], Lianxin Liu[2], Ling Lu[1,6], Feng Cheng[1]
[1]Hepatobiliary Center, The First Affiliated Hospital with Nanjing Medical University, [2]Department of Hepatobiliary Surgery, Centre for Leading Medicine and Advanced Technologies of IHM, The First Affiliated Hospital of USTC, Hefei, China, [3]Department of Hepatobiliary Surgery, Hepatobiliary Institute, Nanjing Drum Tower Hospital Medical School, Nanjing University, Nanjing, China, [4]Department of General Surgery, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, Jiangsu, China, [5]Department of Hepatobiliary Surgery, The Affiliated Huai'an No.1 People's Hospital of Nanjing Medical University, Huai'an, China, [6]Department of General Surgery, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China, [7]Department of General Surgery, Yancheng City No. 1 People's Hospital, Yancheng, China

Background: Hepatectomy offers the best chance for long-term survival in hepatocellular carcinoma (HCC), yet postoperative recurrence remains common. This multicenter study evaluated efficacy and safety of donafenib as postoperative adjuvant treatment in HCC patients at high risk of recurrence.
Methods: We conducted a retrospective, multicenter cohort study including 394 HCC patients at high risk of recurrence underwent radical resection at seven centers between January 2021 and October 2024. High-risk features were defined as tumor diameter >5 cm, multiple lesions, microvascular invasion (MVI) grade 1-2, tumor thrombus, or alpha-fetoprotein ≥200 μg/L.
Results: At data cutoff in August 2025, 219 patients received donafenib-containing adjuvant therapy and 175 underwent observation. Propensity score matching was performed to balance baseline characteristics, yielding 175 matched pairs (all $p>0.05$). Adjuvant donafenib was associated with prolonged median recurrence-free survival (RFS) compared with observation (38.6 vs. 20.4 months; HR 0.592, $p<0.001$), with higher 2- and 3-year RFS rates (63.1% and 59.3% vs. 46.7% and 36.8%). Overall survival (OS) was also improved in the donafenib-containing group (HR 0.528, $p=0.0173$), with a 3-year OS rate of 88.1% versus 71.7% in control group. Multivariate analysis identified MVI and CNLC stage IIIA as independent risk factors for recurrence, whereas postoperative adjuvant donafenib independently reduced risks of recurrence and death. Treatment-related adverse events occurred in 41.6% of patients, with a low incidence of grade 3 events (4.6%) and no grade 4 or 5 toxicities observed.
Conclusions: Postoperative adjuvant donafenib prolongs RFS and OS in patients with high-risk HCC after radical resection, with an acceptable safety profile.

LBS3-2 10273

The Risk of Decompensation in Steatotic Liver Disease-related Hepatocellular Carcinoma after Curative Treatment

Yuki Matsushita[1], Tatsuya Minami[1], Yoshikuni Kawaguchi[2], Akihiko Ichida[2], Ryo Oikawa[2], Mitsuhiro Fujishiro[1], Kiyoshi Hasegawa[2], Ryosuke Tateishi[1]
[1]Department of Gastroenterology, Graduate School of Medicine, the University of Tokyo, [2]Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, Graduate School of Medicine, the University of Tokyo

Background: Network pharmacology has become an increasingly popular approach for uncovering the mechanisms and therapeutic benefits of herbal remedies. However, the wide variability in current methodologies highlights a critical need for systematic assessment to guarantee consistency and reliability. Therefore, this study aimed to critically evaluate network pharmacological strategies, focusing on their ability to identify the underlying mechanisms and therapeutic efficacy of herbal medicines.
Methods: We utilized a holistic strategy encompassing systematic data collection, network construction, and analytical evaluation. Constituents and targets of herbal medicines were rigorously sourced from five separate databases to ensure robust coverage and high data integrity. We applied advanced network algorithms to isolate key targets and forecast therapeutic outcomes, thereby enhancing the analysis's scope. Furthermore, computational predictions were substantiated through experimental validation using prostate cancer models.
Results: Performance evaluations revealed unique trends depending on the network construction and aggregation techniques employed. While methods such as network centrality and path counts demonstrated specific advantages and limitations, assessing the influence on the multiscale interactome provided the superior accuracy in distinguishing known therapeutic effects. By optimizing these conditions, we successfully discovered novel indications for herbal treatments, which were subsequently confirmed via in vitro and in vivo assays.
Conclusion: This research offers a pioneering, comprehensive critique of existing network pharmacology methodologies within the field of herbal medicine. The findings provide essential guidelines for enhancing the precision and reliability of future studies aimed at elucidating the mechanisms and therapeutic potential of herbal drugs.

Young Investigator Award Session 1

YIA1-1 10013

Repurposing Resmetirom Suppresses MASH-associated Hepatocellular Carcinoma, with Mechanistic Implications of MDK/LRP1-mediated Metabolic Reprogramming and Immunosuppression

Vanilla Xin Zhang[1,2], Tina Suo[1,2], Yu Man Tsui[1,2], Karen Man-Fong Sze[1,2], Eva Lee[1,2], Lu Tian[1,2], Jingyi Lu [1,2], Huan Deng[1,2], Abdullah Husain[1,2], Charry Hui[1,2], Joyce Man-Fong Lee[1,2], Daniel Wai-Hung Ho[1,2], Irene Oi-Lin Ng[1,2]
[1]Department of Pathology, The University of Hong Kong, Hong Kong,
[2]State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong

Background: Mechanisms driving metabolic dysfunction-associated steatohepatitis (MASH)-related hepatocellular carcinoma (HCC) remain unclear, limiting therapy. We assessed the translational efficacy of resmetirom, a thyroid hormone receptor ß (THRß) agonist, and delineated pathways underpinning MASH associated hepatocarcinogenesis.
Methods: A western diet/CCl4-induced murine MASH-HCC model and multiple genetically engineered spontaneous HCC models were used to evaluate the effect of Resmetirom, mechanism of tumorigenesis and translational significance. Single cell RNA sequencing profiled liver and tumor tissues. Multicolor immunofluorescence and co-cultures of HCC cells and human hepatic stellate cells (HSCs) with macrophages or T cells were utilized to validate the identified targets.
Results: Repurposing Resmetirom significantly reduced tumor burden and steatosis across models. ScRNA-seq analyses revealed active interaction within the tumor microenvironment, involving HSCs and dysplastic hepatocytes (dys-Heps) with marked upregulation of midkine (MDK), which correlated with shorter relapse-free survival, specifically in non-viral, non-alcohol-related cases in human. Resmetirom treatment not only significantly suppressed tumor growth and reduced steatosis but also decreased MDK expression and increased Thrb levels. In mice, MDK engaged LRP1 to drive M2 like macrophage polarization, fostering progression from MASH to fibrosis and HCC. Macrophage specific Lrp1 silencing abrogated MDK induced M2 polarization and increased cytotoxic cytokine secretion, while LRP1 positive macrophages promoted T cell exhaustion via the CXCL16-CXCR6 axis. Combining Resmetirom and an MDK inhibitor (iMDK) synergistically suppressed tumorigenesis with reduction of LRP1 level in vivo.
Conclusions: Targeting the MDK/LRP1 axis with Resmetirom offers a promising therapeutic strategy for MASH-associated HCC, addressing both metabolic dysfunction and tumor progression.

YIA1-2 10017

Transitional Hepatocytes and Immunosuppressive Macrophages Drive NASH-Associated Liver Cancer Revealed by Single-Cell Transcriptomics

Firdian Makrufardi[1], Annisa Fairuz Nur Azizah[2]
[1]Department of Medicine, Faculty of Medicine, Universitas Negeri Yogyakarta, Indonesia,
[2]Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia

Background: The cellular dynamics and transformation of hepatocytes during disease progression remain poorly defined. This study aims to characterize the hypoxia-associated inflammatory landscape underlying the transition from NASH to HCC using integrated single-cell RNA sequencing (scRNA-seq) data.
Methods: We analyzed single-cell transcriptomic datasets encompassing liver samples from healthy individuals and patients at various NAFLD stages. Quality control, dimensionality reduction, and clustering were conducted using the Seurat pipeline. Subpopulation-specific markers were identified, and pseudotime trajectory analysis was applied to trace hepatocyte transformation. Gene regulatory networks were reconstructed via SCENIC analysis. A murine NASH-to-HCC progression model was used to validate key cellular and molecular findings.
Results: Transcriptomic profiling revealed a distinct hepatocyte population characterized by elevated CYP7A1 expression, predominantly found in pre-neoplastic liver regions. These transitional hepatocytes displayed gene signatures associated with stress responses, inflammation, and cancer-related pathways, while exhibiting reduced expression of healthy hepatocyte markers. Progressive activation of HIF1A signaling indicated a central role of hypoxia in driving this phenotypic shift. Furthermore, macrophage subtypes showed a notable polarization: RACK1+ macrophages transitioned into immunosuppressive TREM2+ cells in response to the hypoxic microenvironment. These TREM2+ macrophages, enriched in NASH and HCC samples, were found to be recruited by tumor cells via the CCL15-CCR1 chemokine axis.
Conclusion: This study provides an integrative single-cell view of how hypoxia orchestrates both hepatocyte transformation and immune modulation in NASH-associated hepatocarcinogenesis. The identification of CYP7A1+ transitional hepatocytes and TREM2+ macrophages as key players highlight potential cellular and molecular targets for early intervention in NAFLD-related liver cancer.

Young Investigator Award Session 1

YIA1-3 10047

Gemcitabine Modulates the Tumor Immune Microenvironment to Enhance Response to Immune-checkpoint Inhibitors in Biliary Tract Cancer

Kenji Nose[1], Naoto Fujiwara[1], Yuki Hayata[1], Hiroto Yuasa[2], Kiyora Izuoka[1], Mina Tempaku[1], Masako Ichishi[2], Naohisa Kuriyama[3], Reiko Yamada[1], Yoshifumi Hirokawa[2], Shugo Mizuno[2], Masatoshi Watanabe[2], Hayato Nakagawa[1]

[1]Department of Gastroenterology and Hepatology, Mie University, Mie, Japan, [2]Department of Oncologic Pathology, Mie University, Mie, Japan, [3]Department of Hepatobiliary Pancreatic and Transplant Surgery, Mie University Graduate School of Medicine, Mie, Japan

Background: While immune checkpoint inhibitors (ICIs) show limited efficacy as monotherapy in biliary tract cancer (BTC), their therapeutic potential is significantly enhanced when combined with gemcitabine-based chemotherapy. However, the precise mechanisms driving this synergy in humans remain to be fully elucidated.

Methods: To characterize gemcitabine-induced modulation of the tumor immune microenvironment in BTC, we evaluated immune cell types in surgically resected BTC specimens from patients who received a neoadjuvant gemcitabine-based regimen (n=47) compared to those without any preceding chemotherapy (n=20). The findings were confirmed in an immune-competent xenograft mouse model. Furthermore, molecular features in modulated immune cells were analyzed using spatial single-cell transcriptomics (CosMx) in a subset of neoadjuvant (n=2) and control (n=2) samples.

Results: Histological assessment revealed a significant reduction in regulatory T cells (Tregs) (13.4 vs. 31.8 cells/mm2; $p<0.001$) and macrophages (2.3 vs. 4.9% CD68 positive area; $p=0.002$) in neoadjuvant samples compared to controls. This Tregs depletion was further validated in gemcitabine-treated mouse models (15 vs. 42 cells/mm2). In four human specimens, CosMx detected a total of approximately 250,000 cells, including 245 (0.1%) Treg (defined by CD4+CD25+FOXP3+). The proportion of Tregs was significantly lower in neoadjuvant (0.05%) compared to control specimens (0.12%, $p<0.001$). Notably, Tregs from neoadjuvant specimens exhibited downregulation of SPP1 (encoding osteopontin) and IL1R1, suggesting a qualitative shift of Treg population toward a diminished immuno-suppressive phenotype.

Conclusion: Gemcitabine-based regimens prime the BTC microenvironment for ICI efficacy by both quantitatively depleting Tregs and qualitatively impairing their suppressive function.

YIA1-4 10065

Strategic Integration of Locoregional Interventions to Optimize Survival Outcomes following first-line ICI Combinations in Advanced Hepatocellular Carcinoma

Masaki Omori[1], Shohei Komatsu[1], Toshifumi Tada[2], Nobuaki Ishihara[3], Takanori Matsuura[2], Eisuke Ueshima[4], Hidetoshi Gon[5], Kenji Fukushima[1], Takeshi Urade[1], Toshihiko Yoshida[1], Keisuke Arai[1], Kosuke Iguchi[1], Motochika Hamanaka[1], Hayata Sano[1], Kazuki Terashima[6], Tomoaki Okimoto[6], Yoshihide Nanno[1], Hiroaki Yanagimoto[1], Masahiro Kido[1], Takumi Fukumoto[1]

[1]Department of Surgery, Division of Hepato-Biliary-Pancreatic Surgery, Kobe University Graduate School of Medicine, [2]Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine, [3]Department of Surgery, Seirei Hamamatsu General Hospital, [4]Department of Radiology, Kobe University Graduate School of Medicine, [5]Department of Surgery, Konan Medical Center, [6]Department of Radiology, Hyogo Ion Beam Medical Center

Background: Managing advanced hepatocellular carcinoma (HCC) after progression on first-line immune checkpoint inhibitor (ICI) combinations is challenging. We evaluated the impact of strategic interventions prior to disease progression (PD) on overall survival (OS).

Methods: From 139 patients receiving 1st-line ICI combinations (Oct 2018 to Oct 2025), 94 were analyzed after excluding those with fewer than two cycles due to adverse events or non-PD-related deaths. Based on best overall response per RECIST v1.1 and SITC consensus, acquired resistance was defined as PD after CR/PR or SD lasting greater than or equal to 6 months (n=53), while primary resistance was PD and SD lasting less than 6 months (n=41).Importantly, locoregional interventions prior to PD were defined as strategic "add-on" therapies; these were not considered as treatment failure or censored.

Results: The acquired resistance group showed a significantly longer median OS than the primary resistance group (26.8 vs. 12.6 months, $p< 0.0001$), while median PPS was comparable (13.2 vs. 10.0 months, $p=0.124$). Post-progression treatment rates after PD were high in both groups (77% vs. 73%). Notably, within the acquired resistance group, strategic add-on therapy prior to PD significantly prolonged OS compared to management without such interventions (median OS: not reached vs. 23.0 months, $p=0.003$).

Conclusions: Strategic "add-on" interventions prior to PD effectively extend 1st-line disease control, achieving a median OS exceeding 2 years in patients with acquired resistance. Proactive integrated management before the definitive failure of 1st-line ICI is crucial for maximizing survival in advanced HCC.

Young Investigator Award Session 2

YIA2-1　10020

Impact of Antihypertensive Drug Selection on Proteinuria Risk During Atezolizumab Plus Bevacizumab Therapy for Hepatocellular Carcinoma

Takashi Kitagataya, Daisuke Yokoyama, Shoichi Kitano, Takatsugu Tanaka, Akimitsu Meno, Naohiro Yasuura, Masatsugu Ohara, Masato Nakai, Takuya Sho, Goki Suda, Naoya Sakamoto
Department of Gastroenterology and Hepatology, Graduate School of Medicine, Hokkaido University, Sapporo, Japan

Background: Atezolizumab plus bevacizumab (AB) therapy is the standard treatment for advanced hepatocellular carcinoma (HCC); however, proteinuria frequently occurs and often necessitates bevacizumab interruption. The impact of antihypertensive drug selection during AB therapy on proteinuria risk remains unclear.
Methods: We retrospectively analyzed 75 patients with advanced HCC who received AB therapy at our institution between August 2020 and August 2025. Time-varying Cox regression analysis was performed to evaluate the impact of antihypertensive drug selection on Grade 2 proteinuria development, with L-type calcium channel blockers (L-CCBs) as the primary exposure variable.
Results: The median observation period was 169 days. L-CCBs were administered to 45 patients (60%), and Grade 2 proteinuria occurred in 22 patients (29.3%). Multivariable analysis identified L-CCB-containing regimens (HR: 3.15, 95% CI: 1.17 to 8.51, p=0.02) and mean systolic blood pressure of 140 mmHg or higher during treatment (HR: 3.09, 95% CI: 1.21 to 7.87, p=0.02) as independent risk factors, along with baseline eGFR below 60 mL/min/1.73m2 and baseline UPCR of 0.15 g/gCre or higher. In the subgroup with well-controlled blood pressure (below 140 mmHg), L-CCB-containing regimens significantly increased proteinuria risk even after adjusting for baseline renal function (HR: 20.4, 95% CI: 1.65 to 251.9, p=0.02).
Conclusions: L-CCB use during AB therapy may increase proteinuria risk. Careful antihypertensive drug selection is warranted, particularly in patients with baseline renal impairment or proteinuria.

YIA2-2　10060

Pretreatment Serum Heparin-Binding Protein as a Predictive Biomarker for Atezolizumab Plus Bevacizumab Therapy in Advanced Hepatocellular Carcinoma

Satoshi Narahara[1], Katsuya Nagaoka[1], Takehisa Watanabe[1], Hiroko Setoyama[1], Kazuhiro Sugi[2], Takanori Suzuki[3], Kentaro Matsuura[3], Shinji Itoh[4], Masaya Onishi[5], Yasuhito Tanaka[1]
[1]Department of Gastroenterology and Hepatology, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan, [2]Department of Gastroenterology and Hepatology, National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan, [3]Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, [4]Department of Surgery and Sciences, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [5]Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Kashiwa, Japan

Background: Although atezolizumab plus bevacizumab (Atezo+Bev) is a standard first-line therapy for advanced hepatocellular carcinoma (HCC), reliable pretreatment biomarkers predicting resistance remain unclear. This study aimed to identify biomarkers associated with resistance to Atezo+Bev and to elucidate the underlying molecular mechanisms.
Methods: Tumor biopsy and surgical specimens obtained before and after Atezo+Bev treatment from eight patients with HCC were analyzed using Visium and Xenium spatial transcriptomics. Patients were classified as responders (R: CR/PR/SD) or non-responders (NR: PD). Functional in vitro experiments were performed using human macrophages. Based on candidate molecules identified in tissue analyses, associations between pretreatment and 3-week post-treatment serum protein levels and treatment response were evaluated in a discovery cohort (n = 37) and validated in an independent cohort (n = 60).
Results: Spatial transcriptomic analyses revealed consistently high intratumoral expression of heparin-binding protein (HBP) in NR patients, detectable even in pretreatment biopsies. Xenium analysis demonstrated close interactions between HBP-high HCC cells and M2 macrophages, while Visium HD identified integrin alpha (ITGA)-mediated cell-cell interactions. In vitro, recombinant HBP increased the expression of CD163 and CD204 in human macrophages, whereas ITGA knockdown significantly suppressed their expression. High serum HBP levels were associated with significantly shorter progression-free survival at both pretreatment and 3 weeks post-treatment, using an ROC-derived cutoff (p = 0.029 and 0.039); these findings were validated in an independent cohort.
Conclusions: Elevated pretreatment serum HBP is associated with primary resistance to Atezo+Bev in advanced HCC through ITGA-mediated macrophage polarization and may serve as a predictive biomarker before treatment initiation.

Young Investigator Award Session 2

YIA2-3 10041

Novel Risk Score Incorporating Type-IV Collagen, Albumin, and Prothrombin Time (CAP score) to Predict 180-Day Surgery-Related Mortality After Liver Resection for Hepatocellular Carcinoma

Tomoaki Hayakawa, Maiko Niki, Genki Tanaka, Takayuki Shimizu, Takatsugu Matsumoto, Takayuki Shiraki, Shozo Mori, Taku Aoki
Department of Hepato-Biliary-Pancreatic Surgery, Dokkyo Medical University, Tochigi, Japan

Background: Accurate preoperative risk assessment is crucial for patients undergoing liver resection for hepatocellular carcinoma (HCC). While existing models like MELD or ALBI grade are used, they have limitations in predicting early postoperative mortality. This study developed and validated a novel scoring system to predict 180-day surgery-related mortality.
Methods: We conducted a retrospective cohort study of who underwent liver resection for HCC between 2000 and 2024. The cohort was divided into training and validation sets based on the operation dates. Multivariate analysis was performed to identify independent preoperative predictors of 180-day surgery-related mortality. Based on these factors, a scoring system was developed and its predictive performance was compared with existing liver function assessment tools using area under the curve (AUC) analysis.
Results: In the training cohort (n=623) and validation cohort (n=574), three independent predictors were identified and assigned 1 point each: type-IV collagen >=7.5 ng/mL, albumin >=3.4 g/dL, and PT-INR >=1.26. In the total cohort, 180-day surgery-related mortality rates for low- (0 points), intermediate- (1-2 points), and high-risk (3 points) groups were 1.2%, 7.1%, and 23.7%, respectively. This CAP score demonstrated superior predictive performance (AUC: 0.728) compared with the MELD score (AUC: 0.557), Child-Pugh classification (AUC: 0.637), and ALBI grade (AUC: 0.668).
Conclusions: The CAP score is a simple, objective, and effective preoperative tool for predicting 180-day surgery-related mortality after liver resection for HCC. It can guide surgical decision-making and perioperative management, providing clear evidence-based estimates of surgical risk.

YIA2-4 10070

Unexpected Rapid Progression of Hepatocellular Carcinoma after Radiofrequency Ablation

Takuma Kaneko[1], Takuma Nakatsuka[1], Keisuke Mabuchi[1], Yuki Matsushita[1], Tomoharu Yamada[1], Tatsuya Minami[1], Masaya Sato[1,2], Ryosuke Tateishi[1], Mitsuhiro Fujishiro[1]
[1]Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[2]Department of Clinical Laboratory Medicine, The University of Tokyo, Tokyo, Japan

Background: Radiofrequency ablation (RFA) is an established treatment for early-stage hepatocellular carcinoma (HCC). However, rapid disease progression, a rare but serious complication, can occur despite technically successful ablation.
Methods: We retrospectively reviewed 3868 patients who underwent 12104 times of RFA for HCC at our institution between February 1999 and December 2024. Rapid progression was defined as early recurrence at the periphery of the ablation area within 6 months after complete ablation that precluded further locoregional therapy.
Results: Twenty patients met the criteria. Number of tumors ranged from 1 to 6 and median size was 21 mm (range, 11-64). Target tumors were located within 5 mm of the primary or secondary portal vein branches in 10 patients (50%). Aggressive imaging features including non-smooth margins, multinodular confluent growth, and irregular rim-like arterial phase hyperenhancement were present in 13, 8, and 3 patients (65%, 40%, and 15%), respectively. AFP ≥200 ng/mL, L3-AFP ≥15%, and DCP ≥100 mAU/mL were presented in 8, 8 and 10 patients, respectively. The median size of recurrent tumors was 55 mm (range, 27-120), and 8 patients (40%) had vascular invasion. After recurrence, 7 patients received best supportive care with a median survival of 68 days; 5 patients received TACE/TAI with a median survival of 93 days; and 8 patients underwent systemic therapy with a median survival of 421 days.
Conclusions: Rapid progression after RFA showed a poor prognosis. Portal vein proximity, aggressive imaging features, and elevated tumor markers may indicate high-risk cases requiring closer post-ablation surveillance.