Published online: July 6, 2023

The 13th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2023)

Novel Insights into the Evolution of Liver Cancer Management

Seoul, Korea, July 6-8, 2023

Abstracts

Guest Editors

Young Nyun Park, Seoul
Do Young Kim, Seoul
Kang Mo Kim, Seoul
Haeryoung Kim, Seoul

Contents

Lecture Abstracts

Poster Abstracts

Abstracts

Lecture Abstracts

Session 1. Surveillance and Imaging Diagnosis for HCC

S1-1

Screening for HCC: From Here to Where?

Morris Sherman

University Health Network, Toronto, Canada

Surveillance for hepatocellular carcinoma (HCC) has a long history, stretching back at least to the 1980s, if not further. Initial studies evaluated the efficacy of alphafetoprotein (AFP) to detect small cancers before these caused clinical symptoms. Subsequently, ultrasound was added to the protocol latterly also desgamma carboxyprothrombin and the L3 fraction of AFP. Japan was the first country to develop a formal surveillance program and is still one of only a few countries all in Asia, where these programs have official government support. However, despite this long history it remains controversial as to whether screening achieves its objective (1). This article will explore some of the reasons why this controversy exists and will look at how surveillance might evolve in future.

The principles of a cancer screening program have been enunciated many years ago (2). First of these is that there should be effective therapy available to treat the cancer that is identified, that either saves lives or at least prolongs lives. Other principles include that the screening tests should not be onerous on either patient, the medical community or on healthcare systems. This means that surveillance should be easily and widely accessible and have wide acceptance among physicians and patients. Finally, the program should be cost effective so as not to lose the opportunity cost that diverting funds to surveillance rather than to other healthcare measures, might involve. Current surveillance programs using biomarkers and/or ultrasound meet many of these criteria, but the use of MRI or CT scanning does not because neither is as widely available as necessary for population surveillance, and even with the abbreviated MRI examination, are probably not cost effective (3).

Despite many years of study and real-life experience we still don't really know whether HCC saves lives or even prolongs life in those with HCC. Such certainty can only be achieved by a randomized controlled trial of surveillance versus no surveillance. This is because the true measure of any cancer surveillance program is its effect on mortality, not survival. Survival is defined as the proportion of patients remaining alive at a fixed period after diagnosis. (4) However, studies that look at survival are subject to a variety of different biases that cloud the interpretation of the results. These include length bias, lead time bias, and overdiagnosis bias. In contrast, mortality is defined as the number of patients dying from the disease over a fixed interval, such as five years and is not really susceptible to such bias (5), although selection bias and ascertainment bias may still be present. An improvement in survival is necessary for an improvement in mortality to occur, but is not sufficient. For common cancers, such as breast or colon or lung, if surveillance is effective, it should be able to reduce overall population mortality (6), but for less common cancers it may not be possible to demonstrate this.

Studies on HCC surveillance to date are mostly retrospective, with all the biases inherent in such studies. What prospective controlled studies do exist have various methodological flaws that limit interpretation. Nonetheless, the majority of studies suggest that survival is enhanced, even after correcting for lead time bias (7-8). Surrogate endpoints, such as size of tumour at detection and the ability to offer potentially curative treatment are improved by surveillance (9-12) and suggest, but do not prove, that surveillance is effective. Cost efficacy analyses mostly, but not universally, suggest that surveillance with biomarkers and/or ultrasound is cost-effective (3,11). Given these results and the lack of definitive studies it is reasonable to assume that surveillance is effective in at least prolonging life in those who develop HCC and to act upon this knowledge.

Despite these considerations surveillance for HCC is not as widely practiced as it should be. There are multiple barriers to the implementation of surveillance programs. First among these is the lack of recognition of the presence of liver disease (13-16). Minor elevations of ALT are often ignored, even those that are above the laboratory upper limit of normal, let alone above the true normal, which is lower than the lab normal. Second, even among those who are diagnosed with liver disease there is a lack of recognition of the presence of cirrhosis (14), because in the minds of many practitioners cirrhosis means ascites or jaundice, whereas these are evidence of liver failure, a late feature of cirrhosis. Hopefully, with more widespread use of Fibroscan or related radiological techniques or algorithms using serological markers (e.g., APRI or Fibrotest), the recognition of cirrhosis in patients with liver disease might improve. Finally, even if surveillance is offered to those diagnosed with cirrhosis, which is by no means universal, compliance with surveillance protocols is less than optimal (17).

Not all patients with cirrhosis will develop HCC, and some patients with liver disease that is not yet cirrhotic will develop HCC. Ideally, surveillance should be limited to those at significant

risk of HCC, whether cirrhotic or not. Assessment of risk, however, is not straightforward. A number of risk scores exist, that were developed mostly on patients with hepatitis B or hepatitis C cirrhosis (18-24). Of these only a few have external validation, and it remains unclear whether any of these scores, or others, developed in broader populations, are universally applicable.

The next issue is the nature of the underlying liver disease and the effect that this might have on surveillance tests. HCC surveillance protocols were developed primarily in patients with chronic hepatitis B. The protocols were effective for chronic hepatitis C as well, but their ability to identify small HCC in patients with either of the other two common liver diseases, alcoholic liver disease or metabolic fatty liver, is less clear. Ultrasound is less sensitive in obese patients and in those with fatty liver, sometimes to the extent that may render ultrasound useless (25,27). The addition of biomarkers to the surveillance protocol is associated with an improvement in sensitivity. Specificity is still an issue in some studies.

Since the incidence of HCC due to hepatitis B is decreasing and will likely continue to decrease (thanks to vaccination and effective therapy) and since HCC due to hepatitis C will also likely decrease in future, the need for surveillance in these patients will decrease. However, since metabolic and alcoholic fatty liver are increasing in incidence virtually all over the world (27,28) the incidence of HCC related to these conditions will likely increase (29). Couple this with the decreased efficacy of ultrasound in these conditions and it becomes less certain that current surveillance protocols will be beneficial.

This in turn, indicates that there is a need for better surveillance tools. There have been various attempts to improve on biomarker surveillance with alphafetoprotein, such as using the change in AFP over time as a marker, (30,31) or correlating AFP with level of ALT, (32) or using desgamma carboxyprothrombin or the L3 fraction of AFP as markers. Currently, the most effective biomarker or group of biomarkers, seems to be the GALAD score, a mathematical derivation based on APF, DCP and AFP-L3 (33). A number of other biomarkers have been tested, such as alpha fucosidase, but these have not gained general acceptance. More recently several attempts have been made to use circulating DNA derived from tumour cells as predictors of the presence of HCC (34). Early results are promising, but whether these new techniques should replace either current biomarkers or even ultrasound is still to be demonstrated.

All the evidence indicates that in well-chosen patients surveillance can detect small HCC's in patients who can be offered the possibility of cure. So, in the absence of level 1 evidence (35,36) we have to act on the knowledge that we have. The information that we have should be a springboard for campaigns to get official support and funding for surveillance programs. The surveillance the programs should include education of physicians about the need to identify liver disease. ALT should be included in the regular health check-up and an elevated ALT should not be ignored. Assessment of liver fat and fibrosis should be part of the routine work-up of these ALT abnormalities by Fibroscan, other forms of elastography or serologic-based algorithms. Once liver disease is recognized application of an appropriate risk score should indicate whether or not surveillance should be undertaken.

The problem of poor compliance by patients must be improved. Some effective methods have already been described (37,38). In addition, family practitioners have a role to play by reinforcing the message. Automated reminders to both patients and physicians and automated arranging of appointments have been shown to improve adherence to a surveillance protocol (38). These should be widely instituted.

It is up to the liver disease physicians, hepatologists and gastroenterologists to push decision makers to institute changes that will improve the outcome of HCC, a cancer that is going to become an even bigger problem in future.

References

1. Lederle FA, Pocha C . Screening for liver cancer: the rush to judgment. Ann Intern Med. 2012 Mar 6;156:387-9.
2. Prorok PC, Hankey BF, Bundy BN. Concepts and problems in the evaluation of screening programs. J Chronic Dis. 1981;34:159-71.
3. Andersson KL, Salomon JA, Goldie SJ, Chung RT. Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol. 2008 Dec;6(12):1418-24.
4. NIH National Cancer Institute. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/survival-rate. Accessed April20 2023
5. WHO Global Health Observatory. https://www.who.int/data/gho/indicator-metadata-registry/imr-details/1157. Accessed April 20 2023
6. A short guide to cancer screening. Increase effectiveness, maximize benefits and minimize harm. Copenhagen: WHO Regional Office for Europe; 2022:p3.
7. Cucchetti A, Trevisani F, Pecorelli A, Erroi V, Farinati F, Ciccarese F et al. Estimation of lead-time bias and its impact on the outcome of surveillance for the early diagnosis of hepatocellular carcinoma. Hepatology 2014 Aug;61:333-41.
8. Toyoda H, Kumada T, Tada T, Mizuno K, Hiraoka A, Tsuji K, et al. Impact of hepatocellular carcinoma aetiology and liver function on the benefit of surveillance: A novel approach for the adjustment of lead-time bias. Liver Int. 2018 Dec;38:2260-2268
9. Singal AG, Zhang E, Narasimman M, Rich NE, Waljee AK, Hoshida Y et al. HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: A meta-analysis. J Hepatol. 2022 Jul;77:128-139.
10. Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. PLoS Med. 2014 Apr 1;11(4):e1001624.
11. Cadier B, Bulsei J, Nahon P, Seror O, Laurent A, Rosa I al. Early detection and curative treatment of hepatocellular carcinoma: A cost-effectiveness analysis in France and in the United States. Hepatology. 2017 Apr;65(4):1237-1248.
12. Kim KM, Kim J, Sinn DH, Kim HS, Kim K, Kang W et al. Treatment for occult hepatocellular carcinoma: does it offer survival advantages over symptom-driven treatment? Scand J Gastroenterol. 2018 Jun;53(6):727-733.
13. Dalton-Fitzgerald E, Tiro J, Kandunoori P, Halm EA, Yopp A, Singal AG. Practice patterns and attitudes of primary

care providers and barriers to surveillance of hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol. 2015 Apr;13:791-8.e1
14. Vaz J, Strömberg U, Midlöv P, Eriksson B, Buchebner D, Hagström H. Unrecognized liver cirrhosis is common and associated with worse survival in hepatocellular carcinoma: A nationwide cohort study of 3473 patients. J Intern Med. 2023 Feb;293(2):184-199.
15. Simmons OL, Feng Y, Parikh ND, Singal AG. Primary Care Provider Practice Patterns and Barriers to Hepatocellular Carcinoma Surveillance. Clin Gastroenterol Hepatol. 2019 Mar;17(4):766-773.
16. Chen VL, Singal AG, Tapper EB, Parikh ND. Hepatocellular carcinoma surveillance, early detection and survival in a privately insured US cohort. Liver Int. 2020 Apr;40:947-955.
17. Farvardin S, Patel J, Khambaty M, Yerokun OA, Mok H, Tiro JA et al. Patient-reported barriers are associated with lower hepatocellular carcinoma surveillance rates in patients with cirrhosis. Hepatology. 2017 Mar;65(3):875-884.
18. Fan R, Papatheodoridis G, Sun J, Innes H, Toyoda H, Xie Q, et al. aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis. J Hepatol. 2020 Dec;73:1368-1378.
19. Li TC, Li CI, Liu CS, Lin WY, Lin CH, Yang SY, Lin CC. Risk score system for the prediction of hepatocellular carcinoma in patients with type 2 diabetes: Taiwan Diabetes Study. Semin Oncol. 2018 Oct;45:264-274
20. Abu-Amara M, Cerocchi O, Malhi G, Sharma S, Yim C, Shah H et al. The applicability of hepatocellular carcinoma risk prediction scores in a North American patient population with chronic hepatitis B infection. Gut. 2016 Aug;65:1347-58.
21. Papatheodoridis GV, Dalekos GN, Idilman R, Sypsa V, Van Boemmel F, Buti Mal. JHEP Predictive performance of newer Asian hepatocellular carcinoma risk scores in treated Caucasians with chronic hepatitis B. JHep Rep. 2021 Apr 20;3:100290.
22. Papatheodoridis G, Dalekos G, Sypsa V, Yurdaydin C, Buti M, Goulis J, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol. 2016 Apr;64:800-6.
23. Yang HI, Yuen MF, Chan HL, Han KH, Chen PJ, Kim DY et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. Lancet Oncol. 2011 Jun;12:568-74.
24. Flemming JA, Yang JD, Vittinghoff E, Kim WR, Terrault NA. Risk prediction of hepatocellular carcinoma in patients with cirrhosis: the ADRESS-HCC risk model. Cancer. 2014 Nov 15;120:3485-93.
25. Singal AG, Conjeevaram HS, Volk ML, Fu S, Fontana RJ, Askari F, Su GL, Lok AS, Marrero JA. Effectiveness of hepatocellular carcinoma surveillance in patients with cirrhosis. Cancer Epidemiol Biomarkers Prev. 2012;21:793–799.
26. 47. Simmons O, Fetzer DT, Yokoo T, Marrero JA, Yopp A, Kono Y, Parikh ND, Browning T, Singal AG. Predictors of adequate ultrasound quality for hepatocellular carcinoma surveillance in patients with cirrhosis. Aliment Pharmacol Ther. 2017;45:169–177.
27. Meera S, M & Popkin B, eds. 2020. Obesity: Health and Economic Consequences of an Impending Global Challenge. Human Development Perspectives. series. Washington, DC: World Bank.
28. Global status report on alcohol and health 2018. Geneva: World Health Organization; 2018.
29. Paik JM, Golabi P, Younossi Y, Mishra A, Younossi ZM. Changes in the Global Burden of Chronic Liver Diseases From 2012 to 2017: The Growing Impact of NAFLD. Hepatology. 2020 Nov;72(5):1605-1616.
30. Bird TG, Dimitropoulou P, Turner RM, Jenks SJ, Cusack P, Hey S et al. Alpha-Fetoprotein Detection of Hepatocellular Carcinoma Leads to a Standardized Analysis of Dynamic AFP to Improve Screening Based Detection. PLoS One. 2016 Jun 16;11(6):e0156801.
31. Choi J, Tayob N, Lim YS. Detecting Early Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Using Longitudinal α-Fetoprotein Screening. Clin Gastroenterol Hepatol. 2022 Aug 27:S1542-3565(22)00814-X.
32. El-Serag HB, Kanwal F, Davila JA, Kramer J, Richardson P.A new laboratory-based algorithm to predict development of hepatocellular carcinoma in patients with hepatitis C and cirrhosis. Gastroenterology. 2014 May;146(5):1249-55.e1.
33. Berhane S, Toyoda H, Tada T, Kumada T, Kagebayashi C, Satomura S et al. Role of the GALAD and BALAD-2 Serologic Models in Diagnosis of Hepatocellular Carcinoma and Prediction of Survival in Patients. Clin Gastroenterol Hepatol. 2016 Jun;14(6):875-886.e6.
34. Xu RH, Wei W, Krawczyk M, Wang W, Luo H, Flagg K, e t al. Circulating tumour DNA methylation markers for diagnosis and prognosis of hepatocellular carcinoma. Nat Mater. 2017 Nov;16(11):1155-1161
35. Jepsen P, West J. We need stronger evidence for (or against) hepatocellular carcinoma surveillance. J Hepatol. 2021 May;74:1234-1239.
36. Poustchi H, Farrell GC, Strasser SI, Lee AU, McCaughan GW, George J. Feasibility of conducting a randomized control trial for liver cancer screening: is a randomized controlled trial for liver cancer screening feasible or still needed? Hepatology. 2011 Dec;54(6):1998-2004.
37. Singal AG, Tiro JA, Murphy CC, Marrero JA, McCallister K, Fullington H,al. Mailed Outreach Invitations Significantly Improve HCC Surveillance Rates in Patients With Cirrhosis: A Randomized Clinical Trial. Hepatology. 2019 Jan;69(1):121-130.
38. Mokdad A, Browning T, Mansour JC, Zhu H, Singal AG, Yopp AC. Implementation of a Voice Messaging System is Associated With Improved Time-to-Treatment and Overall Survival in Patients With Hepatocellular Carcinoma. J Natl Compr Canc Netw. 2016 Jan;14:38-46.
39. Singal AG, Tiro JA, Murphy CC, Marrero JA, McCallister K, Fullington H et al. Mailed Outreach Invitations Significantly Improve HCC Surveillance Rates in Patients With Cirrhosis: A Randomized Clinical Trial. Hepatology. 2019 Jan;69(1):121-130.

S1-2

Emerging Imaging Tools for HCC Surveillance: Benefits and Concerns

Kengo Yoshimitsu

Fukuoka University, Fukuoka, Japan

As for the imaging surveillance tool for hepatocellular carcinoma (HCC), six monthly ultrasound (US) is widely used [1,2], which unfortunately suffers from insufficient sensitivity around 40-50% [1,2]. To compensate this disadvantage, use of MRI as an alternative surveillance tool, either non-contrast or contrast-enhanced, has been advocated by some investigators [3-7]. It has been established that MRI, particularly the one with contrast enhancement using hepatobiliary contrast agent, such as gadoxetate (EOB), surely has excellent and higher diagnostic performance for HCC with an accuracy around 90%, as compared to US. It is therefore obvious that MR would yield better diagnostic accuracy if it is used as a surveillance tool. However, fundamental problems of MRI as a surveillance tool exists; long scan time, high examination cost, and poor accessibility. For the long scan time, non-contrast scan consisting of T2WI and DWI alone [4], or abbreviated EOB-MR protocol [5] have been proposed. High cost is uncontrollable unless governmental support is available, and if we try to increase the number of MR equipment, further cost would be necessary for its installation and construction. It is therefore important to stratify the patients according to the risk levels, and only those at surely high risk should undergo surveillance using MRI.

In this lecture, details would be discussed as for the possibility of using non-contrast, abbreviated EOB-MRI, or full EOB-MRI as surveillance tools for HCC.

References

1. European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012; 56:908-943.
2. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018; 67:358-380.
3. Km HL, An J, Park JA, et al. Magnetic resonance imaging is cost-effective for hepatocellular carcinoma surveillance in high-risk patients with cirrhosis. Hepatology 2019; 69:1599-1613
4. Kim SY, An J, Lim YS, Han S, Lee JY, Byun JH, et al. MRI with liver-specific contrast for surveillance of patients with cirrhosis at high risk of hepatocellular carcinoma. JAMA Oncol 2017; 3:456-463.
5. Park HJ, Jang YH, Kim SY, Lee SJ, Won HJ, Byun JH, et al. Non-enhanced magnetic resonance imaging as a surveillance tool for hepatocellular carcinoma: comparison with ultrasound. J Hepatol 2020;72(4):718–724.
6. Kim DH, Choi SH, Shim JH, et al. Meta-analysis of accuracy f abbreviated Magnetic resonace imaging for hepatocellular carcinoma surveillance: non-contrast versus hepatobiliary phase-abbreviated magnetic resonance imaging. Cancers 2021; 13:2975
7. Park JH, Seo N, Kim SY. Current landscape and future perspectives of abbreviated MRI for hepatocellular carcinoma surveillance. KJR 2022; 23:598-614

S1-3

Diagnostic Strategy and Risk Stratification of Borderline Nodules on Imaging: Emphasis on OATP Transporters, Hemodynamic Changes, and Advanced Imaging Techniques

Jeong Min Lee

Seoul National University, Seoul, South Korea

Accurate diagnosis and risk stratification of borderline nodules on imaging are essential for personalized patient management and improved outcomes. This lecture aims to provide an in-depth overview of the diagnostic strategy and risk stratification approach for borderline nodules detected on advanced imaging modalities, with a focus on the role of organic anion-transporting polypeptide (OATP) transporters, hemodynamic changes, and Kupffer cell function during hepatocarcinogenesis. The presentation will discuss the importance of understanding OATP transporters and their impact on contrast uptake, as well as the hemodynamic alterations in arterial and portal blood flow and the changes in Kupffer cell function and number during hepatocarcinogenesis. Advanced imaging techniques, such as gadoxetic acid-enhanced MRI, Sonazoid-enhanced ultrasound, and diffusion-weighted imaging, will be emphasized for their potential to improve risk stratification of borderline nodules. The lecture will also cover a comprehensive diagnostic strategy that involves initial evaluation, radiologic assessment, and further evaluation techniques, such as biomarkers, molecular testing, and fine-needle aspiration or biopsy. The importance of multidisciplinary teams and personalized management strategies based on risk stratification will be highlighted, along with the crucial role of follow-up imaging and patient education. The goal is to enhance the accuracy of diagnosis and optimize patient outcomes for individuals with borderline nodules on imaging.

S1-4

Developing Biomarkers for Early Detection of HCC

Stephen Lam Chan

The Chinese University of Hong Kong, Hong Kong

Hepatocellular carcinoma (HCC) remains a growing cause of cancer-related death worldwide. One major reason of the high mortality in patients with HCC is the inadequacy of early detection strategies. Current national guidelines recommend semi-annual ultrasound screening together with alpha fetoprotein as surveillance of HCC in high-risk patients, but the sensitivity of this approach is still considerably lower compared to other successful cancer screening programs such as the use of mammogram in breast cancer and colonoscopy for colorectal cancer. Several promising biomarkers such as lens culinaris agglutinin-reactive alpha-fetoprotein (AFP-L3) and des-gamma carboxyprothrombin (DCP) have demonstrated improved sensitivity of early detection of HCC. Recently, circulating cell-free tumour nucleic acids fragments have emerged as potential candidates for early detection of pan-cancer

including HCC. The rapid emergence of these novel biomarkers holds significant promise but will need to undergo appropriate validations before their implementation as part of a surveillance program.

Session 2. Evolving Management of Early HCC

S2-1

Advances in Surgical Management and Evolving Techniques

Pierce Chow[1,2]

[1]Duke-NUS Medical School Singapore; [2]Dept. of HPB Surgery and Transplantation, National Cancer Centre Singapore and Singapore General Hospital, Singapore

Generally, less than 30% of Hepatocellular carcinoma (HCC) are amendable to surgical resection at the of diagnosis but surgery remains one of the most important curative intent modalities in HCC. There is currently greater clarity on selection criteria for patients to achieve a cure in HCC defined as median overall survival (OS) of > 50% at 5-years. The role of downstaging unresectable HCC to resection has also been clarified. The biggest recent impact on surgical management of HCC has been the first positive readout from a RCT on adjuvant therapy in HCC, the IMBraev050. Efficacious adjuvant therapy in HCC will leads to a re-assessment of indications for surgical resection in HCC.

Minimally invasive surgery is currently more widely used for the surgical resection of HCC. Duration of surgery is significantly longer but length of stay has been shorter. There has been a better appreciation of the different levels of difficulty with minimally invasive resection of tumours in different locations in the liver. In experienced centres, minimally invasive resection of HCC has been shown to be safe and many experienced centres have achieved parity (i.e., equivalence) in overall survival compared with open surgical resection.

S2-2

Local Ablation: What's New in 2023?

Hyunchul Rhim

Sungkyunkwan University, Seoul, South Korea

Local ablation is widely accepted as a curative treatment for liver tumors, particularly for early-stage hepatocellular carcinoma (HCC), according to most HCC treatment guidelines. This consensus is based on the cumulative evidence of excellent tumor control outcomes achieved through minimally invasive methods over the past two decades, as demonstrated in numerous cohort studies, randomized controlled trials, and meta-analyses. Despite inherent limitations related to tumor size, location, and aggressiveness, local ablation continues to evolve through significant technological advancements. These include fusion ultrasonography, contrast-enhanced ultrasound, use of artificial fluid, no-touch ablation strategies, and new energy sources such as irreversible electroporation (IRE) and histotripsy. Furthermore, ongoing clinical trials are actively investigating the role of local ablation in the era of immunotherapy. Depending on the results of these studies, local ablation may expand its role as one of immunomodulation to more advanced stage of HCC.

S2-3

Ablative Radiotherapy for Early HCC

Jason Chia-Hsien Cheng

National Taiwan University, Taipei, Taiwan

As radiotherapy (RT) has been integrated into multi-modality treatment for hepatocellular carcinoma (HCC), the selections include photon (X-ray) therapy and particle (proton and carbon) therapy. X-ray therapy is widely accessible and reimbursed by the insurance system, and is composed of mature technology and full-option image guidance. Particle therapy has the dosimetric sparing advantage, with the growing use of proton therapy in HCC but the evolving users of carbon ion therapy. The comprehensive delivery and imaging functions vary between particle therapy systems, but the insurance reimbursement is frequently unavailable. Despite the acceptable local control in the irradiated hepatic tumor, a certain proportion of patients develop intrahepatic and/or extrahepatic metastasis. Higher-intensity radiation by higher dose-per-fraction and fewer fraction-number, including ultra-short stereotactic body radiation therapy (SBRT) (6-20 Gy per fraction for 3-6 fractions) and hypofractionated RT (2.5-5 Gy per fraction for 10-20 fractions) demonstrate improved control of irradiated tumor and potentially reduced incidence of out-of-field metastasis. The comparative effect from the US single-institute and Asian collaborative retrospective studies on SBRT to radiofrequency ablation (RFA) was found with the non-inferior control of small-/medium-sized HCC. The meta-analysis pooling several studies and the US NCDB study using SBRT or RFA on HCC showed comparable local control but the concerned worse survival by SBRT, indicating the selection biases of patients with different disease burden and technical limits between SBRT and RFA. Only one Korean randomized trial on patients of early HCC treated with proton therapy compared with RFA was available and showed the similar survival and local control. The major patterns of failure, either after SBRT or RFA, are still out-field intrahepatic recurrence and extrahepatic metastasis. The developing combined use of SBRT and immunotherapy may shed light in potential out-field control effect on HCC. More cooperative groups for multi-center trials are needed to help form the consensus and establish more supportive evidence.

S2-4

Role of Transarterial Therapy in Early HCC

Hyo-Cheol Kim

Seoul National University, Seoul, South Korea

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is associated with a high mortality rate. Early diagnosis of HCC and timely treatment are crucial for improving survival. Transarterial therapy has been established as a valuable treatment option for early HCC, defined as a solitary tumor less than or equal to 5 cm in size, or up to three nodules each less than or equal to 3 cm in size.

Transarterial therapy includes conventional transarterial chemoembolization (cTACE), drug-eluting bead transarterial chemoembolization (DEB-TACE), and transarterial radioembolization (TARE).

cTACE is the most commonly used transarterial therapy for early HCC. It involves the injection of chemotherapeutic agents mixed with iodized oil (Lipiodol) into the hepatic artery followed by injection of gelatin sponge particles or microspheres, which supplies blood to the tumor, resulting in selective occlusion of the tumor's blood supply. The embolic particles prevent the chemotherapeutic agents from being washed away by the bloodstream, thus increasing their concentration and duration of action at the tumor site. cTACE has been shown to improve overall survival and disease-free survival in patients with unresectable HCC, and it is recommended as an alternative treatment option by major guidelines.

DEB-TACE is a newer TACE technique that uses drug-eluting beads instead of Lipiodol. These beads are loaded with chemotherapeutic agents and slowly release them into the tumor over time, resulting in more targeted and sustained drug delivery to the tumor.

Several studies have compared the efficacy and safety of cTACE and DEB-TACE in the treatment of HCC. Overall, the results have been mixed, with some studies showing no significant difference in overall survival, while others have shown improved outcomes with DEB-TACE. In two studies from Korea, however, cTACE has better tumor response in small HCC < 3cm. In author's institution, cTACE is preferred in small HCC (<3cm) due to better tumor response, and DEB-TACE is preferred in medium-sized HCC (3 – 7cm) due to milder post-embolization syndrome.

TARE is a newer transarterial therapy that involves the intra-arterial injection of microspheres containing a radioactive isotope that emits beta radiation. The microspheres selectively lodge in the tumor's blood vessels, delivering a high dose of radiation to the tumor while sparing the normal liver tissue. TARE has been shown to have better tumor response than TACE, with fewer side effects and a shorter hospital stay. However, it is more expensive than TACE and requires specialized equipment and expertise.

In conclusion, transarterial therapy has become an essential treatment option for early HCC, and cTACE is currently the most commonly used option due to its proven efficacy and accessibility. TARE has emerged as a promising alternative to TACE, with better tumor response and fewer side effects, but it requires specialized equipment and expertise with much higher medical cost.

References

1. Lee IJ, Chun HJ, Chung JW. 2022 Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines for Transarterial Therapy of Hepatocellular Carcinoma: What's New? Korean J Radiol. 2023 Jan;24(1):6-9.
2. Lee M, Chung JW, Lee KH, Won JY, Chun HJ, Lee HC, Kim JH, Lee IJ, Hur S, Kim HC, Kim YJ, Kim GM, Joo SM, Oh JS. Prospective Multi-Center Korean Registry of Transcatheter Arterial Chemoembolization with Drug-Eluting Embolics for Nodular Hepatocellular Carcinoma: A Two-Year Outcome Analysis. Korean J Radiol. 2021 Oct;22(10):1658-1670.
3. Lee IJ, Lee JH, Lee YB, Kim YJ, Yoon JH, Yin YH, Lee M, Hur S, Kim HC, Jae HJ, Chung JW. Effectiveness of drug-eluting bead transarterial chemoembolization versus conventional transarterial chemoembolization for small hepatocellular carcinoma in Child-Pugh class A patients. Ther Adv Med Oncol. 2019 Aug 8;11:1758835919866072.
4. Lee M, Chung JW, Lee KH, Won JY, Chun HJ, Lee HC, Kim JH, Lee IJ, Hur S, Kim HC, Kim YJ, Kim GM, Joo SM, Oh JS. Korean Multicenter Registry of Transcatheter Arterial Chemoembolization with Drug-Eluting Embolic Agents for Nodular Hepatocellular Carcinomas: Six-Month Outcome Analysis. J Vasc Interv Radiol. 2017 Apr;28(4):502-512.
5. Montazeri SA, De la Garza-Ramos C, Lewis AR, Lewis JT, LeGout JD, Sella DM, Paz-Fumagalli R, Devcic Z, Ritchie CA, Frey GT, Vidal L, Croome KP, McKinney JM, Harnois D, Krishnan S, Patel T, Toskich BB. Hepatocellular carcinoma radiation segmentectomy treatment intensification prior to liver transplantation increases rates of complete pathologic necrosis: an explant analysis of 75 tumors. Eur J Nucl Med Mol Imaging. 2022 Sep;49(11):3892-3897.
6. Lewandowski RJ, Gabr A, Abouchaleh N, Ali R, Al Asadi A, Mora RA, Kulik L, Ganger D, Desai K, Thornburg B, Mouli S, Hickey R, Caicedo JC, Abecassis M, Riaz A, Salem R. Radiation Segmentectomy: Potential Curative Therapy for Early Hepatocellular Carcinoma. Radiology. 2018 Jun;287(3):1050-1058.

Session 3. New Trends in Management of Intermediate-Stage HCC

S3-1

Looking into the Intermediate-Stage HCC: Ongoing Effort towards Creating a Subclassification

Fabio Piscaglia[1,2], Mariarosaria Marseglia[1]

[1]Division of Internal Medicine, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy; [2]University of Bologna, Italy

Staging systems in hepatocellular carcinoma are not only based on the tumor burden and extension like in other tumors

(for instance systems like the TNM, based on the assessment of Tumor Node Metastasis), but usually include also some indicators of liver function. This is due to the fact that the liver is an organ whose function is indispensable for living and that HCC arises in a background of chronic liver disease, usually in a cirrhotic stage, in the vast majority of cases. Therefore, death following tumor progression or death following progressive, potentially treatment-induced liver dysfunction are competing risks both detrimental for the patient. Briefly, treatment of liver tumors must not deteriorate liver function to a degree jeopardizing the beneficial oncologic effects.

Such trade-off is particularly difficult in the intermediate stage of HCC, since the tumor masses are indeed still only intrahepatic, but their extension in terms of size and/or of number of hepatic anatomical segments involved, is considerable. Consequently, any surgical or locoregional therapy cannot be too limited and is likely to result in a significant impact on liver function.

The definition of intermediate stage was introduced by the BCLC group in 1999, to identify a subgroup of the extremely broad and previously unique group of unresectable HCC. The intermediate stage, also defined BCLC-B, consists of patients with asymptomatic large multinodular HCC, without vascular involvement or extrahepatic spread and in Child-Pugh class A or B of liver function. The BCLC staging system was the first one to define stages that were possessing a prognostic capacity and were recommending a corresponding treatment strategy. At that time the only recommended treatment for BCLC-B patients was Transarterial Chemoembolization (TACE). One of the main aim and values of the introduction of the BCLC staging system was that the link between integrated tumor stages and recommended treatments avoided "overtreatments" and "futile treatments", such as applications of treatment with too little perspective of cure or leading to a liver failure since too aggressive and consequent shortening of survival when delivered to insufficiently selected patients.

Why a need for a subclassification emerged from real life, starting from a dozen years later?

In the meantime surgical resections have technically improved, with a more widespread use of laparoscopic and now robotic approaches, much better able to preserve liver parenchyma and function despite radical resections, thermal ablation has become more potent with the use of microwaves, radioembolization with Yttrium90 has become relatively widespread, transplant thresholds have been extended to include patients with expanded criteria and downstaging strategies, systemic therapies started to prove able to prolong survival in HCC and hepatological therapies to treat the underlying liver disease (especially in case of viral origin) have been introduced, leading to more "resistant" livers.

All such innovations impacted on the trade-off between curative possibilities of treatments and capacity of liver to preserve its function. Therefore, therapies that in the past had to be hold as "overtreatment" could be now applied appropriately. Consequently, a subclassification of the intermediate stage was felt needed and was first proposed by our group together with a group of international experts based on the literature and personal expertise (Bolondi L et al. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions Semin Liver Dis. 2012;32:348-59). Four new substages were proposed, each of which included not one single treatment options, but a few, with a priority of ranking up to only palliative care. Such classification, which also included a prognostic capacity, was externally validated by other groups and several attempts were proposed to refine it.

Some works tended to test its prognostic capacity in subgroup of patients treatment with one single modality (e.g. TACE). Obviously in this setting the prognostic capacity becomes less potent, due to a preselection of patients (the most fit and the worst of the subclasses, either receiving for instance surgery or only palliative care are no longer included). The attempt must remain that of designing a subclassification that links prognostic capacity and treatment allocation. The definitive answer to this question remains elusive, as the threshold of the tumor burden (i.e. in our case the up-to-seven criteria) cannot be too precise to become broadly utilized, the Child-Pugh classes are suboptimal in defining precisely the liver functional reserve and treatments are continuously improving, both on the surgical capacity and of systemic treatments, introducing often the possibility of combinations that can hardly be contemplated in any classification. The lecture will illustrate some of the recent and ongoing attempts to refine the proposed subclassification.

Such efforts were most commonly addressed to define.

1) Which intermediate stage patients are expected to benefit from a more aggressive surgical approach,
2) New tumor burden thresholds able to stratify patients expected to benefit from locoregional therapies like TACE or TARE,
3) Design scores able to identify patients for whom surgical or locoregional treatments must be considered futile and would be better served by systemic treatments, especially in view of the arrival of new potent and safe agents
4) Expanding the role of liver transplantation in this field
5) Introducing biological biomarkers (e.g. AFP) to define treatment allocation strategies

Additionally research activities are ongoing trying to identify new biomarkers able to identify the treatment benefits of competing therapies, in order to better selected patients subclasses in the future for more appropriate allocation to treatments. At present however no such strategy has a any clear clinical relevance.

S3-2

Expanding the Role of Surgical Resection and Transplantation in Intermediate-Stage HCC

Jongman Kim

Sungkyunkwan University, Seoul, South Korea

Introduction: The Barcelona Clinic Liver Cancer (BCLC) staging system has been extensively validated and is the most commonly used. The BCLC stage B is quite broad and includes a heterogeneous patient population. The recommended treatment is transarterial chemoembolization (TACE) only. There is growing evidence that more aggressive radical treatments such as hepatic

resection and radiofrequency ablation (RFA) are feasible for selected HCC patients with BCLC stage B [1].

In addition, atezolizumab (anti-programmed death-ligand-1 [PD-L1] antibody) plus bevacizumab (anti-vascular endothelial growth factor [VEGF] antibody) has proven to be superior to sorafenib in phase 3 randomized controlled trial (RCT) [2]. However, these new systemic therapies are restricted to HCC patients with Child-Pugh class A, another treatment will be required for BCLC stage B HCC patients with Child-Pugh class B. There seems to be an increasing unmet need between guideline-recommended therapy and recent evidence-based treatment in BCLC stage B HCC.

Hepatic Resection: The optimal candidate for hepatic resection is HCC patients with Child-Pugh class A, without clinical signs of portal hypertension and limited tumor burden [3]. In RCT comparing hepatic resection and TACE for HCC beyond Milan criteria, Yin et al. reported that the 1-, 2-, and 3-year overall survival rates were 76.1%, 63.5%, and 51.5%, respectively, for hepatic resection group compared with 51.8%, 34.8%, and 18.1%, respectively, for TACE group (P<0.001) [1]. In addition, a meta-analysis utilizing one RCT and high-quality nonrandomized studies revealed that a significant survival benefit was shown for hepatic resection (hazard ratio, 0.53; 1-year survival rate for hepatic resection vs. TACE: 84% vs. 68%; 5-year survival rate for hepatic resection vs. TACE: 45% vs. 23%; respectively), suggesting that hepatic resection should be considered as a therapeutic option tailored to a carefully selected group of BCLC stage B HCC patients with well-preserved liver function [4].

Liver Transplantation: The Milan criteria (single tumor ≤5 cm or 3 nodules ≤3 cm) are the most common criteria worldwide. Five-year survival rate and 5-year recurrence rates within the Milan criteria were 71.3% and 12.3%, respectively [5]. The advancement of surgical techniques made it possible for liver transplantation beyond the Milan criteria. Five-year survival rates within the Asan criteria (nodule ≤5 cm, number of nodules ≤6), the University of California San Francisco criteria (single nodule ≤6.5 cm, or 3 nodules ≤4.5 cm with total tumor diameter ≤8 cm), up-to-7 criteria (the sum of maximum tumor diameter and number <7) were 70.9%, 80.9%, and 71.2%, respectively [6]. These findings imply that liver transplantation is a treatment option for selected patients with BCLC stage B HCC. However, the available donor organ shortage is still a critical problem worldwide.

Conclusions: BCLC stage B consists of patients with heterogeneous HCC slightly above the Milan criteria to large/multifocal tumor burden. The standard recommended treatment of BCLC stage B is TACE. However, hepatic resection and liver transplantation have become to be selected treatment options BCLC stage B to prolong survival time.

References

1. Yin, L., et al., Partial hepatectomy vs. transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan Criteria: a RCT. J Hepatol, 2014. 61(1): p. 82-8.
2. Finn, R.S., et al., Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med, 2020. 382(20): p. 1894-1905.
3. Bolondi, L., et al., Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis, 2012. 32(4): p. 348-59.
4. Hyun, M.H., et al., Hepatic resection compared to chemoembolization in intermediate- to advanced-stage hepatocellular carcinoma: A meta-analysis of high-quality studies. Hepatology, 2018. 68(3): p. 977-993.
5. Degroote, H., et al., Extended criteria for liver transplantation in hepatocellular carcinoma. A retrospective, multicentric validation study in Belgium. Surg Oncol, 2020. 33: p. 231-238.
6. Torimura, T. and H. Iwamoto, Optimizing the management of intermediate-stage hepatocellular carcinoma: Current trends and prospects. Clin Mol Hepatol, 2021. 27(2): p. 236-245.

S3-3

To What Extent Can TARE Replace the Role of TACE in the Intermediate-Stage HCC?

Edward Kim

Icahn School of Medicine at Mount Sinai, New York, USA

Introduction: Trans-arterial radioembolization is a locoregional radiation based treatment that is minimally invasive and allows for treatment of lesions in complex anatomic location. Trans-arterial radioembolization (TARE) has been most widely utilized with Yttrium-90 as the radioisotope. TARE rarely causes occlusion of the targeted vessels, and seeds the target tissue with spheres around 40 microns in size. This allows oxygenated blood to potentiate the effects of the radiation over time. There are two matrices currently utilized as a carrier for the Yttrium-90. Glass microspheres have Y90 embedded into the matrix of the glass, allowing for high specific activities and variability in the number of spheres delivered. Resin microspheres have the Y90 bonded to the outside of the sphere, and therefore, the amount of dose is adjusted based on the number of spheres delivered.

The main applications of radioembolization in patients with BCLC early stage HCC are as curative therapy or as bridging/downstaging therapy to achieve and maintain criteria necessary for transplant, and in patients with BCLC intermediate, either as a downstaging or palliative therapy, or advanced stage HCC, as a palliative therapy.

DOSISPHERE was a phase II randomized controlled trial of patients treated with Y90 using standard dosimetry versus personalized/more selective dosimetry. This study included a large proportion of patients with portal tumor vascular invasion and also showed that increased dose was associated with improved outcomes. Patients who had received > 205 Gy had a median overall survival of 26.6 months versus 7 months in patients who received < 205 Gy.

First Main Body: DOSISPHERE was a phase II randomized controlled trial of patients treated with Y90 using standard dosimetry versus personalized/more selective dosimetry. This study included a large proportion of patients with portal tumor vascular invasion and also showed that increased dose was associated with

improved outcomes. Patients who had received > 205 Gy had a median overall survival of 26.6 months versus 7 months in patients who received < 205 Gy (67).

Second Main Body: LEGACY study, which evaluated Local radioEmbolization using Glass microspheres for the Assessment of Tumor Control with Y90 and in 2021, provided supportive data for approval of Y90 glass microspheres by the United States Food and Drug Administration. This study was a retrospective single arm multi-center study that demonstrated that high radiation doses can be delivered to a target lesion resulting in a high objective response rate while sparing surrounding parenchyma. The RASER trial demonstrated prospective data to support the use of TARE in a selective fashion as curative intent for lesions 3 cm and less with no serious adverse events and complete pathologic necrosis in patients with explanted tissue correlating to complete response as per mRECIST.

TRACE study from Dhondt et al demonstrated longer TTP compared to drug eluting bead TACE. This may have implications in downstaging and potentially bridging patients to transplantation.

Conclusions: The role of TARE and the evidence to support its use in selection of patients in the intermediate stage compared to TACE will be discussed.

References

1. Garin E, Tselikas L, Guiu B, Chalaye J, Edeline J, de Baere T, Assenat E, Tacher V, Robert C, Terroir-Cassou-Mounat M, Mariano-Goulart D, Amaddeo G, Palard X, Hollebecque A, Kafrouni M, Regnault H, Boudjema K, Grimaldi S, Fourcade M, Kobeiter H, Vibert E, Le Sourd S, Piron L, Sommacale D, Laffont S, Campillo-Gimenez B, Rolland Y; DOSISPHERE-01 Study Group. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol. 2021 Jan;6(1):17-29. doi: 10.1016/S2468-1253(20)30290-9. Epub 2020 Nov 7. PMID: 33166497.
2. Salem R, Johnson GE, Kim E, Riaz A, Bishay V, Boucher E, Fowers K, Lewandowski R, Padia SA. Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable HCC: The LEGACY Study. Hepatology. 2021 Nov;74(5):2342-2352. doi: 10.1002/hep.31819. Epub 2021 Jun 11. PMID: 33739462; PMCID: PMC8596669.
3. Kim E, Sher A, Abboud G, Schwartz M, Facciuto M, Tabrizian P, Knešaurek K, Fischman A, Patel R, Nowakowski S, Llovet J, Taouli B, Lookstein R. Radiation segmentectomy for curative intent of unresectable very early to early stage hepatocellular carcinoma (RASER): a single-centre, single-arm study. Lancet Gastroenterol Hepatol. 2022 Sep;7(9):843-850. doi: 10.1016/S2468-1253(22)00091-7. Epub 2022 May 23. PMID: 35617978.
4. Dhondt E, Lambert B, Hermie L, Huyck L, Vanlangenhove P, Geerts A, Verhelst X, Aerts M, Vanlander A, Berrevoet F, Troisi RI, Van Vlierberghe H, Defreyne L. 90Y Radioembolization versus Drug-eluting Bead Chemoembolization for Unresectable Hepatocellular Carcinoma: Results from the TRACE Phase II Randomized Controlled Trial. Radiology. 2022 Jun;303(3):699-710. doi: 10.1148/radiol.211806. Epub 2022 Mar 8. PMID: 35258371.
5. Cappelli A, Sangro P, Mosconi C, Deppe I, Terzi E, Bilbao JI, Rodriguez-Fraile M, De Benedittis C, Ricke J, Golfieri R, Sangro B. Transarterial radioembolization in patients with hepatocellular carcinoma of intermediate B2 substage. Eur J Nucl Med Mol Imaging. 2019 Mar;46(3):661-668. doi: 10.1007/s00259-018-4152-7. Epub 2018 Sep 12. PMID: 30209522.
6. Salem R, Padia SA, Lam M, Chiesa C, Haste P, Sangro B, Toskich B, Fowers K, Herman JM, Kappadath SC, Leung T, Sze DY, Kim E, Garin E. Clinical, dosimetric, and reporting considerations for Y-90 glass microspheres in hepatocellular carcinoma: updated 2022 recommendations from an international multidisciplinary working group. Eur J Nucl Med Mol Imaging. 2023 Jan;50(2):328-343. doi: 10.1007/s00259-022-05956-w. Epub 2022 Sep 17. PMID: 36114872; PMCID: PMC9816298.

S3-4

The Potential Role of Systemic Therapy in Intermediate-Stage HCC: A Paradigm Shift?

Masatoshi Kudo

Kindai University, Osaka, Japan

There has been interest in combining systemic and locoregional therapies (LRTs) to increase objective responses, progression-free survival (PFS), and overall survival. Systemic therapy with TKIs has several theoretical benefits, as follows: (1) inducing tumor necrosis, thereby potentially achieving downstaging; (2) reducing hypoxic stress caused by TACE, thus aiming to suppress the hypoxia-induced release of cytokines (eg, vascular endothelial growth factor [VEGF]), which could prime progression and metastasis; and (3) normalizing tumor vasculature, which could enhance the effect of TACE. These theoretical benefits prompted several trials evaluating the combination of sorafenib and TACE, with all failing to show any benefit in the primary outcomes of time to progression (TTP) or PFS. Recently, the Transcatheter Arterial Chemoembolization Therapy In Combination with Sorafenib (TACTICS) trial showed that the combination of sorafenib plus TACE improved PFS (HR, 0.59; 95% CI, 0.41–0.78) compared with TACE alone, although this failed to translate into an OS benefit (36.2 vs 30.8 mo, respectively; HR, 0.86; 95% CI, 0.61–1.22). At this time, existing phase II and phase III studies have failed to show a benefit in proposed primary outcomes. However, there have been questions if overall survival is the optimal primary end point of LRTs, particularly considering continued improvements in postprogression therapies, highlighting a need for validated, accurate, surrogate measures that can be used in clinical trials. Although a moderate correlation between PFS and overall survival has been suggested in systemic therapy trials, it is unclear if this is true for LRTs because prior trials evaluating combination studies failed to show any correlation (r ¼ 0.56). With the introduction of immune checkpoint inhibitors in the advanced-stage setting, there has been renewed interest in evaluating the combination of systemic and LRTs. It is theorized that TACE may induce release of neoantigens, which then could augment responses with immune checkpoint inhibitor therapy, resulting in synergistic effects by using the 2 in combination. Accordingly, there are several

ongoing phase III studies evaluating TACE in combination with immune checkpoint inhibitors.

Session 5. Optimal Strategy for Systemic Therapy for Advanced HCC

S5-1

Optimal First-Line Therapy for HCC

Baek-Yeol Ryoo

University of Ulsan, Seoul, South Korea

Hepatocellular carcinoma (HCC) develops in the condition of uncontrolled growth of hepatic cells caused by the genetic alterations in complex signaling cascades. Therefore, we can expect the effect of targeted agents attacking important targets in carcinogenic pathways along with minimizing general adverse effects. However, we have failed to find the dominant signal pathways in hepatocarcinogenesis, yet.

Sorafenib is a multikinase inhibitor especially inhibiting serine/threonine kinases Raf-1/B-Raf, tyrosine kinases VEGFR-2/-3 and PDGFR-β, which suppresses cancer progression and angiogenesis. Sorafenib is the first systemic therapy prolonged survival significantly in HCC patients. After that sorafenib not only established a proof of concept for the use of multi-kinase inhibitors strategy for the treatment of HCC, but also is the reference standard for systemic therapy for HCC patients.

Nevertheless, subsequent clinical trials using targeted agents have failed in succession for about 10 years. The agents which failed to prove their activity in HCC were sunitinib, linifanib, brivanib, nintedanib in the first-line treatment and axitinib, ramucirumab, brivanib, erlotinib, everolimus, tivantinib, ADI-PEG20 in the second-line treatment after sorafenib failure.

Recently, lenvatinib, another angiogenesis inhibitor, showed non-inferior overall survival in the 1st-line treatment compared with sorafenib in the REFLECT trial. Lenvatinib also showed rather superior response rate, progression free survival, time to progression and preferable toxicity profiles.

For the patients who failed sorafenib treatment, regorafenib and cabozantinib, mainly angiogenesis inhibitors overcame placebo control in RESORCE and CELESTIAL trials.

In addition, nivolumab showed meaningful results for HCC in phase II checkmate 040 trial.

We have now 2 options in the 1st-line and 3 options after sorafenib failure in HCC, with angiogenesis inhibitor or immune checkpoint inhibitor.

However, the current effects of systemic treatments for HCC are far from satisfaction as ever.

By looking at the trials currently conducted for HCC, we are discussing ways to improve the prognosis of HCC patients.

S5-2

Optimal Subsequent Option after First-Line Immuno-Oncology Therapy in Advanced HCC

Andrew X. Zhu

IMab Biopharma, Shanghai, China; Jiahui International Cancer Center, Jiahui Health, Shanghai, China

Based on the results from IMbrave150, atezolizumab plus bevacizumab has emerged as the new standard first line treatment for advanced hepatocellular carcinoma (HCC). The results from HIMALAYA have also led to the recent approval of dual immune checkpoint inhibitors (ICI) tremelimumab and durvalumab. While there are several second line treatment options, the data supporting the regulatory approval of these agents came from studies after sorafenib failure. Therefore, therapeutic sequencing after first-line ICI-based therapy remains a challenge as no available second-line treatment options have been studied in immunotherapy-pretreated patients. In addition, the role of ICI rechallenge in patients with HCC remains unclear due to the lack of evidence from prospective trials. The author will discuss the rationale, current data, and practical considerations including safety profile, clinical and tumor features, as well as potential biomarkers for selecting targeted agents and ICI based therapies after first-line ICI-based therapy.

S5-3

Optimal Subsequent Options after First-Line Multi-Kinase Inhibitor Therapy for Advanced HCC

Chih-Hung Hsu

National Taiwan University, Taipei, Taiwan

The landscape of systemic therapy for advanced hepatocellular carcinoma (HCC) has been evolving rapidly over the past years. In two global, multi-center, randomized phase III trials of first-line systemic therapy for unresectable HCC (IMbrave 150 study and HIMALAYA study), the combination of atezolizumab plus bevacizumab (atezo/bev) and the combination of durvalumab plus tremelimumab (the STRIDE regimen) outperformed sorafenib with a statistically significant improvement of overall survival (OS).

Most treatment guidelines around the World, thus, recommend that both combinations as the preferred first-line systemic therapy for advanced HCC, and that multikinase inhibitors could be considered in cases where the previous options are contraindicated. Although these recommendations appear to be in line with the results of the afore-mentioned randomized phase III trials, they do not genuinely reflect the fact that no direct comparison of atezo/bev or the STRIDE regimen with lenvatinib as first-line therapy for advanced HCC has ever been investigated in prospective clinical trials.

Moreover, several retrospective cohort studies suggest that the efficacy of lenvatinib may be comparable with that of atezo/bev as first-line therapy for advanced HCC.

Overall, multikinase inhibitors including lenvatinib remain an important class of agents as first-line therapy for advanced HCC.

Following failure of first-line multikinase inhibitors especially lenvatinib, multiple treatment options are available, including to-add-on and to-switch strategies. The former strategy can be achieved by agents with the same anti-vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) property plus additional mechanisms of action (MOAs), or by agents with anti-VEGF/VEGFR property in combination with other agents with different MOAs such as immune checkpoint inhibitors (ICIs). The latter strategy is to switch to ICIs or their combinations as second-line therapy.

The presentation will review the current data focusing on the subsequent treatment options following lenvatinib and will discuss future research directions regarding optimal sequential therapy following multikinase inhibitor therapy for advanced HCC.

Session 6. A Deep Dive into the Era of Immuno-Oncology

S6-1

Trajectory of Immune Evolution and Mechanism of Response to Immunotherapy in HCC

Valerie Chew[1], Samuel Chuah[1], Joycelyn Lee[2], Hyung-Don Kim[3], Phuong H.D. Nguyen[1], Martin Wasser[1], Ramanuj DasGupta[4], Haiyan Liu[5], Changhoon Yoo[6], Su Pin Choo[2], Weiwei Zhai[4], Pierce K.H. Chow,[2] David Tai[2]

[1]Translational Immunology Institute (TII), SingHealth-DukeNUS Academic Medical Centre, Singapore; [2] Division of Medical Oncology, National Cancer Centre Singapore; [3] Department of Oncology, Asan Medical Center (AMC), University of Ulsan College of Medicine; [4] Genome Institute of Singapore (GIS), Agency for Science, Technology and Research (A*STAR), Singapore; [5]Immunology Programme, Life Sciences Institute, Immunology Translational Research Program and Department of Microbiology and Immunology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [6] Department of Oncology, Asan Medical Center (AMC), University of Ulsan College of Medicine, Republic of Korea

Despite recent advances in immunotherapy for hepatocellular carcinoma (HCC), patient response rate remains low. This could in part be due to the immune modulation within the tumour microenvironment (TME). Our data using comprehensive analyses including Mass cytometry by time-of-flight (CyTOF), RNA sequencing (both bulk and single-cell RNA sequencing) and multiplexed immunohistochemistry (mIHC) on HCC tumour tissues demonstrated heterogeneous immune landscapes in HCC. We have uncovered immune intra-tumoral heterogeneity (immune-ITH) as a hallmark of tumour evolution and disease progression in HCC that is associated with higher mutational burden and immune evasion (Nguyen & Ma et al Nat Com 2021)1. Understanding its underlying mechanisms driving this immune evolution process could allow us to design novel and personalized immunotherapeutic strategies to prevent, reverse or limit progression of HCC. Following this discovery, we further explored the trajectory of immune evolution along HCC progression. In our most recent report, Nguyen & Wasser et al Nature Com 20222, we describe extensive immune remodelling in HCC patients from stage I to III tumours. This shows that immune evasion occurs in a progressive manner peaking at intermediate stage of HCC tumours.

More recently, we profiled the immune cells from responding and non-responding HCC patients treated with anti-PD-1 ICB using both CyTOF and single-cell RNA seq3. First of all, we identified distinct immune subsets, particularly CXCR3+ CD8 T effector memory (TEM) cells, that are related to reponse as well as immune-related adverse effects (irAEs) from HCC patients treated with anti-PD-1 ICB. We performed in-depth cellular interaction analysis using CellPhoneDB4 on our scRNA seq data to identify the expression of receptors and ligands on CXCR3+ CD8 TEM cells, which was the key target subset. We observed distinct tumour necrosis factor (TNF) interactions between CXCR3+ CD8 TEM and myeloid cell populations, with TNF-TNFRSF1B (encodes for TNFR2) enriched in Res, but TNF-TNFRSF1A (encodes for TNFR1) enriched in patients with reduced irAEs. This indicates that distinct TNF pathways could be harnessed as potential interventions to enhance response while controlling irAEs in ICB treatment. Following that, we investigated the effect of anti-TNFR1 or anti-TNFR2 blockade when used in combination with anti-PD-1 blockade in immunocompetent C57BL/6 mice inoculated with hepatoma cells via hydrodynamic tail-vein injection5-7. We found that all mice receiving combination treatments showed a strong reduction in the number of tumour nodules as compared anti-PD-1 monotherapy; in particular, all mice treated with anti-PD-1 + anti-TNFR2 combination displayed no tumour burden at harvest and showed no signs of increased toxicity (Chuah et al. J Hep 20223). Our data hence showed that differential blockade of TNFR1 or TNFR2 combined with anti-PD-1 therapy could uncouple response and irAEs, thereby proposing anti-PD-1 and anti-TNFR2 combination as a novel ICB combination strategy.

References

1. Nguyen PHD, Ma S, Phua CZJ, et al. Intratumoural immune heterogeneity as a hallmark of tumour evolution and progression in hepatocellular carcinoma. Nat Commun. Jan 11 2021;12(1):227. doi:10.1038/s41467-020-20171-7
2. Nguyen PHD, Wasser M, Tan CT, et al. Trajectory of immune evasion and cancer progression in hepatocellular carcinoma. Nat Commun. Mar 17 2022;13(1):1441. doi:10.1038/s41467-022-29122-w
3. Chuah S, Lee J, Song Y, et al. Uncoupling immune trajectories of response and adverse events from anti-PD-1 immunotherapy in hepatocellular carcinoma. J Hepatol. Apr 14 2022;doi:10.1016/j.jhep.2022.03.039
4. Efremova M, Vento-Tormo M, Teichmann SA, Vento-Tormo R. CellPhoneDB: inferring cell-cell communication from combined expression of multi-subunit ligand-receptor complexes. Nat Protoc. Apr 2020;15(4):1484-1506. doi:10.1038/s41596-020-0292-x
5. Liu Y, Song Y, Lin D, et al. NCR(-) group 3 innate lymphoid cells orchestrate IL-23/IL-17 axis to promote hepatocellular carcinoma

development. EBioMedicine. Mar 2019;41:333-344. doi:10.1016/j.ebiom.2019.02.050
6. Ma S, Cheng Q, Cai Y, et al. IL-17A produced by gammadelta T cells promotes tumor growth in hepatocellular carcinoma. Cancer Res. Apr 1 2014;74(7):1969-82. doi:10.1158/0008-5472.CAN-13-2534
7. Lin D, Lei L, Liu Y, et al. Membrane IL1alpha Inhibits the Development of Hepatocellular Carcinoma via Promoting T- and NK-cell Activation. Cancer Res. Jun 1 2016;76(11):3179-88. doi:10.1158/0008-5472.CAN-15-2658

S6-2

Rechallenging of Immuno-Oncology Treatment after Complications: Can It Be Done Safely?

Stephen Lam Chan

The Chinese University of Hong Kong, Hong Kong

Use of immune checkpoint inhibitors is associated with occurrence of immune related adverse events (IRAEs). Most of these IRAEs are mild to moderate grade, which may resolve spontaneously or with use of steroids. Decision to rechallenge patients with immunotherapy after occurrence of IRAEs is multifactorial, with key consideration factors including the type of IRAEs, severity of the IRAE, time to recovery of IRAE and benefits of immunotherapy. In general, rechallenge with immune checkpoint inhibitors is feasible in selected patients following occurrences of IRAEs but close monitoring and discussion with patients is important. More details will be highlighted in the lecture.

S6-3

Neo-Adjuvant or Adjuvant Immunotherapy in HCC: Where Are We Now?

Ann-Lii Cheng

National Taiwan University, Taipei, Taiwan

Adjuvant immunotherapy (AI) after resection of operable HCC has recently welcomed the first successful attempt – IMbrave 050 trials, in which one year of atezo-bev significantly improved recurrence-free survival (Chow P et al AACR 2023). True neoadjuvant or perioperative (pre-op + post-op) adjuvant immunotherapy is relatively difficult in HCC, as clinically resectable HCC is often firsthandly resected. Until now, only a few very small-sized pilot studies are reported.

Neoadjuvant immunotherapy (NAI) has a notable hypothetical benefit over AI. While AI is given after resection of tumors, NAI is given to an intact tumor bed, which harbour abundant anti-tumor immune cells. Activation of the latter is expected to activate the largest possible amount of the cytotoxic anti-tumor CD8 T cells, which would help eradicate micro-metastases. This notion has been validated in malignant melanoma, non-small cell lung cancer, and triple-negative breast cancer.

We have recently completed a relatively large series (N=43) of neo-adjuvant phase II trial by TCOG (Taiwan Cooperative Oncology Group). Potentially resectable HCC patients received 2-4 courses of ipilimumab plus nivolumab before resection. Among the 24 patients resected, major pathologic response (> 90% necrosis) was observed in 8 (33.3%) patients. Patients after resection enjoyed a significantly better overall survival. These results support the use of neoadjuvant immunotherapy in potentially resectable HCC patients. However, it remains to be seen whether large-scale phase III trials of neoadjuvant immunotherapy on "truly resectable" HCC patients can also be done in the future.

S6-4

Immuno-Oncology in the Treatment of HCC: Future Perspectives

Richard S. Finn

University of California, Los Angeles, LA, USA

The past several years have been a revolution in the management of advanced HCC. The introduction of immunotherapy-based regimens with checkpoint inhibitors has markedly improved survival in the front-line. Several unmet needs have been highlighted by these advances. We will discuss these concepts and how they will impact future developments including new targets for therapy, overcoming de novo and acquired resistance, how to optimally sequence the agents we have post-immunotherapy, and how to integrate immunotherapy into early stage HCC.

Session 7. Emerging Therapy and Precision Medicine

S7-1

Novel Targets in HCC

Augusto Villanueva

Icahn School of Medicine at Mount Sinai, New York, USA

There are currently 10 drugs approved by the US Food and Drug administration for the therapy of patients with advanced stage hepatocellular carcinoma (HCC). This includes tyrosine kinase inhibitors (e.g., sorafenib, Lenvatinib, regorafenib, cabozantinib), and immune checkpoint inhibitor-based combination therapies (e.g., atezolizumab plus bevacizumab, tremelimumab plus durvalumab). Most effective therapies targe angiogenesis, but notable, other potent antiangiogenics have shown limited efficacy or significant toxicity in HCC (e.g., linifanib, sunitinib). It is still unclear the mechanism that makes this preferential efficacy for some antiangiogenics over others. It has been suggested that

excessive anti-angiogenesis in cirrhosis could increase toxicity. New therapies under evaluation explore new immune targets beyond CTLA4 and PD-1/PD-L1. CAR-T therapy is also under evaluation with limited success. The potential benefit of targeting oncogene addiction events in HCC (e.g., FGF19 overexpression) has been tested in early phase clinical trials. In summary, new targets are being explored, but several issues remain to be addressed, such as the impact of intratumoral heterogeneity and clonal evolution in the future of target development for HCC.

S7-2

CAR T-Cell Therapy for the Solid Tumors Including HCC: Prospects and Challenges

Kyungho Choi

Seoul National University, Seoul, South Korea

Chimeric antigen receptor (CAR) T cell therapy is a form of cell therapy in which T lymphocytes from the cancer patients were isolated and genetically modified to express CAR on the cell surface. CAR is a fusion receptor with antibody portion recognizing tumor antigen linked to intracellular signaling modules to activate T cells. Thus, CAR-T cells can be activated upon binding to tumor cells specifically and eliminate tumor cells using cytotoxicity of T cells. Much attention has been paid to CAR-T cell therapy in recent years, because it showed a remarkable efficacy for treatment of relapsed or refractory hematological malignancies. Currently, six CAR T-cell drugs are approved by US FDA for treatment of CD19-positive leukemia/lymphomas and BCMA-positive multiple myeloma. However, the efficacy of this type of cellular drug for solid tumor treatment including hepatocellular carcinoma has not been established in the clinical setting yet.

In this talk, I will discuss the hurdles against success of CAR T-cell therapy for solid tumors and potential strategies to overcome those hurdles.

S7-3

Promising Agents in Early Clinical Trials for Unresectable HCC

Masafumi Ikeda

National Cancer Center Hospital East, Kashiwa, Japan

Atezolizumab plus bevacizumab, durvalumab plus tremelimumab, durvalumab, sorafenib and lenvatinib have been established to be standard treatments as a first-line systemic therapy for unresectable hepatocellular carcinoma (HCC), and regorafenib, cabozantinib and ramucirumab have been established as second-line treatments. How to utilize these regimens is an important issue to be solved in daily practice. In Japan, a prospective, observational, large-scale multicenter study of systemic therapy for HCC (PRISM study) and exploratory research on angiogenesis-related and tumor-immunity-related factors (PRISM-Bio study) are underway to establish real-world evidence from real-world data.

All established drugs are angiogenetic inhibitors that inhibit VEGF or immune checkpoint inhibitors in unresectable HCC. In addition, no specific biomarkers have been fully clarified for predictive tumor response or resistance to the therapy. Various genetic alterations have also been investigated, but no molecular targeted agents suitable for major genome alterations such as TERT, TP53, and CTNNB1 in HCC have been found. The development of further drugs for HCC is in a difficult situation. However, some interesting clinical trials are also underway. Molecular targeted agents of Wnt/β-catenin signaling pathway inhibitor, immune-oncology agents targeted LAG-3, TIM-3 and TIGIT, bispecific antibody of anti-PD-1/PD-L1 antibody, anti-CTLA-4 antibody, and Glypican-3, antibody drug conjugate (ADC) targeted some specific molecule such as Glypican 3, and CAR T Cell Therapy, etc, are undergoing several clinical trials for unresectable HCC. We expect that new standard treatments will emerge from these drugs under development. This paper reviews promising agents in early clinical trials in for patients with advanced HCC and outlines trends in the development of new agents for systemic therapy.

S7-4

Radiation Therapy in HCC: Future Perspectives

Jinsil Seong

Yonsei University, Seoul, South Korea

Therapeutic landscape of hepatocellular carcinoma (HCC) has evolved during past decades. Most prominently, role of loco-regional treatment has been well defined and use of combination immunotherapy has been the standard of care in advanced disease. Consequently, more patients are moving forward from palliation to cure, even in advanced setting.

Radiotherapy (RT) has historically been less commonly used in the treatment of hepatocellular carcinoma (HCC) due to concerns about liver toxicity and the risk of radiation-induced liver disease. However, recent advances in radiation techniques and technologies have renewed interest in the use of radiotherapy in the management of HCC. Therefore, therapeutic high dose radiation can be precisely delivered to the tumor using image-guided intensity modulated radiotherapy, which serves as a platform technology in stereotactic ablative radiotherapy (SABR). Particle beam radiotherapy (PBT) allows better protection of nontumor liver owing to its unique physical characteristics, Bragg peak. It may widen indications of radiotherapy even for the patients with relatively uncompensated liver function, which can be equally shared by proton and carbon ion PBT. In addition to physical benefit, carbon ion PBT presents an additional biological benefit; 3-fold or higher relative biological effectiveness (RBE) compared to x-ray of proton. In real world practice, a substantial number of HCC patients presents acquired therapeutic refractoriness and simultaneous liver dysfunction resulting from repeated local therapies involving transarterial therapies. High RBE of carbon ion PBT may help those patients.

Furthermore, immuno-modulatory effect of radiation has

been uncovered and opened a new paradigm in cancer therapy. Immunotherapeutic approach with IO dugs, mostly immune checkpoint inhibitors (ICIs), frequently faces a substantial challenge related to dysfunctional T cells. Currently, reinvigoration of exhausted/dysfunctional T-cells appears to be a key in improving oncologic outcome of immune-oncologic (IO) therapy. In principle, radiotherapy induces an immune-mediated antitumor response besides its well-known cytoreductive cell killing. Its effect can be summarized as following; induction of antigen release and immunogenic cell death; induction of antigen-presenting cell maturation and antigen presentation; induction of T-cell recruitment and infiltration; induction of tumor cell sensitization to immune-mediated cell death. Through these mechanisms, immune modulation effect of radiotherapy on tumor microenvironment converts immune status of tumor from cold to hot by reinvigoration of tumor infiltrating T-cells, which is a key factor in effective IO treatment. Also, it has been shown that modulation action can be different according to the dose level of radiation. This notion can be applied in various scenario of combining radiotherapy with IO therapy involving low dose radiation for modulation of immune microenvironment of liver as well as pulsed delivery of ablative high dose radiation to activate memory B cells. Since these novel approaches are currently tested in other solid cancers, more validation is required.

To summarize, technological advance and immune modulation by radiotherapy may open a new paradigm in management of HCC.

References

1. Lee BM, Seong J. Radiotherapy as an immune checkpoint blockade combination strategy for hepatocellular carcinoma. W J Gastroenterol 2021;27:919-927
2. Sharabi AB, Nirschl CJ, Kochel CM, Nirschl TR, Francica BJ, Velarde E, Deweese TL, Drake CG. Stereotactic Radiation Therapy Augments Antigen-Specific PD-1-Mediated Antitumor Immune Responses via Cross-Presentation of Tumor Antigen. Cancer Immunol Res 2015; 3: 345-355
3. Gupta A, Probst HC, Vuong V, Landshammer A, Muth S, Yagita H, Schwendener R, Pruschy M, Knuth A, van den Broek M. Radiotherapy promotes tumor-specific effector CD8+ T cells via dendritic cell activation. J Immunol 2012; 189: 558-566
4. Kono H, Rock KL. How dying cells alert the immune system to danger. Nature Reviews Immunology 2008; 8: 279-289
5. Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, Fu YX. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest 2014; 124: 687-695
6. Chakraborty M, Abrams SI, Camphausen K, Liu K, Scott T, Coleman CN, Hodge JW. Irradiation of tumor cells up-regulates Fas and enhances CTL lytic activity and CTL adoptive immunotherapy. J Immunol 2003; 170: 6338-6347
7. Lugade AA, Moran JP, Gerber SA, Rose RC, Frelinger JG, Lord EM. Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. J Immunol 2005; 174: 7516-7523
8. Patel RR, He K, Barsoumian HB, Chang JY, Tang C, Verma V, et al. High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. Radiother Oncol 2021; 162:60-67.
9. Moore C, Hsu CC, Chen WM, Chen BP, Han C, Story M, et al. Personalized ultrafractionated stereotactic adaptive radiotherapy (PULSAR) in preclinical models enhances single-agent immune checkpoint blockade. Int J Radiat Oncol Biol Phys 2021;110:1306-16.

Session 8. Recent Updates of Intrahepatic Cholangiocarcinoma

S8-1

Pathological and Molecular Features of Intrahepatic Cholangiocarcinoma

Peter Schirmacher

University Hospital Heidelberg, Heidelberg, Germany

In recent years the histopathological and molecular definition of Intrahepatic Cholangiocarcinoma (iCCA) has made tremendous progress leading to improved diagnostic precision and classification and in consequence improved therapeutic options and concepts. Comprehensive analyses have shown that iCCA, which currently encompasses all biliary cancers arising proximal the second order bile ducts, has to be subdivided into two biologically, diagnostically and clinically different entities, i.e. large duct iCCA (ld-iCCA) and small duct iCCA (sd-iCCA), which are substantially different by etiology, macroscopy, histological features, molecular alterations, prognosis and thus also therapeutic approaches. Interestingly, heredity and established tumor syndromes show little, if any impact in iCCA pathogenesis.

While ld-iCCA is comparable in all its characteristics to extrahepatic CCA, sd-iCCA shares the etiology of HCC, while providing molecular alterations fundamentally different from HCC and ld-iCCA; the characteristic molecular, morphological, immunohistological and clinical features will be presented; in addition, there is increasing evidence, that sd-iCCA contains several low frequency, morpho-molecularly defined subentities, which may sum up to a significant fraction of sd-iCCA, which represents a constellation comparable to HCC.

Furthermore, especially sd-iCCA, represents the most rewarding entity in regard to molecular alterations that can be approached by targeted therapy; estimates have reached up to 70% of sd-iCCA showing alterations being potentially druggable and meanwhile four different types of alterations (FGFR2-TL, NTRK-TL, MSI, IDH1mut) have meanwhile reached approval in different countries and many more (HRD, BRAF, ALK-, ROS-, RET-TLs) have been reported and await respective treatment approaches.

Thus, precise morpho-molecular characterisation of iCCA and

comprehensive testing for molecular therapeutic targets represent urgent diagnostic needs in order to more specifically tailor iCCA therapy and improve its prognosis.

S8-2

Surgical Management of Intrahepatic Cholangiocarcinoma: A Comparison with HCC

Etsuro Hatano

Kyoto University, Kyoto, Japan

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer after hepatocellular carcinoma (HCC), and its incidence is increasing worldwide. Surgical resection is considered the best treatment option for achieving long-term survival in both malignancies. However, the heterogeneity of ICC at the clinical, genomic, and epigenetic levels represents challenges in standardizing the surgical management.

Based on available evidence and our experience, this presentation highlights the current and emerging surgical principles for the management of ICC. It consists of five key elements: I) Patient selection, including the topic of oncologic selection or future liver remnant augmentation strategies; II) Principles of oncologic resection; III) The role of neoadjuvant and adjuvant therapies; IV) Re-do surgery; and V) Minimally invasive surgery.

To provide a comprehensive perspective, this presentation also highlights the different features between HCC and ICC in the context of surgical management. By focusing on these aspects, this presentation aims to enhance the understanding and optimize the surgical management of ICC.

S8-3

Systemic Therapy for Intrahepatic Cholangiocarcinoma: Current and Future Perspectives

Do-Youn Oh

Seoul National University, Seoul, South Korea

Biliary tract cancer (BTC) is a heterogenous group not only in primary origin but also in molecular characteristics. Somatic alterations in the KRAS, TP53, CDKN2A, SMAD4, BAP1, ARID1A, are commonly observed. Around 38.9% of biliary tract cancer cases have been known to harbor potentially targetable genetic alteration including FGFR1, FGFR2, FGFR3, PIK3CA, ALK, EGFR, ERBB2, BRAF, AKTS, IDH1, IDH2, CCND1, CCND3, MDM2, BRCA1 and BRCA. Targeting those molecular alterations are now being tried in clinical studies. We've already got good results for targeting FGFR fusion/translocation, IDH1 mutation, BRAF V600E mutation. In case of FGFR fusion/translocation and IDH1 mutation is more commonly observed in intrahepatic cholangiocarcinoma.

BTC has immunogenic features. Immune checkpoint inhibitors are being tested in BTC. Monotherapies of these immune checkpoint inhibitors have shown modest efficacy in general. The combination of dual immune checkpoint inhibitors, combination with cytotoxic chemotherapy, combination with antiangiogenic agents, combination with multi-target TKIs are being tested. Now, we have the first success of immunotherapy in BTC with TOPAZ-1 study (NCT03875235).

With that, exploration of new immunotherapeutic tools, development of optimal biomarker for immunotherapy, new therapeutic targets, new combination of immunotherapy and targeted agents are expected in near future to improve clinical outcomes of BTC.

S8-4

The Importance of Local Tumor Control for Inoperable Intrahepatic Cholangiocarcinoma

Christopher Crane

Memorial Sloan Kettering Cancer Center, New York, USA

Intrahepatic cholangiocarcinoma (IHCC) is a disease with high rates of mortality largely owing to its infiltrative nature, propensity for metastatic disease spread, and resistance to chemotherapy. Only 12% of all patients have localized disease at presentation, and of these patients with localized disease, less than 40% undergo cancer-directed surgery1. Although intrahepatic cholangiocarcinoma has a dominant distant spread pattern, in the absence of effective local tumor control the cause of death is due to liver decompensation secondary to partial obstruction of the biliary tree or portal venous inflow leading to hepatic parenchymal loss, or complete obstruction of the hepatic venous outflow, leading to acute liver failure. Patients with resected tumors have a substantial median survival benefit by preventing this liver decompensation from the primary tumor and shifting the cause of disease related death from local to distant disease. In order to maximize survival duration for inoperable patients, it is critical to integrate effective local treatment with improving systemic therapies in order to achieve local tumor control when resection is not possible.

Owing to the dominant pattern of distant disease spread, patients with localized tumors are usually treated initially with systemic therapy if they are not candidates for surgery. After maximal response or toxicity limitation, the second line treatment is typically considered.

Second line FOLFOX chemotherapy only modestly improves outcome over the supportive care (6.2 vs 5.3 mo)2. Although there are newer systemic therapies to consider, they probably do not have the same median survival benefit that effective local tumor control can offer. Among the locoregional options, ablative dose radiation and hepatic arterial infusion pump chemotherapy and have both been shown to achieve durable local tumor control and prolonged median survival, whereas embolic therapies have not resulted in a clear survival improvement over historical control.

Technological advances in radiation oncology have enabled the routine delivery of ablative radiation doses even for tumors greater

than 10cm. This has translated into substantial prolongation survival provided an ablative dose is given. Palliative doses achieve only temporary tumor stabilization and do not achieve maximal benefit. A retrospective dose response analysis of patients given definitive radiation therapy for inoperable intrahepatic cholangiocarcinoma in 2002–2014 at MD Anderson identified 79 consecutive patients, most of whom had large tumors (median diameter 7.9 cm [range 2.2–17 cm]). Seventy patients (89%) had received systemic chemotherapy before radiation, which was given to doses of 35–100 Gy (median 58.05), for a median BED of 80.5 Gy (range 43.75–180 Gy). At a median follow-up time of 33 months (range 11–93 months), the median OS time after diagnosis was 30 months and the 3-year OS rate was 44%. Radiation dose was the single most important prognostic factor; higher doses correlated with improved local control and OS. The 3-year OS rate for those receiving BED >80.5 was 73% versus 38% for those receiving lower doses (P=0.017), and the 3-year local control rate was significantly higher (78%) after a BED >80.5 Gy than after lower doses (45%, P=0.04). As a continuous variable, BED also significantly influenced local control (P=0.0097) and OS (P=0.0045) 3. No significant treatment-related toxicity was noted. These results suggest that a BED >80.5 Gy seems to be ablative for large intrahepatic cholangiocarcinomas, with long-term survival rates that compare favorably to resection. A subsequent multi-institutional phase II study of high-dose 15 fraction hypofractionated proton beam therapy for liver tumors included 37 IHCC inoperable patients with median tumor size of 6.0 cm. Planned dose was 67.5GyE in 15 fractions for peripheral tumors and 58.05GyE in 15 fractions (chosen out of concern for a risk of biliary stricture in central tumors). An updated analysis with a follow-up of 45.9 among the survivors IHCC. Revealed a with a median survival duration of 20.8 months with 12.3% alive at 5 years (95% CI 0.03–0.27)4.An interesting thing about this trial is that the threshold for local tumor control was identified to be 67.5GyE. During the trial, the 58.05GyE dose level was abandoned in favor of 67.5GyE due to multiple infield progression events. Following that, there were no cases of in-field progression with the 67.5GyE dose and no biliary strictures4,5. All of the local progression was in the patients who received 58.05GyE94. We do not recommend using that dose.

In contrast, embolization with yttrium-90 (90Y) 6-8 and transarterial chemoembolization 9,10 have not shown a clear benefit. It is difficult to compare results from embolic therapy studies to other studies evaluating local treatments such as resection and ablative radiation because of local tumor control has generally not been reported. Cross study comparisons are also difficult due to selection bias and the inherent heterogeneity of the population. This makes local tumor control a very important metric to assess the efficacy of treatment. Nevertheless, the more confoundable endpoint of median survival has been consistently reported to be in the 12-15 month range, which is similar to systemic therapy alone (and are not different among TACE, TACE with drug eluting beads, and more recently yttrium-90 (90Y), which is indicative a failure to achieve durable local tumor control with any embolic treatment). In contrast, high rates of local intrahepatic tumor control and improved survival clearly superior to embolic therapies have been reported by limited institutions using hepatic arterial infusion therapy11.

In summary, local tumor control is a prerequisite for the curative treatment of IHCC. The effective options are resection, HAI pump treatment, and ablative dose radiation.

References

1. Tan JC, Coburn NG, Baxter NN, et al: Surgical management of intrahepatic cholangiocarcinoma--a population-based study. Ann Surg Oncol 15:600-8, 2008
2. Lamarca A, Palmer DH, Wasan HS, et al: Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol 22:690-701, 2021
3. Tao R, Krishnan S, Bhosale PR, et al: Ablative Radiotherapy Doses Lead to a Substantial Prolongation of Survival in Patients With Inoperable Intrahepatic Cholangiocarcinoma: A Retrospective Dose Response Analysis. J Clin Oncol 34:219-26, 2016
4. Roberts HJ, Hong TS, Ly L, et al: Long-Term Results of a Multi-Institutional Phase II Study of Hypofractionated Proton Beam Irradiation of Unresectable Primary Liver Tumors. International Journal of Radiation Oncology*Biology*Physics 114:S120, 2022
5. Hong TS, Wo JY, Yeap BY, et al: Multi-Institutional Phase II Study of High-Dose Hypofractionated Proton Beam Therapy in Patients With Localized, Unresectable Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma. J Clin Oncol 34:460-8, 2016
6. Ibrahim SM, Mulcahy MF, Lewandowski RJ, et al: Treatment of unresectable cholangiocarcinoma using yttrium-90 microspheres: results from a pilot study. Cancer 113:2119-28, 2008
7. Saxena A, Bester L, Chua TC, et al: Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. Ann Surg Oncol 17:484-91, 2010
8. Al-Adra DP, Gill RS, Axford SJ, et al: Treatment of unresectable intrahepatic cholangiocarcinoma with yttrium-90 radioembolization: a systematic review and pooled analysis. Eur J Surg Oncol 41:120-7, 2015
9. Kim JH, Yoon HK, Sung KB, et al: Transcatheter arterial chemoembolization or chemoinfusion for unresectable intrahepatic cholangiocarcinoma: clinical efficacy and factors influencing outcomes. Cancer 113:1614-22, 2008
10. Kuhlmann JB, Euringer W, Spangenberg HC, et al: Treatment of unresectable cholangiocarcinoma: conventional transarterial chemoembolization compared with drug eluting bead-transarterial chemoembolization and systemic chemotherapy. Eur J Gastroenterol Hepatol 24:437-43, 2012
11. Boehm LM, Jayakrishnan TT, Miura JT, et al: Comparative effectiveness of hepatic artery based therapies for unresectable intrahepatic cholangiocarcinoma. J Surg Oncol 111:213-20, 2015

Parallel Session 1. From Bench to Bedside and Beyond

PS1-1

Deciphering the Immune and Vascular Microenvironment of HCC

Michiie Sakamoto

International University of Health and Welfare, Tokyo, Japan

In advanced hepatocellular carcinoma (HCC), combined regimen of the anti-PD-L1 antibody atezolizumab and the VEGF neutralizing antibody bevacizumab (Atezo+Bev) has become the first-line therapy. In other types of cancer also, immunotherapies have achieved better response, and immuno-oncological understanding of cancer is becoming more important. So, deciphering pathological and molecular features of not only tumor itself but also tumor microenvironment in HCC is mandatory. Pathologically, advanced HCC is characterized by vascular rich stroma, little fibrous stroma and relatively scant inflammatory cell infiltration. However, if we see in more detail, they show quite variable and more complicated features in each tumor. We reported immune subtype and immunovascular subtype of HCC using multiplex immunohistochemical analysis on surgically resected HCC. Immune high tumors seem relatively rare in HCC, while they have better prognosis than immune low tumor. Interestingly these microenvironmental features seem to have an additional impact as well as some association with molecular features of HCC. Accumulating evidences indicate CTNB1 mutation is strongly associated with lower lymphocytic infiltration and less response to immunotherapy. Moreover, angiogenic and less angiogenic tumor exist in immune low subtype. There is no doubt that pathological evaluation can give detailed spatial distribution and population of immune cells and tumor vasculature. It is also explored if imaging diagnosis can be applied to prospect some of these features of tumor and tumor microenvironment. Here I will overview these pathological features of tumor and tumor microenvironment of HCC and discuss how they can be applied in the era of immunotherapy.

References

1. Matsuda K, Kurebayashi Y, Masugi Y, Yamazaki K, Ueno A, Tsujikawa H, Ojima H, Kitago M, Itano O, Shinoda M, Abe Y, Sakamoto M. Immunovascular microenvironment in relation to prognostic heterogeneity of WNT/β-catenin-activated hepatocellular carcinoma. Hepatol Res. In press.
2. Kurebayashi Y, Matsuda K, Ueno A, Tsujikawa H, Yamazaki K, Masugi Y, Kwa WT, Effendi K, Hasegawa Y, Yagi H, Abe Y, Kitago M, Ojima H, Sakamoto M. Immunovascular classification of HCC reflects reciprocal interaction between immune and angiogenic tumor microenvironments. Hepatology. 2022, 75: 1139-1153.
3. Kurebayashi Y, Ojima H, Tsujikawa H, Kubota N, Maehara J, Abe Y, Kitago M, Shinoda M, Kitagawa Y, Sakamoto M. Landscape of immune microenvironment in hepatocellular carcinoma and its additional impact on histological and molecular classification. Hepatology. 2018, 68: 1025-1041.
4. Tsujikawa H, Masugi Y, Yamazaki K, Itano O, Kitagawa Y, Sakamoto M. Immunohistochemical molecular analysis indicates hepatocellular carcinoma subgroups that reflect tumor aggressiveness. Hum Pathol. 2016, 50:24-33.
5. Ueno A, Masugi Y, Yamazaki K, Komuta M, Effendi K, Tanami Y, Tsujikawa H, Tanimoto A, Okuda S, Itano O, Kitagawa Y, Kuribayashi S, Sakamoto M. OATP1B3 expression is strongly associated with Wnt/β-catenin signalling and represents the transporter of gadoxetic acid in hepatocellular carcinoma. J Hepatol. 2014, 61: 1080-1087.

PS1-2

Molecular Landscape of Liver Cancer and Its Clinical Implications

Xin Wei Wang[1,2]

[1]Liver Cancer Program and 2Laboratory of Human Carcinogenesis, Center for Cancer Research; [2]National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Liver cancer is among the top five deadliest cancers in the world, especially in Southeast Asia and Sub-Saharan Africa, and its incidence rates continue to increase in recent decades. Despite considerable efforts towards the development of new prevention, diagnosis and treatment strategies, the improvement of cancer survival is modest. Defined as the unique genotypic and phenotypic differences of cancer cells within a single tumor (intra-tumor) or amongst different patients (inter-tumor), tumor heterogeneity has consistently been linked to worse clinical outcomes in solid malignancies. Liver cancer mainly consists of two clinical types, i.e., hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), each of which could be further divided into several clinical and molecular subtypes. Chronic liver diseases due to viral hepatitis, alcohol consumption, chemical carcinogens, or nonalcoholic fatty liver disease/nonalcoholic steatohepatitis, are major global health burdens that increase the risk of HCC while parasitic infections may be linked to CCA. It is unclear how complex etiological factors determine tumor subtypes and whether common features may be shared among HCC and CCA. Given the presence of so many clinical and molecular variables, it is imperative to develop well-defined cohorts that include diverse etiologies, race/ethnicities, sex and age, which provides an unbiased platform by minimizing confounding factors to study liver cancer types. Accordingly, we have established several national and international collaborative projects, including the NCI-CLARITY study, the NCI-UMD cohort study, the NCI-Mongolian cohort study, and the TIGER-LC (Thailand) consortium. We have applied molecular-based technologies such as genomics, transcriptomics, metabolomics and microbiomics, including single-cell omics to comprehensively analyze biopsies from diverse populations, in order to better characterize heterogeneity among and within patients, to further define tumor molecular subtypes with unique tumor biology and

to understand tumor evolution in response to treatment. Recently, we have developed a paradigm-shift approach by determining individuals' virome as an early onset of HCC to improve risk prediction and early diagnosis of liver cancer. These studies have led to the discovery of new tools of early diagnosis of HCC, new cell types and drivers in HCC and CCA, potential new mechanisms of therapy resistance and tumor progression, and new insights into the evolutionary patterns of liver cancer. Our past and future ability to translate our research findings towards patient management through the identification of molecular-based knowledge for understanding of liver cancer pathophysiology with the application of early detection and treatment of liver cancer may have a considerable impact on clinical practice and public health.

PS1-3

Charting Cancer Cell Plasticity in HCC with Multi-Omic Data

Stephanie Ma

The University of Hong Kong, Hong Kong

Hepatocellular Carcinoma (HCC), in particular those driven by hepatitis B virus and non-alcoholic fatty liver disease, is one of the most prevalent and aggressive malignancies in this region. Despite definite improvements in the outcome of patients with this disease, the overall prognosis is still unsatisfactory because of late presentation, drug resistance and frequent tumor recurrence. Unlocking phenotypic plasticity has become known as a new emerging hallmark of cancer, with the feature endowing cancer cells with the capacity to shift dynamically between a differentiated state, with limited tumorigenic potential, and an undifferentiated or cancer stem-like cell (CSC) state, which is responsible for long-term tumor growth. In addition, it confers the ability to transit into distinct CSC states with different competence to invade, disseminate and seed metastasis. Cancer cell plasticity has been linked to the epithelial-to-mesenchymal transition program and relies not only on cell-autonomous mechanisms, but also on signals provided by the tumor microenvironment and/or induced in response to therapy. There are strong reasons to believe cancer cell plasticity represents an important root of HCC recurrence and therapy resistance. Knowledge of the molecular/cellular targets and mechanisms driving this root is of importance as this can provide novel opportunities for therapeutic interventions. This talk will cover recent findings in our lab in this area.

PS1-4

Spatial Heterogeneity and Immune Evasion Mechanism of Circulating Tumor Cells in HCC

Xin-Rong Yang

Fudan University, Shanghai, China

The relapse of hepatocellular carcinoma (HCC) resulting from hematogenous metastasis is a frequent occurrence that significantly affects the long-term outcomes of patients [1]. Hematogenous metastasis in HCC is a spatially and temporally dynamic process, encompassing various stages such as dissemination, metastasis, immune evasion, and colonization, ultimately leading to the formation of recurrent or metastatic lesions. Circulating tumor cells (CTCs), which are tumor cells that have disseminated into the bloodstream, have emerged as a key focus in bridging the primary and metastatic tumors.

We investigated the clinical relevance and underlying mechanisms of CTCs during hematologic dissemination in our study. In a previous study, we discovered that CTCs exhibited enhanced survival capabilities in the bloodstream through the process of epithelial-to-mesenchymal transition (EMT). We also established a correlation between CTCs isolated from different vascular sites and organ-specific metastasis [2]. To further understand the transcriptomic evolution of CTCs along the path of hematogenous dissemination in HCC, we analyzed the transcriptome of CTCs collected from four key vascular sites: suprahepatic inferior vena cava (hepatic outflow tract/before pulmonary circulation), radial artery (after pulmonary circulation), cubital vein (after peripheral microcirculation), and portal vein (the inflow tract of the liver). Through this comprehensive analysis, we provided a detailed description of the transcriptomic changes that occur in CTCs during their journey through the bloodstream in HCC.

Moreover, we identified the dynamic activation of the P38-MAPK-MAX signaling pathway in CTCs during circulation, which promoted the expression of CC chemokine ligand 5 (CCL5). This, in turn, facilitated the recruitment of regulatory T cells (Tregs) to suppress local anti-tumor immunity and support the survival of CTCs [3]. Overall, CTCs exhibit significant spatial and temporal heterogeneity and are intricately involved in the immune response. The spatial heterogeneity of CTCs may help explain the phenotypic differences observed between primary tumors and metastatic tumors.

References

1. Li, J., et al., Clinical applications of liquid biopsy as prognostic and predictive biomarkers in hepatocellular carcinoma: circulating tumor cells and circulating tumor DNA. Journal of Experimental & Clinical Cancer Research : CR, 2018. 37(1): p. 213.
2. Sun, Y.-F., et al., Circulating Tumor Cells from Different Vascular Sites Exhibit Spatial Heterogeneity in Epithelial and Mesenchymal Composition and Distinct Clinical Significance in Hepatocellular Carcinoma. Clinical Cancer Research : an Official Journal of the American Association For Cancer Research, 2018. 24(3): p. 547-559.
3. Sun, Y.-F., et al., Dissecting spatial heterogeneity and the immune-evasion mechanism of CTCs by single-cell RNA-seq in hepatocellular carcinoma. Nature Communications, 2021. 12(1): p. 4091.

Parallel Session 2. APPLE-KLCA Joint Symposium: Virus and HCC

PS2-1

Prevention of HBV-Related HCC: Antiviral Therapy

Young-Suk Lim

University of Ulsan, Seoul, South Korea

A prospective cohort (REVEAL) study1 showed that the risk of hepatocellular carcinoma (HCC) increase with increasing levels of baseline serum hepatitis B virus (HBV) DNA up to 106 copies/mL (about 5 log10 IU/mL), irrespective of serum alanine aminotransferase (ALT) levels and HBeAg status, in chronic hepatitis B (CHB) patients. Nonetheless, the association between very high HBV DNA levels (especially >6 log10 IU/mL) and HCC risk remains unclear, especially in middle-aged and old HBeAg-positive patients with normal ALT levels. Accordingly, antiviral treatment of the patients with high HBV DNA and normal ALT levels is controversial.

Recently we have analyzed the association between a broad range of serum HBV DNA levels and long-term HCC risk in a total of 6949 HBeAg-positive and HBeAg-negative, non-cirrhotic, treatment-naïve CHB patients who are not generally indicated for antiviral therapy by current practice guidelines because of no significant ALT level elevation.2 We found that the association between HBV DNA levels and HCC risk is not linear but parabolic in these patients. The HCC risk was highest at moderate HBV DNA levels 6.3 log10 IU/mL, with decreasing HCC risk at higher and lower HBV DNA levels. Very high HBV DNA levels (>8 log10 IU/mL) showed the lowest HCC risk which was not significantly different from that of very low HBV DNA levels (≤4 log10 IU/mL). The similar findings were consistently observed in all age subgroups.

Our another study have demonstrated that untreated non-cirrhotic HBeAg-positive CHB patients with persistently normal ALT levels were associated with significantly higher risks of HCC than the immune-active phase patients treated with nucleos(t)ide analogs for elevated ALT levels.3 Further, untreated non-cirrhotic HBeAg-negative CHB patients with high viral load and no significant ALT elevation had higher risks of clinical events than treated HBeAg-negative active hepatitis phase patients with elevated ALT.4

Based on our recent findings, we suggest to use the terms "high replication phase," "moderate replication phase," and "low replication phase", which may help to distinctively indicate the HCC risk and the necessity of treatment in CHB patients. Since the highest HCC risk is at moderate viral load, CHB patients who persistently have moderate levels of HBV DNA (4–8 log10 IU/mL) may be indicative of antiviral treatment regardless of HBeAg and ALT elevation to reduce the risk of HCC. However, most patients with HBV DNA >8 log10 IU/mL may eventually have progressive decline in the HBV DNA levels and subsequently increasing risk of HCC. Therefore, to prevent the risk of HCC to the greatest possible degree, our data suggest that antiviral treatment may also have to be initiated with HBV DNA levels >8 log10 IU/mL, regardless of ALT levels, especially in patients with CHB older than 30 years.

It has been unclear whether the level of serum HBV DNA at baseline impacts the on-treatment risk of HCC in HBeAg positive, non-cirrhotic patients with CHB. We found that on-treatment HCC risk increased incrementally with decreasing baseline HBV DNA levels in the range of ≥5.00 log10 IU/mL in those patients.5 Therefore, early initiation of antiviral treatment with a high viral load (≥8.00 log10 IU/mL) may maintain the lowest risk of HCC in those patients.

We also found that starting antiviral therapy in immune-tolerant phase is cost-effective compared with delaying the treatment until the active hepatitis phase in CHB patients, especially with increasing HCC risk, decreasing drug costs and consideration of productivity loss.6 Simplifying and expanding treatment eligibility for CHB would save many lives and be highly cost-effective when combined with high diagnostic rates.7

Collectively, a simplified treatment algorithm may have to be recommended to initiate treatment in all CHB patients older than 30 years with serum HBV DNA levels >2,000 IU/mL, regardless of HBeAg status and ALT levels. Accumulating data on the long-term efficacy and safety of anti-HBV drugs with high potency, high genetic barrier to resistance, and decreasing cost may facilitate earlier treatment initiation.

References

1. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65-73.
2. Kim GA, Han S, Choi GH, et al. Moderate levels of serum hepatitis B virus DNA are associated with the highest risk of hepatocellular carcinoma in chronic hepatitis B patients. Aliment Pharmacol Ther 2020;51:1169-1179.
3. Kim GA, Lim YS, Han S, et al. High risk of hepatocellular carcinoma and death in patients with immune-tolerant-phase chronic hepatitis B. Gut 2018;67:945-952.
4. Choi GH, Kim GA, Choi J, et al. High risk of clinical events in untreated HBeAg-negative chronic hepatitis B patients with high viral load and no significant ALT elevation. Aliment Pharmacol Ther 2019;50:215-226.
5. Choi WM, Kim GA, Choi J, et al. Increasing on-treatment hepatocellular carcinoma risk with decreasing baseline viral load in HBeAg-positive chronic hepatitis B. J Clin Invest 2022;132:e154833.
6. Kim HL, Kim GA, Park JA, et al. Cost-effectiveness of antiviral treatment in adult patients with immune-tolerant phase chronic hepatitis B. Gut 2021;70:2172-2182.
7. Lim YS, Ahn SH, Shim JJ, et al. Impact of expanding hepatitis B treatment guidelines: A modelling and economic impact analysis. Aliment Pharmacol Ther 2022;56:519-528.

PS2-2

Balancing the Risks and Benefits of Long-Term Antiviral Therapy for HBV

Wai-Kay Seto

The University of Hong Kong, Hong Kong

Long-term nucleos(t)ide analogue therapy is currently used in the treatment of active chronic hepatitis B. The indications of treatment expand beyond active disease, and also include prophylaxis during pregnancy, immunosuppressive therapy and direct antiviral therapy for chronic hepatitis C. Entecavir, tenofovir disoproxil fumarate and tenofovir alafenamide are generally safe and well-tolerated, with their safety record justified by long-term real-world data. While there are concerns on the long-term renal and bone safety of tenofovir disoproxil fumarate, it remains the most suitable HBV antiviral for women of child-bearing age contemplating pregnancy. There has been much research on the safe and effective cessation of nucleos(t)ide analogue treatment, and while novel biomarkers can offer robust prediction, this has yet to be implemented into treatment guidelines. There is current debate on expanding treatment indications to patients with quiescent disease, on the basis on oncoprotection against hepatocellular carcinoma. And while such an approach has been proven to be cost-effective, the benefits of expanded treatment still requires clinical validation. Novel treatment options aiming for a functional cure will emerge in the future, further impacting risk and benefit considerations when initiating treatment for HBV.

PS2-3

Latest Update of Direct-Acting Antiviral Treatment for HCV

Eiichi Ogawa

Kyushu University, Fukuoka, Japan

An estimated 58 million people globally have chronic hepatitis C virus (HCV) infection, with approximately 1.5 million new infections occurring each year. Chronic hepatitis C (CHC), if left untreated, commonly leads to progressive liver disease. In addition to liver-related complications, CHC can also cause multiple extrahepatic manifestations that increase morbidity and mortality.

Since 2014, short-course, well-tolerated, all-oral, interferon-free direct-acting antivirals (DAA) have revolutionized HCV treatment, with cure rates approaching 100%. All treatment-naïve and treatment experienced patients with recently acquired or chronic HCV infection, even in those with decompensated cirrhosis, should quickly start treatment. The primary goal of HCV therapy is to cure the infection, defined as achieving a sustained virological response (SVR) with HCV RNA undetectable in serum or plasma at 12 weeks or 24 weeks after the end of antiviral therapy.

Treatment with pangenotypic regimens, such as sofosbuvir/velpatasvir (SOF/VEL) for 12 weeks or glecaprevir/pibrentasvir (GLE/PIB) for 8-12 weeks, can be initiated without knowledge of the genotype; moreover, testing for HCV resistance prior to these first-line regimens is not necessary. However, liver disease severity must be assessed prior to DAA treatment because regimens comprising an HCV protease inhibitor, such as GLE or voxilaprevir (VOX), are contraindicated for patients with decompensated cirrhosis or with previous episodes of decompensation. Patients with compensated cirrhosis and HCV genotype 3 should be treated with SOF/VEL plus ribavirin for 12 weeks, SOF/VEL/VOX for 12 weeks, or GLE/PIB for 12-16 weeks. Patients with severe renal impairment, including those with end-stage renal disease on hemodialysis, should be treated with DAAs according to the general recommendations. Drug-drug interaction risk assessment prior to initiating therapy is required for all patients undergoing treatment with a DAA, especially for those coinfected with HIV. HCV resistance testing prior to the retreatment of patients who failed to be cured by any of the DAA-containing treatment regimens would be useful for guiding retreatment according to the probability of response. For example, patients with NS5A P32 deletions do not respond to GLE/PIB and require treatment with SOF/VEL/VOX or SOF/VEL plus ribavirin.

The risk of reinfection should be carefully explained to positively modify negative behaviors in at-risk populations, and retreatment should be offered without delay to those patients who are

PS2-4

Impact of Direct-Acting Antiviral Therapy on HCC: Occurrence, Recurrence, and Prognosis

Hyung Joon Yim

Korea University, Ansan, South Korea

Chronic hepatitis C virus (HCV) infection is one of the major risk factors for developing hepatocellular carcinoma (HCC). The annual risk of HCC is around 3% in patients with liver cirrhosis related to HCV infection.1 Although approximately 80-90% of HCC occurs in the presence of liver cirrhosis in patients with chronic HCV infection, those without cirrhosis are not free from HCC risk.1 Hence, surveillance of HCC may be needed in HCV patients with or without liver cirrhosis.

It was previously demonstrated that interferon treatment reduces the risk of occurrence as well as recurrence of HCC in HCV-infected patients.2 However, there have been debates on the risk of HCC in patients treated with DAAs. In the early stages of DAA era, early occurrence and recurrence of HCC was suspected in patients with HCV-related liver cirrhosis who were treated with DAAs.3 However, subsequent studies reported that incidence of HCC decreases up 70% after achievement of sustained virological response (SVR) by DAAs.4 The incidence was not different between post-interferon and post-DAA treatment. The same effect was observed in the retrospective studies from the USA and a prospective study from Europe. A study performed in Korea showed the similar results. A meta-analysis showed that patients treated with DAA had a reduced risk of death (HR; CI = 0.44; 0.38-0.52), decompensation (HR; CI = 0.54; 0.38- 0.76) and HCC occurrence (HR; CI = 0.72; 0.61- 0.86).

The preventive effect of DAA on recurrence of HCC in patients

with chronic HCV infection was un-clearer. This is attributed to the heterogenicity of HCC stages included in the studies. When the rate was estimated in early stage HCC patients with curative therapies, patients received DAA treatment showed a better prognosis compared with those who did not it.6 However, patients with BCLC B or C stages, the benefit of DAA needs to be further evaluated.

Overall, treatment with DAA for HCV infection reduces occurrence of HCC in high risk patients, decreased recurrence of HCC in patients with early stage, and improves survival.

References

1. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011; 365:1118–27
2. Masuzaki R, Yoshida H, Omata M. Interferon reduces the risk of hepatocellular carcinoma in hepatitis C virus-related chronic hepatitis/liver cirrhosis. Oncology. 2010;78 Suppl 1:17-23.
3. Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol. 2016;65:727-733.
4. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol. 2018;68;25-32.
5. Sahakyan Y, Lee-Kim V, Bremner KE, Bielecki JM, Krahn MD. Impact of direct-acting antiviral regimens on mortality and morbidity outcomes in patients with chronic hepatitis c: Systematic review and meta-analysis. J Viral Hepat. 2021;28:739-754.
6. Cabibbo G, Celsa C, Calvaruso V, et al. Direct-acting antivirals after successful treatment of early hepatocellular carcinoma improve survival in HCV-cirrhotic patients. J Hepatol. 2019;71:265-273.

Parallel Session 3. Debatable Topics in HCC

PS3-1

The Era of Diversity: Does Conventional TACE Still Work?

Jin Wook Chung

Seoul National University, Seoul, South Korea

Before the introduction of new systemic agents (when sorafenib was the only 1st line systemic agent), conventional chemoembolization (cTACE) has been a mainstay in the real-world practice for both intermediate- and advanced-stage HCCs in Asia. In early-stage hepatocellular carcinoma (HCC), cTACE has been widely utilized as an alternative option when curative treatments are not feasible [1].

However, there are recent challenges in the role of cTACE in the management of HCCs. They include new systemic agents in advanced stage, drug-eluting-bead chemoembolization (DEB-TACE) and radioembolization (TARE) in intermediate stage, and external beam radiotherapy (EBRT) in early stage.

With introduction of new 1st line systemic agents including atezolizumab plus bevacizumab, durvalumab plus tremelimumab and lenvatinib, the objective response rate of systemic agents soared up to 33% with considerable rates of complete response and potential conversion to curative options [2-4]. As a results, in advanced HCC with vascular invasion or high tumor burden, systemic therapies are increasingly being applied as initial treatment for hepatocellular carcinoma. Recent advances in TARE with advanced personalized dosimetry revealed improved survival outcome by using a higher radiation dose than the standard dose [5]. In a single HCC smaller than 8 cm, radiation segmentectomy or tumorectomy by selective TARE achieved complete tumor response in over 80% of cases [6, 7]. There is growing evidence that EBRT including stereotactic ablative radiotherapy and proton beam therapy can be an alternative to local ablation [8. 9].

What will be the role of cTACE in the future? With advances in competing treatment modalities, the role of cTACE will continue to shrink. The main losing area will be the conditions when cTACE should be performed nonselectively, when cTACE causes severe postembolization syndrome or when the initial treatment outcome is not satisfactory. In general, nonselective cTACE shows worse local tumor control rate than selective cTACE and requires repeated procedure for residual or recurrent tumors which may progressively deteriorate liver function. In case of unsatisfactory initial response, conversion to other therapies are more likely to work better [10].

However, cTACE is also making progress. Advances in cone-beam CT and microcatheter technology enable more precise tumor targeting by superselective procedure, which leads to better tumor control and less parenchymal damage. Among intraarterial treatments for HCC, cTACE is best suited for selective procedure. Highly selective cTACE can be safely performed even in patients with compromised liver function. In small HCCs, cTACE demonstrated better tumor response than DEB-TACE [11, 12]. Even though selective TARE shows better local control rate than cTACE, cost effectiveness and availability issue need to be addressed. Therefore, selective cTACE will survive as an initial treatment option for early and intermediate-stage HCCs considering its high objective response rate and minimal parenchymal damage, especially in multifocal disease. In advanced HCC with localized disease, cTACE can play a significant role as alone or in combination with EBRT or systemic therapy [13]. Also, cTACE will maintain its dominant role to treat recurrent tumors after curative treatments or residual tumor after TARE. In conclusion, cTACE will remain one of the leading HCC treatments for the next decade.

References

1. Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE study. Liver Int 2015;35:2155-2166
2. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-1173

3. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894-1905
4. Abou-Alfa GK, Chan SL, Kudo M, Lau G, Kelley RK, Furuse J, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA. J Clin Oncol 2022;4_suppl:379
5. Garin E, Tselikas L, Guiu B, Chalaye J, Edeline J, de Baere T, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol 2021;6:17-29
6. Salem R, Johnson GE, Kim E, Riaz A, Bishay V, Boucher E, et al. Yttrium-90 radioembolization for the treatment of solitary, unresectable HCC: the LEGACY study. Hepatology 2021;74:2342-2352
7. Kim E, Sher A, Abboud G, Schwartz M, Facciuto M, Tabrizian P, et al. Radiation segmentectomy for curative intent of unresectable very early to early stage hepatocellular carcinoma (RASER): a single-centre, single-arm study. Lancet Gastroenterol Hepatol. 2022;7:843-850.
8. Rim CH, Lee JS, Kim SY, Seong J. Comparison of radiofrequency ablation and ablative external radiotherapy for the treatment of intrahepatic malignancies: A hybrid meta-analysis. JHEP Rep 2022;5:100594
9. Kim TH, Koh YH, Kim BH, Kim MJ, Lee JH, Park B, Park JW. Proton beam radiotherapy vs. radiofrequency ablation for recurrent hepatocellular carcinoma: A randomized phase III trial. J Hepatol. 2021 Mar;74(3):603-61.
10. Kudo M, Ueshima K, Chan S, Minami T, Chishina H, Aoki T, et al. Lenvatinib as an initial treatment in patients with intermediate-stage hepatocellular carcinoma beyond up-to-seven criteria and Child-Pugh A liver function: a proof-of-concept study. Cancers. 2019;11:1084.
11. Lee IJ, Lee JH, Lee YB, Kim YJ, Yoon JH, Yin YH, et al. Effectiveness of drug-eluting bead transarterial chemoembolization versus conventional transarterial chemoembolization for small hepatocellular carcinoma in Child-Pugh class A patients. Ther Adv Med Oncol 2019;11:1758835919866072
12. Ikeda M, Arai Y, Inaba Y, Tanaka T, Sugawara S, Kodama Y, Aramaki T, et al. Conventional or drug-eluting beads? Randomized controlled study of chemoembolization for hepatocellular carcinoma: JIVROSG-1302. Liver Cancer. 2022 Jun 15;11(5):440-450.
13. Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC) Korea. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. Clin Mol Hepatol. 2022 Oct;28(4):583-705.

PS3-2

Technical Issues in TACE: Focusing on Korean Recommendations

In Joon Lee

National Cancer Center Korea, Goyang, South Korea

Korean liver cancer association (KLCA) announced the fourth revision of KLCA-NCC Korean practice guideline for the management of HCC in 2022, and the KLCA practical recommendations for TACE in 2023.

Superselective TACE can maximize therapeutic effects while minimizing injury to normal parenchyma. Its use is a critical factor that significantly impacts treatment outcomes. Consequently, superselective TACE has been included as a recommendation in the 2022 KLCA-NCC guideline. The detailed technical issues for superselective TACE, including the microcatheter system and cone-beam CT, as well as the ideal candidate for this procedure, are described in the KLCA practical recommendations for TACE.

TACE is included in cTACE using Lipiodol-based emulsion and DEB-TACE using drug-eluting microspheres. The detailed implementation method of TACE varies from country to country, and the approach used in Korea differs somewhat from that used in Western countries. Three RCTs conducted in the West have shown that DEB-TACE produces similar treatment results to TACE. However, recent studies conducted in Korea and Japan suggest that DEB-TACE may be less effective than cTACE in treating small HCCs (≤3 cm). The technical details of cTACE and DEB-TACE in Korea are also described in the KLCA practical recommendations for TACE.

This presentation will describe the detailed technical issues in TACE, with an emphasis on the Korean style based on KLCA recommendations, which differ from those of Western countries.

PS3-3

Role of Surgical Resection for HCC with Portal Vein Tumor Thrombosis

Ying-Hong Shi

Fudan University, Shanghai, China

Hepatocellular Carcinoma (HCC) often invades the portal venous system, resulting in portal vein tumour thrombosis (PVTT). Surgical resection could improve survival rate of HCC with PVTT.

In the field of neoadjuvant therapy, neoadjuvant RT provided significantly better postoperative survival outcomes than surgery alone. Combined TACE, combined TKI/anti-PD-1 antibodies showed promising result in conversing unresectable HCC to resectable HCC. Also, combined TACE, TKI and anti-PD-1 antibodies downstaging therapy led to higher of curative conversion resection rate. In mechanism study, we found that organ specific responses rate was higher in PVTT, and the TKI combined anti-PD-1 responder group had a lower frequency of naïve CD8+ T cells than the non-responder group.

In the field of adjuvant therapy, adjuvant apatinib therapy is a potential effective treatment. Adjuvant Lenvatinib after radical resection of HCC with PVTT showed promising result. Moreover, Adjuvant TACE and sorafenib may provide an effective way for control of HCC with PVTT after surgery. Finally, Adjuvant Atezolizumab and Bevacizumab significantly improved RFS patients with HCC patients with PVTT.

In future, an RCT called Talentop which is a multicenter, randomized study evaluating the efficiency and safety of hepatic resection for selected HCC with macrovascular invasion after initial atezo+ bev is enrolling patients in China, this trial may answer the feasibility of neoadjuvant atezo+ bev in HCC with PVTT. Moreover, mRNA vaccine combined with anti-PD-1 would shed light on adjuvant therapy in preventing high-risk recurrence rate of HCC with PVTT.

PS3-4

Integration of Systemic and Locoregional Therapy in HCC

Joong-Won Park

National Cancer Center Korea, Goyang, South Korea

The therapeutic management of hepatocellular carcinoma (HCC) has traditionally varied based on evidence-based practice guidelines, with locoregional therapy being the preferred treatment option for unresectable early to intermediate stages HCC and systemic therapy being recommended for advanced HCC. The integration of systemic and locoregional therapy in HCC has undergone a paradigm shift with innovative systemic therapies like atezolizumab plus bevacizumab and durvalumab plus tremelimumab. These therapies promise enhanced survival rates and decreased adverse event profiles, potentially revolutionizing traditional treatment methodologies.

Current recommendations suggest systemic therapy for patients needing repeated locoregional interventions, even in cases of localized HCC and those unresponsive to recurrent locoregional treatment. However, the arrival of effective and less-toxic immunotherapeutic agents is anticipated to redefine these recommendations regarding indications and administration timing.

The emergence of immunotherapies for HCC influences the choice of first-line treatment and necessitates a reassessment of secondary or subsequent treatments for patients responsive to immunotherapies. The treatment strategy requires careful consideration, weighing the benefits of applying locoregional treatment post-immunotherapy or combining systemic and locoregional immunotherapy.

Despite the absence of studies comparing the first-line treatment of atezolizumab plus bevacizumab with locoregional therapy, there is an ongoing phase 3 Randomized Controlled Trial (RCT) investigating transarterial chemoembolization (TACE) combined with immunotherapy. Although past phase 3 RCTs of combination therapy with TACE and tyrosine kinase inhibitors (such as sorafenib and brivanib) have been unsuccessful for advanced HCC, there is renewed hope for the amalgamation of TACE, TARE or external beam radiotherapy (EBRT) and immunotherapy.

While current immunotherapeutic agents have improved overall survival and progression-free survival rates compared to the past, they still fall short compared to outcomes from other cancers. In the absence of definitive biomarkers, it is posited that a combination or sequential approach incorporating locoregional treatments is crucial for enhancing the treatment outcomes in HCC patients.

Parallel Session 4. Application of Artificial Intelligence (AI) in Liver Cancer

PS4-1

AI-Based Cancer Screening Using Liquid Biopsy

Eunhae Cho

GC Genome, Yongin, South Korea

There are several companies currently developing liquid biopsy-based early cancer screening tests. Some of these companies include Grail, Freenome, Guardant Health and Thrive. These tests use various biomarkers, such as ctDNA and protein markers, to detect cancer at early stage. Some of these tests have already shown promising results in clinical trials, and they have the potential to revolutionize cancer diagnosis and improve patient outcomes. The representative test, Galleri® multi-cancer early detection test detects a cancer signal across more than 50 types of cancer, many of which are not commonly screened for today. Mutation, changes in methylation and cell free DNA fragment information, or a fusion of such features are used in early cancer detection technology. Artificial intelligence is crucial for these complicated features.

GC Genome have conducted cf-WGS from more than 1,000 cancer and 3,000 healthy individuals and used artificial intelligence to create algorithm which can detect cancer at early stage. We used cfDNA fragment size, end motif, mutation density and signatures, and copy number aberrations as important features. Our algorithms are remarkably accurate in predicting both the presence of cancer as well as the location of the malignancy (1). We are currently conducting validation for the purpose of health checkup test in thousands of people, and it is anticipated that the results will be helpful to a significant number of people.

References

1. Integrative modeling of tumor genomes and epigenomes for enhanced cancer diagnosis by cell-free DNA. Nat Commun. 2023 Apr 10;14(1):2017

PS4-2

Qualitative and Quantitative Imaging Biomarkers to Predict Prognosis of HCC

Seung Soo Lee

University of Ulsan, Seoul, South Korea

Imaging plays critical role in the diagnosis and management of hepatocellular carcinoma (HCC). In patients at risk, HCC can be diagnosed based on typical imaging findings. Liver imaging reporting and data system (LI-RADS) is a standardized system for HCC imaging that has been integrated into American Association for the Study of Liver Disease (AASLD) clinical practice guidance. LI-RADS categorizes liver nodules in at-risk patients according to the probability of HCC, and LR-5 category indicates definite HCC. LI-RADS also defines LR-M features to achieve high specificity in HCC diagnosis, with the presence of one or more LR-M features indicating liver malignancy not specific for HCC. The LI-RADS system not only helps the diagnosis of HCC but also has prognostic implications since HCCs exhibiting LR-M features are associated with earlier recurrence and poorer survival after resection (1).

There have been continuous efforts to find imaging biomarkers that reflect biologic behavior of HCCs. Microvascular invasion (MVI) is a well-known factor associated with poor prognosis of HCC. Imaging findings such as non-smooth tumor margins, arterial peritumoral enhancement, and peritumoral hypointensity on gadoxetic acid-enhanced hepatobiliary phase (HBP) images suggest the presence of MVI (2). Radiologic findings that reflect pathologic features of HCCs associated with aggressive behavior, such as positive stemness markers (CK-19) (3,4), macrotrabecular massive subtype (5), and TP53 mutation (6), have also been discovered. Recently high-throughput sequencing and gene expression profiling have identified distinct two subclasses of HCCs with different chromosomal stability and biologic behavior, i.e., proliferative HCCs and non-proliferative HCCs (7). Imaging may help stratify HCCs into proliferative or non-proliferative subtypes. Gadoxetic acid is hepatocyte specific contrast agent which is actively taken up by hepatocyte through organic anionic transporter (OATP) 1B3. Mutation in CTNNB1 encoding β-catenin results in overexpression of organic anionic transporter (OATP) 1B3. Therefore, HCCs exhibiting high signal intensity on HBP images are associated with CTNNB1 mutation, lower alpha fetoprotein, and better prognosis (8). In contrast, HCCs in proliferative subtypes frequently show TP53 mutation and CK-19 expression, tending to show low signal intensity on HBP images (4,6). Taken together, the imaging characteristics of HCCs in terms of morphology, enhancement, and signal intensity may help stratify HCCs according to their aggressiveness and biologic behavior.

Diffusion-weighted imaging provides a quantitative metric to express the degree of diffusion-related signal decay, known as the apparent diffusion coefficient (ADC). ADC reflects cell density in tissue and has been suggested as quantitative biomarker associated with tumor differentiation and biologic behavior (4,8). Radiomics, a computerized image analysis process involving the extraction and processing of numerous quantitative features from images, may enable comprehensive analysis of image-derived features, potentially allowing for diagnostic and prognostic information that cannot be obtained from classic visual image analysis. Previous research showed the potentials of radiomics in predicting pathologic subtypes and treatment outcomes of HCCs (9). However, there are obstacles hindering its clinical application, such as labor intensive and time-consuming segmentation process, long computation times, and reproducibility issues resulting from the dependency of radiomics on imaging techniques. Therefore, further validation and technical improvements are required.

References

1. Choi SH, Lee SS, Park SH, et al. LI-RADS Classification and Prognosis of Primary Liver Cancers at Gadoxetic Acid-enhanced MRI. Radiology 2019;290:388-397. doi: 10.1148/radiol.2018181290
2. Lee S, Kim SH, Lee JE, Sinn DH, Park CK. Preoperative gadoxetic acid-enhanced MRI for predicting microvascular invasion in patients with single hepatocellular carcinoma. J Hepatol 2017;67:526-534. doi: 10.1016/j.jhep.2017.04.024
3. Jeong HT, Kim MJ, Kim YE, Park YN, Choi GH, Choi JS. MRI features of hepatocellular carcinoma expressing progenitor cell markers. Liver Int 2012;32:430-440. doi: 10.1111/j.1478-3231.2011.02640.x
4. Choi SY, Kim SH, Park CK, et al. Imaging Features of Gadoxetic Acid-enhanced and Diffusion-weighted MR Imaging for Identifying Cytokeratin 19-positive Hepatocellular Carcinoma: A Retrospective Observational Study. Radiology 2018;286:897-908. doi: 10.1148/radiol.2017162846
5. Rhee H, Cho ES, Nahm JH, et al. Gadoxetic acid-enhanced MRI of macrotrabecular-massive hepatocellular carcinoma and its prognostic implications. J Hepatol 2021;74:109-121. doi: 10.1016/j.jhep.2020.08.013
6. Kitao A, Matsui O, Zhang Y, et al. Dynamic CT and Gadoxetic Acid-enhanced MRI Characteristics of P53-mutated Hepatocellular Carcinoma. Radiology 2023;306:e220531. doi: 10.1148/radiol.220531
7. Calderaro J, Ziol M, Paradis V, Zucman-Rossi J. Molecular and histological correlations in liver cancer. J Hepatol 2019;71:616-630. doi: 10.1016/j.jhep.2019.06.001
8. Kitao A, Matsui O, Yoneda N, et al. Hepatocellular Carcinoma with beta-Catenin Mutation: Imaging and Pathologic Characteristics. Radiology 2015;275:708-717. doi: 10.1148/radiol.14141315
9. Sung YS, Park B, Park HJ, Lee SS. Radiomics and deep learning in liver diseases. J Gastroenterol Hepatol 2021;36:561-568. doi: 10.1111/jgh.15414

PS4-3

AI Based Pathology: A New Generation of Biomarkers for HCC

Julien Calderaro

Henri Mondor University Hospital, Créteil, France

AI is currently revolutionizing medicine, and in particular

image based fields such as pathology. A wide array of models have been develop to assist diagnosis, and extract clinically relevant information from digital slides. This lecture will focus on the application of AI based pathology for liver cancers.

The main opportunities and challenges will be discussed.

PS4-4

Predicting HCC Risk Using Artificial Intelligence

Jeong-Hoon Lee

Seoul National University, Seoul, South Korea

The prediction models are essential to improve medical practice, as far as they were established and validated properly. The prediction model may prognosticate patients' outcome, stratify risk groups to individualize their management, and maximize the cost-effectiveness of clinical practice. Although a number of prediction models have been developed, only a small fraction of these models are adopted in real-world clinical practice and, unfortunately, many published models are not utilized in practice as the predictive accuracy is suboptimal. There might be several reasons for producing suboptimal models, such as small number of samples in both training and validation sets and a low prediction accuracy of conventional regression statistics. In this regard, combining big data and the artificial intelligence (AI) modelling method is hopefully anticipated to upgrade the studies on developing a prediction model.

Our group has published an AI model to predict hepatocellular carcinoma (HCC) risk in chronic hepatitis B (CHB) patients undergoing antiviral treatment.1 Using a gradient-boosting machine algorithm, the model was developed using 6,051 Korean CHB patients and was validated in two external independent Korean (5,817 patients) and Caucasian (1,640 patients) validation cohorts. In the final model (designated as PLAN-B, find at https://planbhcc.com), the presence of cirrhosis, age, platelet count, kind of antiviral agent (entecavir or tenofovir disoproxil fumarate [TDF]), sex, serum levels of alanine aminotransferase, HBV DNA, albumin, and bilirubin, and HBeAg status at baseline were utilized. This PLAN-B model showed comparable discriminant function to model utilizing 17 variables at the first HBV DNA suppression under 2,000 IU/mL as well as at baseline, and outperformed preexisting prediction models including PAGE-B, modified PAGE-B, REACH-B, and CU-HCC in both Korean (c-index=0.79 vs. 0.64–0.74, all P<0.001) and Caucasian (c-index=0.81 vs. 0.57–0.79, all P<0.05 except for modified PAGE-B) validation cohorts. A calibration function of PLAN-B was also satisfactory. Now, we are trying to increase calibration function of the prediction model by incorporating additional variables such the presence of metabolic risk factors (i.e., diabetes, hypertension, dyslipidemia, and obesity),2 the use of chemopreventive agents (e.g., aspirin and statins),3-6 and body compositions using CT segmentation (e.g., total muscle mass, and visceral fat mass). In parallel, another AI model (designated as PLAN-S, find at https://planshcc.com) to select an optimal first-line antiviral treatment among entecavir and TDF considering differential HCC risk and other adverse events of TDF (i.e., bone loss and renal dysfunction) has been also developed and validated using multinational cohorts.7 The PLAN-S model was derived using 8 variables and can determine if an individual patient belong to the TDF-superior or TDF-nonsuperior group. In the TDF-superior group of the each cohort, TDF was associated with a significantly lower risk of HCC than ETV (hazard ratio=0.60–0.73, all P<0.05). In the TDF-nonsuperior group, however, there was no statistically significant difference between the 2 drugs (hazard ratio=1.16–1.29, all P>0.1).

These AI models could be utilized to personalize the management of CHB patients. A subgroup of patients with minimal risk of HCC according to the PLAN-B model may not have to undergo regular HCC surveillance considering cost-benefit. The PLAN-S model can advise to select an antiviral drug that is best for the patient for each patient. These AI models can be evolved by adding more variables form more patients.

References

1. Kim HY, Lampertico P, Nam JY, Lee HC, Kim SU, Sinn DH, Seo YS, et al. An artificial intelligence model to predict hepatocellular carcinoma risk in Korean and Caucasian patients with chronic hepatitis B. J Hepatol 2022;76:311-318.
2. Lee YB, Moon H, Lee JH, Cho EJ, Yu SJ, Kim YJ, Zoulim F, et al. Association of Metabolic Risk Factors With Risks of Cancer and All-Cause Mortality in Patients With Chronic Hepatitis B. Hepatology 2021;73:2266-2277.
3. Lee M, Chung GE, Lee JH, Oh S, Nam JY, Chang Y, Cho H, et al. Antiplatelet therapy and the risk of hepatocellular carcinoma in chronic hepatitis B patients on antiviral treatment. Hepatology 2017;66:1556-1569.
4. Goh MJ, Sinn DH, Kim S, Woo SY, Cho H, Kang W, Gwak GY, et al. Statin Use and the Risk of Hepatocellular Carcinoma in Patients With Chronic Hepatitis B. Hepatology 2020;71:2023-2032.
5. Jang H, Lee YB, Moon H, Chung JW, Nam JY, Cho EJ, Lee JH, et al. Aspirin use and risk of hepatocellular carcinoma in patients with chronic hepatitis B with or without cirrhosis. Hepatology 2022;76:492-501.
6. Simon TG, Duberg AS, Aleman S, Chung RT, Chan AT, Ludvigsson JF. Association of Aspirin with Hepatocellular Carcinoma and Liver-Related Mortality. N Engl J Med 2020;382:1018-1028.
7. Hur MH, Park MK, Yip TC, Chen CH, Lee HC, Choi WM, Kim SU, et al. Personalized Antiviral Drug Selection in Patients With Chronic Hepatitis B Using a Machine Learning Model: A Multinational Study. Am J Gastroenterol 2023.

Parallel Session 5. A New Era of Liver Transplantation Oncology

PS5-1

Extended Criteria for Liver Transplantation in HCC

Toru Ikegami

The Jikei University School of Medicine, Tokyo, Japan

In Japan, one third of the indications for living donor liver transplantation (LDLT) has been hepatocellular carcinoma although the annual number has declined since the mid-2000's. Because the 5-year survival of LDLT in total is 82.9% and the recurrence free survival after hepatic resection for Stage 1 hepatocellular carcinoma (HCC) is 82.5%, the acceptable survival rate of LDLT for HCC with extended criteria might be >80% at 5-year. The extended criteria in LDLT for HCC has been discussed by size and numbers, by tumor marker, by NLR or LMR, or by PET scan. The most classic extended criteria, in terms of size and number, has been presented as Tokyo criteria with 5-5 rule or UCSF criteria with Single tumor < 6.5cm or less than three tumors and total tumor diameter < 8cm, and total tumor volume criteria with 115 mm^3 as the cut off by Toso, et al. Many extended criteria in LDLT for HCC has been presented from the institutes of Japan and Korea. In Japan, Kaido, et al reported that Kyoto criteria Tumor number <10, tumor size < 5 cm, DCP < 400 ng/ml has the most significant inclusion/exclusion power among the similar criterion in Japan. In Korea, MoRAL score calculated by 11 √DCP + 2√AFP was reported and it seems strong power for inclusion/exclusion power. In Japan, Shimamura, et al analyzed whole Japanese national data for creation of new criteria for achieving a 5-year recurrence rate of < 10%, by evaluating n=965 patients, and concluded that <5 cm, n<5, AFP<500 included more patients in the new criteria with recurrence rate < 10%. It has been the new insurance limit since than in Japan. It has been also reported that NLR and LMR could be among the determinant factors for recurrence-free survival after LDLT for HCC in Japan, and TRAIN (Time–Radiological-response–Alpha-fetoprotein–Inflamation) score including NLR as well as number, size and tumor marker has been reported for representing NLR included in the scoring system for predicting survival after liver transplantation (LT) for HCC. The significance of PET scan for representing tumor behavior undergoing LT for HCC has been also among the topics. Finally, the feasibility of using immune check-point inhibitors has been the recent topics after LT, and review for the recent articles will be done in this paper.

PS5-2

Down-Staging and Waiting Times for Liver Transplantation in Advanced HCC

Dong Jin Joo

Yonsei University, Seoul, South Korea

Not all the hepatocellular carcinoma (HCC) can safely be treated by liver transplantation. Obviously, there should limitations to overcome HCC recurrence after liver transplantation. Traditionally, Milan criteria has been introduced as a safe edge to select patients who could have less recurrence rate of HCC after liver transplantation. However, this criterion is too limited to cure HCC patients. Thus, many centers have tried to overcome this limitation and expand the criteria.

Recently, many centers have been reported their own extended criteria with diverse parameters such as tumor volume, numbers, tumor markers, or SUV on PET. However, merely expanding the indication of liver transplantation for those advanced HCC patients is not enough to make the survival rate improved. The more advanced HCC, we could have the more HCC recurrence after liver transplantation. Thus, several centers have been trying to do down-staging before liver transplantation with various modalities. Waiting period after loco-regional treatment for down-staging should be necessary before liver transplantation to check tumor biology and responsiveness. Few Asian centers that are performing mostly living donor liver transplantation introduced successful down-staging to do liver transplantation even in the patients who had portal vein tumor thrombosis. This could be worthy challenge but still has higher HCC recurrence than the conventional criteria even though the results could be acceptable considering those patients' survival rate with other treatments.

We are still struggling with this issue how we could go with liver transplantation to treat locally far-advanced HCC. Liver transplant indication should be carefully expanded to give survival benefit to whom have advanced HCC but show good response after locoregional treatment.

References

1. Lee KW, Park JW, Joh JW, Kim SJ, Choi SH, Heo JS, Lee HH, Lee DS, Park JH, Yoo BC, Paik SW, Koh KC, Lee JH, Choi MS, Lee SK. Can we expand the Milan criteria for hepatocellular carcinoma in living donor liver transplantation? Transplant Proc 2004; 36: 2289-90.
2. Yao FY. Expanded criteria for hepatocellular carcinoma: down-staging with a view to liver transplantation--yes. Semin Liver Dis 2006; 26: 239-47.
3. Kwon CH, Kim DJ, Han YS, Park JB, Choi GS, Kim SJ, Joh JW, Lee SK. HCC in living donor liver transplantation: can we expand the Milan criteria? Dig Dis 2007; 25: 313-9.
4. Takada Y, Ito T, Ueda M, Sakamoto S, Haga H, Maetani Y, Ogawa K, Ogura Y, Oike F, Egawa H, Uemoto S. Living donor liver transplantation for patients with HCC exceeding the Milan criteria: a proposal of expanded criteria. Dig Dis 2007; 25: 299-302.
5. Hoffmann K, Hinz U, Hillebrand N, Radeleff BA, Ganten

TM, Schirmacher P, Schmidt J, Buchler MW, Schemmer P. Risk factors of survival after liver transplantation for HCC: a multivariate single-center analysis. Clin Transplant 2011; 25: E541-51.
6. Wigg A, Hon K, Mosel L, Sladden N, Palumbo K. Down-staging of hepatocellular carcinoma via external-beam radiotherapy with subsequent liver transplantation: a case report. Liver Transpl 2013; 19: 1119-24.
7. Han DH, Joo DJ, Kim MS, Choi GH, Choi JS, Park YN, Seong J, Han KH, Kim SI. Living Donor Liver Transplantation for Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis after Concurrent Chemoradiation Therapy. Yonsei Med J 2016; 57: 1276-81.

PS5-3

The Role of Transplantation in Combined Hepatocellular-Cholangiocarcinoma

Linda Wong

University of Hawaii, Honolulu, USA

Combined Hepatocellular and cholangiocarcinoma (HCC/CC) is a rare primary hepatic malignancy which is generally associated with poor prognosis due to its aggressive behavior. Because HCC/CC is such a rare entity, there are no established consensus guidelines or large studies to compare diagnostic or treatment modalities.

Surgical options are generally accepted as the best option for possible cure, however these lesions generally have a higher post-surgical recurrence rates compared to HCC alone. Like HCC, both liver resection and transplantation are options but which is chosen likely depend on the tumor size and extent of disease as well as the underlying liver function.

A review of 497 patients in the US SEER database (2004-2015) who had HCC/CC had 119 patients who underwent liver resection and 50 patients who underwent liver transplant (LT). The best predictors for 5-year survival included tumors < 5 cm and having undergone liver resection or transplant. LT had the highest Hazard Ratio for predicting 5-year survival. Asians and Pacific Islanders had a higher chance of 5-year survival compared to Whites and Blacks, for unclear reasons.

A multicenter analysis of 12 centers in the US reported 208 cases of HCC/CC who underwent LT. They found that patients with HCC/CC who met Milan had similar overall 5-year survival to those with HCC who met Milan, however there was much higher recurrence rate (23.1% compared to 11.5%). Patients who underwent transplant had improved disease free survival over resection.

The largest reported study of treatment for HCC/ICC was a meta-analysis of 42 observational studies with 1390 patients who underwent liver resection and 301 who underwent transplant for HCC/CC. In this particular analysis, there was no significant difference in survival and recurrence between liver resection and transplant.

Liver transplantation for HCC/CC is a reasonable option for select patients. Survival can be favorable however recurrence remains a problem. Many patients will not qualify for LT and patients may not sustain the wait for a suitable organ. More studies will need to be done to determine if locoregional therapy prior to LT will help bridge or downstage patients with this malignancy. Studies will also be needed to determine if immunosuppressive protocols or therapy can minimize the chance of recurrence.

References

1. Sempokuya T, Wien EA, Pattison R, Ma JH, Wong LL Factors associated with 5-year survival of combined hepatocellular and cholangiocarcinoma World J Hepatol 2020 Nov 27;12(11):1020-1030. doi: 10.4254/wjh.v12.i11.1020.
2. Dageforde LA, Vachharajani N, Tabrizian P, Agopian V et al. Multi-Center Analysis of Liver Transplantation for Combined Hepatocellular Carcinoma-Cholangiocarcinoma Liver Tumors Am Coll Surg. 2021 Apr;232(4):361-371. doi: 10.1016/j.jamcollsurg.2020.11.017. Epub 2020 Dec 13.
3. Li DB, Si XY, Wang SJ, Zhou YM. Long-term outcomes of combined hepatocellular-cholangiocarcinoma after hepatectomy or liver transplantation: A systematic review and meta-analysis. Hepatobiliary Pancreat Dis Int. 2019 Feb;18(1):12-18. doi: 10.1016/j.hbpd.2018.10.001. Epub 2018 Oct 25.

PS5-4

Multidisciplinary Approach for Post-Liver Transplantation Recurrence

Kenneth Siu Ho Chok

The University of Hong Kong, Hong Kong

Recurrent hepatocellular carcinoma after a liver transplant has been regarded as a terminal disease. Recurrent tumours often progressed rapidly under suppressed host immunity. Recent advances in immunosuppression, systemic and local therapy have led to a paradigm shift in management strategy. Patients with oligo-recurrence i.e., recurrent tumours limited in number and locations are treated with radical intent, by a combination of systemic and loco-regional therapy.

Dual-tracer Positron Emission Tomography-Computed Tomography provides comprehensive and precise staging after recurrence. It effectively diagnoses early recurrence and differentiates oligo-recurrence from more advanced disease. When oligo-recurrence is confirmed, radical therapy is associated with improved survival outcomes. Concomitant systemic control is essential. Targeted therapy will remain the mainstay systemic therapy in patient with post-transplant recurrence because immunotherapy is associated with fatal graft rejection. Mammalian Target of Rapamycin inhibitor-based immunosuppression also offers anti-tumour effect and is associated with improved survival in patients with recurrence. Apart from disease volume, clinical surrogates of tumour biology also determine prognosis and they included timing of recurrence and level of AFP upon recurrence. When poor prognostic factors are present, the benefit of radical therapy is reduced. The patient's fitness, procedural morbidity and

prognosis are important considerations when formulating the treatment plan for patients with post-transplant hepatocellular carcinoma recurrence.

Parallel Session 6. Recent Advance of Surgical Resection for HCC: Expanding the Surgical Indication

PS6-1

Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) for Unresectable HCC

Jian Zhou

Fudan University, Shanghai, China

Insufficient future liver remnant (FLR) is the bottleneck of liver surgery while the complexity of liver anatomy or technique is no longer obstacle. Liver tumors with insufficient FLR are considered as primarily unresectable. Resection after induction of FLR hypertrophy (two-stage hepatectomy, TSH) remains the mainstay though another strategy (resection after conversion therapy) is increasingly applied 1. Portal vein embolization (PVE) is traditional method for FLR hypertrophy but is with limited FLR increase and resection rate, especially in patient with chronic liver disease 2-4. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has emerged as a potential alternative to the PVE. ALPPS can induce rapid FLR hypertrophy and provides high tumor resection rate 5. Meanwhile, the safety of ALPPS has been considerably improved in recent years and the morbidity and mortality has been comparable to major hepatectomy although it has ever been criticized by early reports 5,6. As to colorectal cancer liver metastasis (CRLM) which is mostly indicated for ALPPS, ALPPS has become a therapeutic choice and recommended by some guidelines7. The oncological results showed that CRLM patients benefit well from ALPPS. The 1 year, 3 year and 5-year overall survival (OS) is >86, 50% and 27%, whereas the 1-year, 3-year and 5-year disease-free survival (DFS) is 59-67%, 13% and 12%, respectively 8-10. Studies including randomized controlled trial (RCT) show that ALPPS provides higher resection rate while the morbidity and mortality are similar with PVE-TSH 11. Patients undergoing PVE fail to achieve sufficient FLR can be rescued by ALPPS with successful rate of nearly 100% 11-13.

Recently ALPPS is increasingly applied for hepatocellular carcinoma (HCC) 14-24. Although early report by ALPPS registry report relatively high mortality and morbidity that invoke concerning about the safety of ALPPS for HCC 16, increasing studies including RCT show that ALPPS for HCC is feasible and patient with HCC can benefit from ALPPS 14-24. One of the major concerns regarding ALPPS for HCC is FLR hypertrophy in patients with chronic liver diseases. The FLR hypertrophy is negatively correlated with the severity of liver fibrosis 16,17,23. The fibrotic/cirrhotic liver is generally with limited hypertrophy through conventional ALPPS. Fortunately, a novel ALPPS variant, TAE-salvaged ALPPS (Zhou's ALPPS), has emerged and has been showed to be able to induce sufficient FLR increase in patients with severe fibrosis or cirrhosis and salvage patients who failed to conventional ALPPS 25,26. Another concern is the safety of ALPPS for HCC. The early report by international ALPPS registry reported high mortality (31%) and morbidity (62.9 %), which had ever sparked great controversy. However, several recent studies with large cohort showed that the 90-day mortality is 5.3-11.1% and overall morbidity is about 46.5% (major complication (≥IIIa) rate: 11.1-20.7%) 17,18,23,24. Technique modification has also been applied to decrease the mortality and morbidity. Anterior approach and minimally invasive approach including laparoscopic and robotic ALPPS have been used 19-21,27,28. The partial ALPPS is the most widely used ALPPS variant. However, it should be cautiously used for HCC patients with chronic liver disease. Chan et al 29 reported that partial ALPPS was with more limited FLR hypertrophy and higher mortality & morbidity as compared with classic ALPPS. Tourniquet ALPPS and radiofrequency ablation ALPPS (RALPPS) are also attempted and shown to be able to improve safety 22,30. But the FLR hypertrophy is relatively limited and long duration is often required as compared with conventional ALPPS. In some cases, rescue RALPPS is needed 31. The most concerning of ALPPS for HCC is the oncological benefits. Several studies including RCT report that the 1-year, 3-year and 5-year OS is 64.2%, 60.2%-65.8% and 46.8%, whereas the 1-year, 3-year and 5-year DFS is 47.6%, 43.9% and 25.0%, respectively 18,23,24. As compared with other treatments, RCT study or propensity Score Matching (PSM) analysis showed that the overall survival of ALPPS was superior to Transcatheter arterial chemoembolisation (TACE) and TACE+PVE, or comparable to PVE-TSH 17,23,24. However, large RCT studies are still needed to clarify the role of ALPPS for HCC.

References:

1. Sun HC, Zhou J, Wang Z, et al. Chinese expert consensus on conversion therapy for hepatocellular carcinoma (2021 edition). Hepatobiliary Surg Nutr 2022;11(2):227-252. (In eng). DOI: 10.21037/hbsn-21-328.
2. Zhang L, Yang Z, Zhang S, Wang W, Zheng S. Conventional Two-Stage Hepatectomy or Associating Liver Partitioning and Portal Vein Ligation for Staged Hepatectomy for Colorectal Liver Metastases? A Systematic Review and Meta-Analysis. Front Oncol 2020;10:1391. (In eng). DOI: 10.3389/fonc.2020.01391.
3. Tschuor C, Croome KP, Sergeant G, et al. Salvage parenchymal liver transection for patients with insufficient volume increase after portal vein occlusion -- an extension of the ALPPS approach. Eur J Surg Oncol 2013;39(11):1230-5. (In eng). DOI: 10.1016/j.ejso.2013.08.009.
4. Vyas SJ, Davies N, Grant L, et al. Failure of portal venous embolization. ALPPS as salvage enabling successful resection of bilobar liver metastases. J Gastrointest Cancer 2014;45 Suppl 1:233-6. (In eng). DOI: 10.1007/s12029-014-9643-6.
5. Lang H, de Santibanes E, Schlitt HJ, et al. 10th Anniversary of ALPPS-Lessons Learned and quo Vadis.

Ann Surg 2019;269(1):114-119. (In eng). DOI: 10.1097/sla.0000000000002797.
6. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg 2012;255(3):405-14. (In eng). DOI: 10.1097/SLA.0b013e31824856f5.
7. Zhou J, Sun H, Wang Z, et al. Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2019 Edition). Liver Cancer 2020;9(6):682-720. (In eng). DOI: 10.1159/000509424.
8. Schadde E, Ardiles V, Robles-Campos R, et al. Early survival and safety of ALPPS: first report of the International ALPPS Registry. Ann Surg 2014;260(5):829-36; discussion 836-8. (In eng). DOI: 10.1097/sla.0000000000000947.
9. Schadde E, Raptis DA, Schnitzbauer AA, et al. Prediction of Mortality After ALPPS Stage-1: An Analysis of 320 Patients From the International ALPPS Registry. Ann Surg 2015;262(5):780-5; discussion 785-6. (In eng). DOI: 10.1097/sla.0000000000001450.
10. Petrowsky H, Linecker M, Raptis DA, et al. First Long-term Oncologic Results of the ALPPS Procedure in a Large Cohort of Patients With Colorectal Liver Metastases. Ann Surg 2020;272(5):793-800. (In eng). DOI: 10.1097/sla.0000000000004330.
11. Sandstrom P, Rosok BI, Sparrelid E, et al. ALPPS Improves Resectability Compared With Conventional Two-stage Hepatectomy in Patients With Advanced Colorectal Liver Metastasis: Results From a Scandinavian Multicenter Randomized Controlled Trial (LIGRO Trial). Ann Surg 2018;267(5):833-840. (In eng). DOI: 10.1097/sla.0000000000002511.
12. Enne M, Schadde E, Bjornsson B, et al. ALPPS as a salvage procedure after insufficient future liver remnant hypertrophy following portal vein occlusion. HPB (Oxford) 2017;19(12):1126-1129. (In eng). DOI: 10.1016/j.hpb.2017.08.013.
13. Sparrelid E, Gilg S, Brismar TB, Lundell L, Isaksson B. Rescue ALPPS is efficient and safe after failed portal vein occlusion in patients with colorectal liver metastases. Langenbecks Arch Surg 2017;402(1):69-75. (In eng). DOI: 10.1007/s00423-016-1524-y.
14. Lai Q, Mennini G, Larghi Laureiro Z, Rossi M. Uncommon indications for associating liver partition and portal vein ligation for staged hepatectomy: a systematic review. Hepatobiliary Surg Nutr 2021;10(2):210-225. (In eng). DOI: 10.21037/hbsn-20-355.
15. Deng Z, Jin Z, Qin Y, et al. Efficacy of the association liver partition and portal vein ligation for staged hepatectomy for the treatment of solitary huge hepatocellular carcinoma: a retrospective single-center study. World Journal of Surgical Oncology 2021;19(1):95. DOI: 10.1186/s12957-021-02199-1.
16. D'Haese JG, Neumann J, Weniger M, et al. Should ALPPS be Used for Liver Resection in Intermediate-Stage HCC? Ann Surg Oncol 2016;23(4):1335-43. (In eng). DOI: 10.1245/s10434-015-5007-0.
17. Wang Z, Peng Y, Hu J, et al. Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy for Unresectable Hepatitis B Virus-related Hepatocellular Carcinoma: A Single Center Study of 45 Patients. Ann Surg 2020;271(3):534-541. (In eng). DOI: 10.1097/sla.0000000000002942.
18. Chan A, Zhang WY, Chok K, et al. ALPPS Versus Portal Vein Embolization for Hepatitis-related Hepatocellular Carcinoma: A Changing Paradigm in Modulation of Future Liver Remnant Before Major Hepatectomy. Ann Surg 2019 (In eng). DOI: 10.1097/sla.0000000000003433.
19. Chan AC, Pang R, Poon RT. Simplifying the ALPPS procedure by the anterior approach. Ann Surg 2014;260(2):e3. (In eng). DOI: 10.1097/sla.0000000000000736.
20. Chan AC, Poon RT, Lo CM. Modified Anterior Approach for the ALPPS Procedure: How We Do It. World J Surg 2015;39(11):2831-5. (In eng). DOI: 10.1007/s00268-015-3174-6.
21. Chan AC, Poon RT, Chan C, Lo CM. Safety of ALPPS Procedure by the Anterior Approach for Hepatocellular Carcinoma. Ann Surg 2016;263(2):e14-6. (In eng). DOI: 10.1097/sla.0000000000001272.
22. Cai X, Tong Y, Yu H, et al. The ALPPS in the Treatment of Hepatitis B-Related Hepatocellular Carcinoma With Cirrhosis: A Single-Center Study and Literature Review. Surg Innov 2017;24(4):358-364. (In eng). DOI: 10.1177/1553350617697187.
23. Li PP, Huang G, Jia NY, et al. Associating liver partition and portal vein ligation for staged hepatectomy versus sequential transarterial chemoembolization and portal vein embolization in staged hepatectomy for HBV-related hepatocellular carcinoma: a randomized comparative study. Hepatobiliary Surg Nutr 2022;11(1):38-51. (In eng). DOI: 10.21037/hbsn-20-264.
24. Chan A, Zhang WY, Chok K, et al. ALPPS Versus Portal Vein Embolization for Hepatitis-related Hepatocellular Carcinoma: A Changing Paradigm in Modulation of Future Liver Remnant Before Major Hepatectomy. Ann Surg 2021;273(5):957-965. (In eng). DOI: 10.1097/sla.0000000000003433.
25. Wang Z, Peng Y, Sun Q, et al. Salvage transhepatic arterial embolization after failed stage I ALPPS in a patient with a huge HCC with chronic liver disease: A case report. Int J Surg Case Rep 2017;39:131-135. (In eng). DOI: 10.1016/j.ijscr.2017.07.034.
26. Peng Y, Wang Z, Qu X, et al. Transcatheter arterial embolization-salvaged ALPPS, a novel ALPPS procedure especially for patients with hepatocellular carcinoma and severe fibrosis/cirrhosis. Hepatobiliary Surgery and Nutrition 2022;11(4):504-514. (https://hbsn.amegroups.com/article/view/95042).
27. Serenari M, Ratti F, Zanello M, et al. Minimally Invasive Stage 1 to Protect Against the Risk of Liver Failure: Results from the Hepatocellular Carcinoma Series of the Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy Italian Registry. J Laparoendosc Adv Surg Tech A 2020;30(10):1082-1089. (In eng). DOI: 10.1089/lap.2020.0563.
28. Hu M-G, Wang J, Yin Z-Z, Liu R. First two-stage robotic ALPPS in HCC patients with hepatic vein invasion: a step-by-step procedure from a clinical case. World Journal of Surgical Oncology 2021;19(1):58. DOI: 10.1186/s12957-021-02170-0.
29. Chan ACY, Chok K, Dai JWC, Lo CM. Impact of split completeness on future liver remnant hypertrophy in associating liver partition and portal vein ligation for staged

hepatectomy (ALPPS) in hepatocellular carcinoma: Complete-ALPPS versus partial-ALPPS. Surgery 2017;161(2):357-364. (In eng). DOI: 10.1016/j.surg.2016.07.029.
30. Wang Q, Yan J, Feng X, et al. Safety and efficacy of radiofrequency-assisted ALPPS (RALPPS) in patients with cirrhosis-related hepatocellular carcinoma. Int J Hyperthermia 2017;33(7):846-852. (In eng). DOI: 10.1080/02656736.2017.1303752.
31. Wang Q, Chen S, Yan J, et al. Rescue radiofrequency ablation or percutaneous ethanol injection: a strategy for failed RALPPS stage-1 in patients with cirrhosis-related hepatocellular carcinoma. BMC Surg 2021;21(1):246. (In eng). DOI: 10.1186/s12893-021-01241-z.

PS6-2

Surgical Resection of Multiple HCCs

Shin Hwang

University of Ulsan, Seoul, South Korea

Multifocality of hepatocellular carcinoma (HCC) indicates presence of occult tumors in the liver. A large HCC with multiple small tumors is usually not indicated for surgical resection because such small tumors can be regarded as metastatic tumors. By contrast, relatively small multiple HCCs have been regarded as multifocal tumors, thus being indicated for surgical resection. A Korean single-center study revealed that risk factors for post-resection recurrence included total tumor diameter ≥ 6 mm, alpha-fetoprotein ≥ 400 ng/mL and indocyanine green retention rate at 15 minutes ≥ 15%. Another Korean single-center study suggested that, among patients with two or three HCCs, no radiologic vascular invasion, and tumor diameters ≤ 5 cm, surgical resection is recommended only in those without cirrhosis, compared with those who underwent transarterial chemoembolization (TACE). Early multiple tumor recurrence after resection of oligonodular HCCs is a common finding, thus repeated sessions of TACE have been frequently followed. Considering such high risk of post-resection recurrence, wait-and-see policy after TACE can be used as eligibility criteria for stage surgical resection. Protocol TACE at 1 month after surgical resection can be a reasonable adjuvant treatment, as shown in the experience with resection of large HCC. ADV score, which is calculated by multiplying α-fetoprotein and des-γ-carboxyprothrombin concentrations and tumor volume, is an integrated prognostic predictor of HCC following liver resection and transplantation. ADV score <5log can be used as a prognostic indicator for surgical resection of oligonodular HCCs. So far, there is no convincing guidelines for surgical resection of multiple HCCs. Individualized therapeutic approach is necessary to enhance the treatment outcomes in resection of multiple HCCs after consideration of morphological tumor extent, tumor biology, liver cirrhosis, and general condition of the patients.

PS6-3

Surgical Resection for Intrahepatic and Extrahepatic Recurrent HCC

Etsuro Hatano

Kyoto University, Kyoto, Japan

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. Of the available treatment options, surgical resection can yield significant benefit in the setting of the first occurrence. Meanwhile, it should be acknowledged that the extremely high recurrence ratio of HCC requires the optimal management; however, the available guidelines does not show definitive recommendation due to the lack of evidences.

From the available data, surgical resection appears to offer substantial benefits for both intrahepatic and extrahepatic recurrences of HCC, if an appropriate patient selection is performed ahead. To optimize the value of surgical resection for recurrent HCC, this presentation focuses on the surgical perspective of HCC recurrence, categorizing it into i) intrahepatic recurrence, ii) extrahepatic recurrence, and iii) concomitant intra and extrahepatic recurrence.

The objective of this presentation is to enhance understanding and optimize the surgical management of recurrent HCC by highlighting the existing evidence in the surgical perspective.

PS6-4

Laparoscopic Repeated Liver Resection for Recurrent HCC

Zenichi Morise

Fujita Health University, Toyoake, Japan

Treatment of multicentric metachronous recurrence is one of the major issues for HCC patients with chronic liver diseases as neoplastic backgrounds. Although indications of laparoscopic liver resection (LLR) have been expanded, there are increased risks of intraoperative complications and conversion in repeat LLR. Adhesion from previous surgeries and deformity of the major structures from resections increase the difficulties of tumor localization and the risk of disorientation leading to vessel injury and insufficient tumor margin. On the other hand, LLR could make postoperative adhesion from previous surgery lighter and, also, the lap-specific "caudal approach" decreases the needs for adhesiolysis when the adhesion does not affect needed surgical field. LLR using preoperative simulation and intraoperative navigation can make the risks above mentioned lower and earn the advantages above mentioned.

We experienced 50 repeat LLR and 15 multiple-repeat (up to 5) LLR. In the comparison between 152 primary LLR vs 50 repeat LLR vs 15 multiple-repeat LLR, excluding the cases with combined resection of the other organs and more-than-section LLR, operation time, intraoperative bleeding, LOS, conversion and morbidity were Mean 319(Median 300): 310(275): 303(274) min,

281(100): 281(50): 436(75) ml, 18(14): 18(13): 24(15)days, 4/152: 1/50: 1/15cases, 13/152: 5/50: 2/15cases. There were no significant differences, although longer operation time and larger amount of bleeding are usually observed in open repeat surgery due to (usually total) adhesiolysis.

Furthermore, our conducted international multicenter study of 42 high-volume liver surgery centers with 1582 patients (648 laparoscopic and 934 open surgery cases) showed that laparoscopic (vs. open) repeat liver resection for HCC resulted in less intraoperative blood loss (P=0.01), a longer operation time (P=0.07), and similar survival time (median 4582 days vs. 3264 days, P=0.0855) after propensity score-based matching. Furthermore, when 620 cases without the proximity to major vessels (less complicated cases) were selected and earned propensity score-based matching groups of lap and open repeat LR were compared, less blood loss (P=0.001) and less morbidity (P=0.034) were shown with comparable operation time in lap repeat LR group. It was also speculated that repeat LLR caused less liver functional deterioration than open repeat liver resection.

There should be a chance to prolong the overall survival of HCC patients by using LLR as a powerful local therapy which can be applied repeatedly with minimal deterioration of liver function.

Parallel Session 7. Various Classification of Liver Cancer towards Precision Medicine

PS7-1

Morphological Classification of HCC and Potential Clinical Implications

Haeryoung Kim

Seoul National University, Seoul, South Korea

Although hepatocellular carcinoma (HCC) is simply defined as a malignant neoplasm demonstrating hepatocellular differentiation, there is considerable diversity in the molecular and histological features. In the recent several years, associations between specific morphological features and molecular alterations of HCCs have been identified, resulting in several histopathological variants of HCCs that are not only unique in morphology but also have translational implications.

One example is macrotrabecular-massive HCC, which is defined as an HCC that demonstrates the characteristic macrotrabecular pattern in at least 50% of the tumor area. This variant is characterized by more frequent TP53 alterations, FGF19 amplifications and an aggressive behavior. In addition, vessels-encapsulating-tumor-clusters (VETC) patterns are frequently seen in this variant; this feature has been demonstrated to be a negative prognostic factor and potentially a predictor for effective response to sorafenib treatment. Scirrhous HCC is another example of a histological variant. It demonstrates more frequent TSC1/TSC2 mutations and TGF-β pathway activation, and although the clinical outcome is still controversial, this variant has been associated with aggressive clinicopathological features and survival has shown to be poorer compared to conventional HCCs in the larger tumors. Steatohepatitic HCC is another distinctive variant of HCC which demonstrates histological features of steatohepatitis in the tumor, such as tumor cell steatosis, ballooning of tumor cells, inflammatory cell infiltration and the characteristic perisinusoidal pattern of fibrosis. It is more frequently associated with alterations in the IL-6/JAK/STAT pathway and underlying metabolic syndrome. With the increasing global prevalence of non-alcoholic fatty liver disease, it is expected that the relative frequency of this variant will rise over the next few decades. In this talk, the various histological variants of HCC and the associated translational implications will be discussed.

PS7-2

Stratification of HCC: Cellular, Molecular and Blood-Based Biomarkers

Irene Oi-Lin Ng

The University of Hong Kong, Hong Kong

Our increasing understanding of hepatocellular carcinoma (HCC) biology holds promise for personalized care and the development of drugs. However, HCC is characterized by significant inter-tumoral heterogeneity, as well as considerable molecular and genetic heterogeneity. This presentation attempts to highlight the recent advances in dissecting the cellular and molecular features for biomarkers in HCC for better patient stratification for treatment and management. Recent data will be discussed, and representative examples will be shared to demonstrate important molecular targets and molecular biomarkers of HCC identified by genomic, genetic and molecular analysis of patients' HCC samples. The tumor microenvironment is composed of many different cellular and non-cellular components that together drive tumor growth, invasion, metastasis, and response to therapies. There is increasing evidence supporting the importance of tumor microenvironment in providing a favorable and supportive niche to expedite HCC development. Studies of the tumor immune microenvironment propose different classes of HCC patients according to the expression signatures of immune cells. Recently, the cutting-edge technology of single cell analysis has provided important information of its intratumoral heterogeneity and is able to identify important sub-populations, including the immune landscape. In addition, the molecular determinant of response to immune checkpoint inhibitor is a hot topic which will improve the understanding and facilitate potential patient selection for the treatment. Discoveries and insight into the complex pathways have created opportunities for molecular targets and biomarkers and new therapeutic approaches for this malignant disease.

PS7-3

Correlation of Imaging and Molecular-Pathologic Subtypes of HCC

Jin Young Choi

Yonsei University, Seoul, South Korea

Hepatocellular carcinoma (HCC) is a heterogeneous group of tumors that exhibit varying degrees of biologic aggressiveness, as determined by tumor grade, vascular invasion, and pathologic and molecular classification. While our understanding of the prognostic implications of different pathologic and molecular phenotypes of HCC is still evolving, emerging data suggest that certain imaging features, as well as radiologic, pathologic, or radiologic-molecular phenotypes, may enable prediction of patient prognosis.

Although imaging plays an important role in the diagnosis of HCC, current imaging algorithms do not incorporate prognostic features or subclassification of HCC based on biologic aggressiveness. In this lecture, I will review the current knowledge of the histologic heterogeneity of HCC, correlated with features on liver MRI. Additionally, HCC subtype classification according to transcriptomic profiles will be outlined with description of histologic, genetic and molecular characteristics of some relatively well-established morphologic subtypes, namely the low proliferation class and the high proliferation class.

Further research on the radiological characteristics of HCC subtypes may ultimately enable non-invasive diagnosis and serve as a biomarker for predicting prognosis, molecular characteristics, and therapeutic response. A multidisciplinary effort to develop an integrated radiologic and clinical diagnostic system for the various HCC subtypes is necessary for precise patient management.

PS7-4

Biopsy for HCC: Tissue or Liquid?

Xin-Rong Yang

Fudan University, Shanghai, China

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a leading cause of cancer-related deaths worldwide[1]. Accurate diagnosis and characterization of HCC are crucial for effective treatment planning. Traditionally, tissue biopsy has been the gold standard for diagnosing HCC, providing histological and molecular information. But it is associated with potential complications, such as bleeding and tumor seeding, and may not always be feasible due to tumor location or patient comorbidities[2, 3]. In the past decade, liquid biopsy has emerged as a promising non-invasive alternative for early detecting and monitoring HCC. Liquid biopsy offers several advantages over tissue biopsy, including the ability to capture tumor heterogeneity, enable repeated sampling, and provide real-time monitoring of tumor dynamics. By analyzing substances such as circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), circulating micro-RNA (miRNA) and exosomes, etc, liquid biopsy can offer a more comprehensive understanding of tumor heterogeneity and facilitate the development of personalized treatment strategies.

For over a decade, our research group has been dedicated to the field of liquid biopsies, specifically focusing on circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA). Our extensive investigations have systematically explored the crucial roles of CTCs in HCC metastasis and recurrence. Building upon this knowledge, we have successfully established an early warning system based on CTCs for clinical applications. To enhance CTC detection in HCC patients and enable subsequent single-cell staining, morphological analysis, and genome sequencing, we have developed the ChimeraX platform—an automated CTC detection platform. This platform has significantly improved the CTC enrichment rate [4]. Utilizing droplet digital PCR (ddPCR) technology, we have achieved successful detection of ctDNA in HCC patients. This approach allows for the discrimination of early-stage HCC, identification of mutations for targeted therapy, and prediction of prognosis following immunotherapy [5, 6]. In our research, we utilized the 5hmC-Seal technique to develop a 32-gene diagnostic model that accurately distinguishes early HCC (stage 0/A) based on the Barcelona Clinic Liver Cancer staging system from non-HCC cases. This model demonstrated superior performance compared to the traditional biomarker α-fetoprotein (AFP), with a validation set area under the curve (AUC) of 88.4% [7]. Furthermore, we have established a 7-miRNAs-based diagnostic model that significantly improves the sensitivity (81.8%) and specificity (83.5%) of HCC diagnosis. This model proves particularly effective in AFP-negative and very early-stage HCC cases, outperforming traditional plasma biomarkers and imaging tools [8]. This examination has been implemented in multiple clinical medical centers in China.

In sum, liquid biopsy holds immense promise as a minimally invasive tool for early detection, dynamic monitoring, and assessment of therapeutic targets in HCC. Through our research efforts, we strive to contribute to the advancement and application of liquid biopsy techniques in the field of HCC.

References

1. Sung, H., et al., Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians, 2021. 71(3): p. 209-249.
2. Krebs, M.G., et al., Practical Considerations for the Use of Circulating Tumor DNA in the Treatment of Patients With Cancer: A Narrative Review. JAMA Oncology, 2022. 8(12): p. 1830-1839.
3. Gonçalves, E., et al., DNA methylation fingerprint of hepatocellular carcinoma from tissue and liquid biopsies. Scientific Reports, 2022. 12(1): p. 11512.
4. Wang, P.-X., et al., Circulating tumor cell detection and single-cell analysis using an integrated workflow based on ChimeraX® -i120 Platform: A prospective study. Molecular Oncology, 2021. 15(9): p. 2345-2362.
5. Huang, A., et al., Detecting Circulating Tumor DNA in Hepatocellular Carcinoma Patients Using Droplet Digital PCR Is Feasible and Reflects Intratumoral Heterogeneity. Journal of Cancer, 2016. 7(13): p. 1907-1914.
6. Zhu, G.-Q., et al., Serial circulating tumor DNA to predict early recurrence in patients with hepatocellular carcinoma: a

prospective study. Molecular Oncology, 2022. 16(2): p. 549-561.
7. Cai, J., et al., Genome-wide mapping of 5-hydroxymethylcytosines in circulating cell-free DNA as a non-invasive approach for early detection of hepatocellular carcinoma. Gut, 2019. 68(12): p. 2195-2205.
8. Zhou, J., et al., Plasma microRNA panel to diagnose hepatitis B virus-related hepatocellular carcinoma. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 2011. 29(36): p. 4781-4788.

Presidential Lecture

Evolution of APPLE and Liver Cancer Management

Norihiro Kokudo, Peipei Song

National Center for Global Health and Medicine, Tokyo, Japan

Liver cancer is most prevalent in the Asia-Pacific region, accounting for more than half of all cases worldwide. The Asia-Pacific Primary Liver Cancer Expert Association (APPLE) was developed to facilitate the exchange of international and regional expertise in the research and management of liver cancer. The APPLE Conference started in Incheon in 2010, followed by Osaka in 2011, Shanghai in 2012, Busan in 2013, Taipei in 2014, Osaka in 2015, Hong Kong in 2016, Singapore in 2017, Seoul in 2018, Sapporo in 2019, and Shanghai in 2022. And this year, APPLE 2023 Conference goes back to Seoul again. Moreover, since the great success of APPLE Single Topic Conference 2020 organized by Prof. Ghassan K Abou-Alfa and Prof. Linda L Wong, APPLE expanded to the American Continent and became a more influential Asia-Pacific academic society. We look forward to the APPLE 2024 Conference to be held in Hawaii.

Along with the continuous growth of APPLE, we have been experiencing a dramatic development of new drugs coming up in the field of liver cancer. Since the introduction of sorafenib in 2008, at least 6 regimens have been approved in Japan. According to the Japanese nationwide registry of systemic therapy for HCC named Hepatoma Registry of Integrating and Aggregating Electric Health Records (HERITAGE), 6,400 treatment lines (sorafenib 2,319, lenvatinib 2,559, atezolizumab plus bevacizumab 768, regorafenib 406, ramucirumab 251, cabozantinib 71) have been identified in 4,307 cases treated between 2015 and 2022 (Asaoka 2023 ASCO-GI). The MDT approach has become more crucial for the optimal management of each patient. Adjuvant or neoadjuvant systemic treatment strategy for liver resection or RFA has also become an important clinical issue and now at least several prospective trials are on-going. Real-world big data analytics using artificial intelligence (AI) may be a future promising direction. APPLE Association will continue to provide an ideal platform to facilitate the exchange of international and regional expertise in the research and management of liver cancer.

State-of-the-Art Lecture 1

When We Should Consider the Biopsy for Diagnosis, Subtyping, and Prognostication of Primary Liver Cancer: Radiologist's Perspective

Kathryn J. Fowler

University of California San Diego, San Diego, USA

I will discuss role of biopsy in diagnosis of HCC and review the potential for prognostic information.

Also, I will explain the current landscape of therapy and how tissue sampling may impact treatments.

State-of-the-Art Lecture 2

Systemic Therapies for HCC: Expanding Indications

Ghassan Abou-Alfa

Memorial Sloan Kettering Cancer Center, New York, USA

The advent of novel therapeutics for HCC has been monumental. This is especially critically needed at the time the incidence and mortality of HCC continue to increase, especially with the global expansion of non-alcoholic fatty liver disease as the most newly further appreciated risk factor.

Hepatocellular carcinoma novel therapies are mostly based on the better understanding of its biologic add to the start of a better understanding of its tumor immune microenvironment. Further appreciation of the genetic profile lagged behind, but already ongoing in view of the now very appreciated need for pathology diagnosis and thus access to tissue for next generation sequencing, hoping this will help identify novel targeted therapeutic approaches.

Checkpoint inhibitors in combination with other checkpoint inhibitors antiangiogenic therapy has been the most gratifying advent in systemic therapy. The combination of durvalumab plus tremelimumab has shown an improvement in overall survival of 16.43 months compared to single agent sorafenib 13.77 months. Atezolizumab plus bevacizumab also showed a clinical and statistical improvement in overall survival of 19.2 months compared to sorafenib 13.2 months. Camrelizumab plus rivoceranib also showed an improvement in overall survival of 22.1 months also a clinical and statistical improvement in overall survival compared to sorafenib 15.2 months.

A thorough understanding of the demographics and HCC etiologies in those studies is key. The positive overall survival outcomes are not to be compared but be understood in the context of the demographics of each study population. While all patients independent of the HCC etiology did fare well using the different combination therapies, patients with hepatitis B etiology fared the best outcome, followed by hepatitis C, then non-viral. This explains

how the two hepatitis B etiology enriched populations studies atezolizumab plus bevacizumab and camrelizumab plus rivoceranib showed the best of overall survival outcome. A recent real-world data study of atezolizumab plus bevacizumab though, showed a reduced improvement in overall survival to 15.74 months, reflective of the global more diverse population among all etiologies. This is like the largest study in first line HCC, the HIMALAYA durvalumab plus tremelimumab study global population of close to 1200 patients. This is further best understood in the camrelizumab plus rivoceranib with significant overall survival improvement of 22.l versus 15.2 compared to sorafenib with more than 70% of the subject have hepatitis B etiology based HCC.

Other combinations especially with tyrosine kinase inhibitors has been disappointingly negative though. An evaluation of lenvatinib plus pembrolizumab versus lenvatinib showed no significant improvement in overall survival for the combination, with impressive improvement in overall survival of 19 months for single agent lenvatinib. Same for atezolizumab plus cabozantinib compared to sorafenib. These studies suggest an equivalency of single agent checkpoint inhibitors and tyrosine kinase inhibitors. This is further proven by the HIMALAYA study secondary endpoint that showed equivalent median overall survival of 16.56 months for single agent durvalumab compared to 13.77 months for sorafenib. Similarly, tislelizumab showed noninferior medial overall survival of 15.9 months to sorafenib 14.1 months in patients with unresectable HCC.

These positive outcomes and robust improvements in overall survival facilitated a reverse trend of using systemic therapy for locally advanced disease. This is supported by the better understanding and the different categories of locally advanced disease and the appreciation of demonstrated benefit for systemic therapy compared to local therapy in the beyond up to seven criteria tumors (measured by diameters of largest lesion added to the total number of lesions in the liver). Further developments are already underway exploring the combination of local therapy plus checkpoint inhibitors and even with added anti-FGF tyrosine kinase inhibitors like in the EMERALD-3 study.

The story continues to evolve and sure more data will be coming. For sure what one may have thought as a straightforward positive outcome of combination or single agent checkpoint inhibitors therapies. While further data and better understanding to come out, this did not yet take away the value of the single agent tyrosine kinase inhibitors, still the most commonly accessed therapy worldwide.

State-of-the-Art Lecture 3

Update on the Molecular-Pathological Features of HCC and Cholangiocarcinoma

Young Nyun Park

Yonsei University, Seoul, South Korea

Two main primary liver carcinomas are hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA). HCC is heterogeneous in moleculopathological features and biologic behavior. Large-scale genetic studies of HCC have been accumulated, and a pathological-molecular classification of HCC has been proposed. According to updated WHO Classification of Digestive System Tumors 5th edition, about 35 % of HCCs can be classified into distinct histopathological subtypes according to their molecular characteristics. Among the recently identified subtypes, macrotrabecular massive (MTM)-HCC, neutrophil-rich HCC, vessels encapsulating tumor clusters (VETC)-HCC, and progenitor phenotype HCC (HCC with CK19 expression) are associated with poor prognosis, and lymphocyte-rich HCC subtype is related to better prognosis.

HCC with K19 expression, 4–28% of HCCs shows clinical characteristics of higher serum alpha-fetoprotein (AFP) levels, frequent association with chronic hepatitis B, and lymph node metastasis. Histomorphologically, K19-positive HCCs demonstrate a more infiltrative growth, poor differentiation, more frequent vascular invasion, and more intratumoral fibrous stroma than K19-negative HCCs. From the molecular aspect, K19-positive HCCs have been matched with various gene signatures associated with stemness and poor prognosis, including the G1 group, S2 class, cluster A, proliferation signature, vascular invasion signature, and cholangiocarcinoma-like gene expression trait. K19-positive HCCs also show upregulated signatures related to transforming growth factor-β pathway and epithelial-to-mesenchymal transition (EMT). The main regulators of K19 expression include hepatocyte growth factor-MET paracrine signaling by cancer-associated fibroblast, epidermal growth factor-epidermal growth factor receptor signaling, laminin, and DNA methylation. K19-positive HCCs are characterized by increased telomere length, increased expression of hTERT and shelterin complex proteins, and increased chromosomal instability compared to K19-negative HCCs.

MTM-HCC, 5–20% of HCCs shows macrotrabeculae (> 6~10 cells in thickness) in at least 50% of the tumor. The molecular feature of this variant is characterized by frequent TP53 mutation, FGF19 amplification and angiogenesis activation including high ANGPT2 mRNA levels. MTM-HCCs show frequent HBV infection, frequent vascular invasion, poor differentiation, CK19 expression, high serum AFP levels and a poor clinical outcome. VETC-HCC, about 19% of HCCs shows high serum AFP levels, larger tumor size, poor differentiation, macrotabecular pattern, and frequent vascular invasion. Interestingly, VETC-HCC and MTM-HCC show a tendency of pulmonary metastasis, in contrast to lymph node metastasis in HCC with K19 expression.

iCCA is an aggressive primary liver malignancy with an increasing incidence worldwide. Recently, histopathologic classification of small duct type and large duct type iCCA has been introduced. Small duct type iCCA is composed of non-mucin-producing cuboidal cells, whereas large duct type iCCA is composed of mucin-producing columnar cells, reflecting different cells of origin. Large duct type iCCA shows more invasive growth and poorer prognosis than small duct type iCCA. The liver milieu of small duct type iCCA often shows chronic liver disease related to hepatitis B or C viral infection, or alcoholic or non-alcoholic fatty liver disease/ steatohepatitis, in contrast to large duct type iCCA that is often related to hepatolithiasis and liver fluke infection. Data from recent large-scale exome analysis have revealed the

heterogeneity in the molecular profiles of iCCA, showing that small duct type iCCA exhibit frequent BAP1, IDH1/2 hotspot mutations and FGFR2 fusion, in contrast to frequent mutations in KRAS, TP53, and SMAD4 observed in large duct type iCCA. Multi-omics analysis have proposed several molecular classifications of iCCA, including inflammation class and proliferation class. The inflammation class is enriched in inflammatory signaling pathways and expression of cytokines, while the proliferation class activates oncogenic growth signaling pathways.

Interestingly, an integrative analysis of transcriptome profiles of primary liver cancer revealed an iCCA-like HCC and HCC-like iCCA, suggesting a continuous molecular spectrum between HCC and iCCA. iCCA-like HCC is characterized by expression of the progenitor cell-like trait, TP53 mutations, and rim arterial-phase hyperenhancement in MRI and shows more aggressive behavior compared to typical HCC. HCC-like iCCA is mainly histopathological small duct type, associated with HCC-related etiologic factors and shows a better prognosis compared to typical iCCA. Diverse pathologic features of HCC and iCCA and their associated multi-omics characteristics are currently under active investigation, thereby providing insights into precision therapeutics for patients with HCC and iCCA. This lecture will provide the latest knowledge on the histopathologic classification of HCC and iCCA and their associated molecular features, ranging from tumor microenvironment to genomic and transcriptomic research.

Poster Abstracts

Oral Poster Presentation

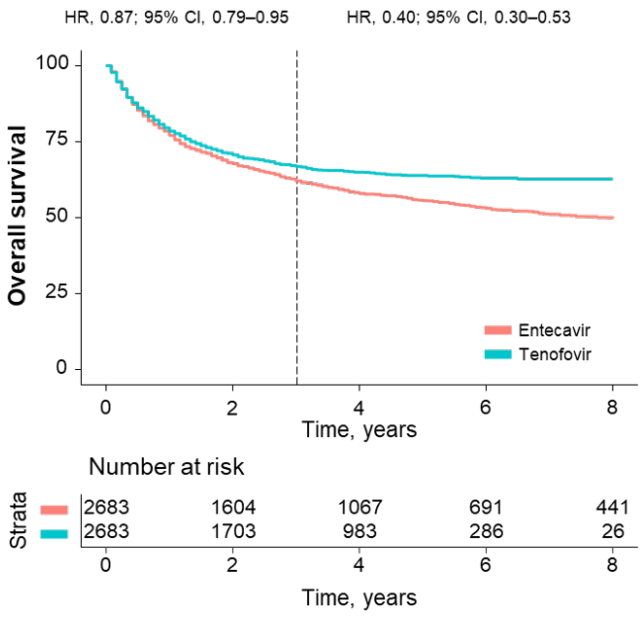
OP-01

A Better Prognosis of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Receiving Tenofovir Compared with Entecavir

Sung Won Chung, Hyun Jun Um, Jonggi Choi, Danbi Lee, Ju Hyun Shim, Kang Mo Kim, Young-Suk Lim, Han Chu Lee, Won-Mook Choi

Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: Whether tenofovir or entecavir has different effects on the prevention of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) in secondary and tertiary preventive settings remains controversial. This study was aimed to compare the long-term prognosis of HCC between tenofovir and entecavir in patients with chronic hepatitis B (CHB). **Methods:** CHB patients who were diagnosed with HCC between November 2008 and December 2018 and were treated with either entecavir (n = 3,469) or tenofovir (n = 3,056) at a tertiary center in Korea were included. The effect of tenofovir vs. entecavir on the prognosis of HBV-related HCC was evaluated in a propensity score (PS)-matched cohort. Various predefined subgroup analyses were performed. **Results:** The mean (SD) age was 54.6 (9.1) years, and 4,351 patients (81.1%) of the PS-matched cohort of 5,366 patients were male. During a median follow-up period of 3.0 years, entecavir-treated patients had a mortality rate of 43.0%, whereas tenofovir-treated patients had a mortality rate of 33.5%. Overall survival (OS) was better in tenofovir-treated patients compared with entecavir-treated patients (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.73–0.88). The difference in OS probability between the two groups became more pronounced over time. The magnitude of the risk difference in OS after 3 years of HCC diagnosis (HR, 0.40; 95% CI, 0.30–0.53) was more prominent than that within 3 years (HR, 0.87; 95% CI, 0.79–0.95). In all subgroup analyses, tenofovir was associated with a better OS than entecavir, except for those with advanced or terminal stage HCC. For those who received curative-intent treatment, recurrence-free survival (HR, 0.83; 95% CI 0.73–0.95) and OS (HR, 0.63; 95% CI 0.50–0.79) were better with tenofovir compared with entecavir. **Conclusions:** In patients with HBV-related HCC, tenofovir showed a better prognosis than entecavir, especially in those who survived longer. **Keywords:** Antiviral, Nucleotide Analogue



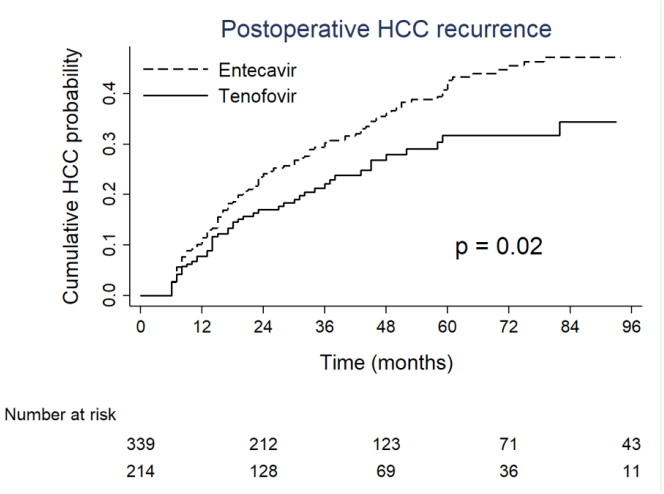
OP-02

Comparison of the Effects of Entecavir and Tenofovir Disoproxil Fumarate on Recurrence of Hepatocellular Carcinoma after Surgical Resection in Chronic Hepatitis B

Eun Jee Lim, Jihye Kim, Gwang Hyeon Choi, Eun Sun Jang, Sook-Hyang Jeong, Jin-Wook Kim

Department of Medicine, Seoul National University Bundang Hospital and Seoul National University College of Medicine, Republic of Korea

Aims: Use of nucleos(t)ide analogues (NAs) such as entecavir (ETV) or tenofovir disoproxil fumarate (TDF) may reduce the risk of hepatocellular carcinoma (HCC) recurrence after curative resection in patients with chronic hepatitis B. However, there is a disagreement regarding whether ETV or TDF provide a same beneficial effect after surgical treatment of HCC. Therefore, we investigated the effect of TDF or ETV on recurrence and progression-free survival of HCC after curative surgery in chronic hepatitis B patients. **Methods:** This retrospective cohort study analyzed 553 patients who received either ETV (n=339) or TDF (n=214), after excluding those who were followed up for less than 6 months. We used Kaplan-Meier estimation to evaluate HCC recurrence and progression-free survival in patients treated with ETV or TDF and used a multivariable-adjusted cox proportional hazard model to compare the results between the two groups. **Results:** The median age of patients was 61 years (ETV group 62 years, TDF group 59 years) and 78.48% were male (ETV group 76.4%, TDF group 81.8%). The median follow-up duration was 32 months (ETV group 33 months, TDF group32 months). The cumulative HCC recurrence rate was 9, 21, 27 and 38% after 12, 24, 36 and 60 months, respectively. By multivariable-adjusted analysis, more recurrence was observed with younger patients (hazard ratio[HR] = 0.970, 95% CI = 0.955-0.986, p value = 0.000), male (HR = 1.704, 95% CI = 1.117-2.600, p value = 0.013), lower albumin level (HR = 0.543, 95% CI = 0.389-0.757, p value = 0.000) and use of TDF compared to ETV (HR = 0.612, 95% CI = 0.434-0.864, p value = 0.005). **Conclusions:** This study showed that TDF treatment was associated with a significantly lower risk of HCC recurrence following curative surgery compared to ETV treatment among patients with chronic hepatitis B infection. Further research is required to determine the long-term effect of ETV and TDF on HCC recurrence and progression-free survival. **Keywords:** HCC, Entecavir, TDF, Chronic HBV



OP-03

IMbrave050: Adjuvant Atezolizumab+Bevacizumab VS Active Surveillance in Hepatocellular Carcinoma Patients at High Risk of Disease Recurrence Following Resection or Ablation

Han Chu Lee[1], Ann-Lii Cheng[2], Pierce Chow[3], Ahmed Kaseb[4], Masatoshi Kudo[5], Shukui Qin[6], Adam Yopp[7], Lars Becker[8], Sairy Hernandez[9], Bruno Kovic[10], Qinshu Lian[9], Ning Ma[9], Chun Wu[11], Minshan Chen[12]

[1]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]National Taiwan University Cancer Center and National Taiwan University Hospital, Taipei, Taiwan; [3]National Cancer Centre Singapore, Singapore and Duke-NUS Medical School Singapore, Singapore; [4]MD Anderson Cancer Center, Houston, Texas, USA; [5]Kindai University, Osaka, Japan; [6]Jinling Hospital of Nanjing University of Chinese Medicine, Nanjing, China; [7]UT Southwestern Medical Center, Dallas, Texas, USA; [8]F. Hoffmann-La Roche, Basel, Switzerland; [9]Genentech, Inc., South San Francisco, California, USA [10]Hoffmann-La Roche Limited, Mississauga, Ontario, Canada; [11]Roche (China) Holding Ltd., Shanghai, China; [12]Sun Yat-sen University Cancer Center, Guangdong Province, China

Aims: In IMbrave050 (NCT04102098), adjuvant atezolizumab +bevacizumab demonstrated a statistically significant and clinically

meaningful improvement in recurrence-free survival (RFS) vs active surveillance with generally manageable safety in patients at high risk of hepatocellular carcinoma (HCC) recurrence following resection or ablation with curative intent (Chow, AACR 2023). Here, we report patient-reported outcomes (PRO). **Methods:** Patients were randomized to Arm A (atezolizumab+bevacizumab) or Arm B (active surveillance). Arm A received atezolizumab 1200 mg + bevacizumab 15 mg/kg IV q3w for one year (17 cycles). Arm B underwent active surveillance for one year and could crossover to atezolizumab+bevacizumab following recurrence. Pre-specified exploratory analyses included change from baseline in global health status (GHS)/quality of life (QoL) and physical, role, emotional, and social functioning. Clinically meaningful deterioration was defined as a ≥10-point decrease. Patients completed the IL42–EORTC QLQ-C30 (reduced) questionnaire at baseline and then at every odd treatment/surveillance visit through Cycle 17. **Results:** There were 334 patients in both Arms A and B. Median follow-up was 17.4 mo (clinical cutoff date: 21 Oct 2022). IL42 completion rates remained at ≥93% in both arms from baseline through treatment/surveillance Cycle 17, and mean baseline scores were high and similar for all utilized scales. Mean changes from baseline were not considerable through Cycle 17 and were similar between arms as evidenced by overlapping 95% CIs. Patients' GHS/QoL and functioning was maintained through Cycle 17, with no clinically meaningful deterioration observed at any time. **Conclusions:** PRO outcome analyses revealed similar overall health-related QoL (HRQoL) and functioning between atezolizumab+bevacizumab and active surveillance, and that treating high-risk HCC patients with adjuvant atezolizumab+bevacizumab following procedures with curative intent did not result in a clinically meaningful deterioration in HRQoL or function. **Keywords:** Liver Cancer, Hepatocellular Carcinoma, IMbrave050, Atezolizumab, Bevacizumab

OP-04

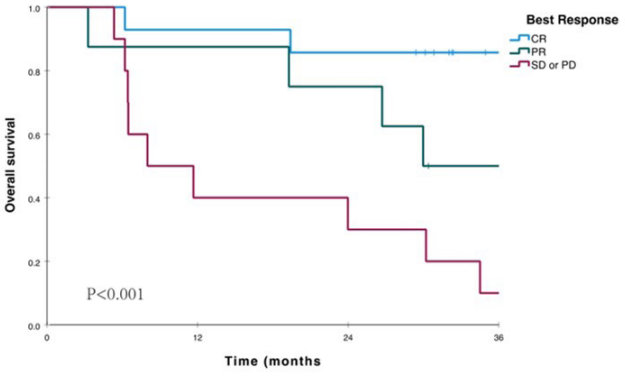
Radiological Response as a Predictor of Overall Survival in Locally Advanced Hepatocellular Carcinoma: Analysis of START-FIT Phase II Trial

Chi Leung Chiang, Keith Wan Hang Chiu, Kenneth Sik Kwan Chan, Francis Ann Shing Lee, Wing Chiu Dai, Tai Chung Lam, Wenqi Chen, Natalie Sean Man Wong, Venus Wan Yan Lee, Vince Wing Hang Lau, Nancy Kwan Man, Feng Ming (Spring) Kong, Albert Chi Yan Chan

[1]Department of Clinical Oncology, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, and University of Hong Kong-Shenzhen Hospital, Hong Kong; [2]Department of Diagnostic Radiology, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong and Department of Diagnostic and Interventional Radiology, Queen Elizabeth Hospital, Hong Kong; [3]Department of Nursing, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong; [4]Department of Clinical Oncology, Tuen Mun Hospital, Hong Kong; [5]Department of Surgery, Queen Mary Hospital, Hong Kong; [6]Clinical Oncology Center, University of Hong Kong-Shenzhen Hospital, Hong Kong; [7]Medical Physics Unit, Department of Clinical Oncology, Tuen Mun Hospital, Hong Kong; [8]Department of Diagnostic Radiology, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong and Department of Radiology, Gleneagles Hospital, Hong Kong; [9]Department of Surgery, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong

Aims: The START-FIT trial reported combined loco-regional therapy and immunotherapy is a promising conversion therapy. We presented the 3-year survival outcome and post-hoc analyses of the relationship between objective response rate (ORR) by Modified Response Evaluation Criteria in Solid Tumors (mRECIST) and overall survival (OS). **Methods:** Total 33 patients with locally advanced hepatocellular carcinoma who were not suitable for curative treatment were recruited into a single-arm, phase II trial. Participants received TACE on day 1, followed by stereotactic body radiotherapy (27·5–40·0Gy in five fractions) at day 28. Avelumab (10 mg/kg) was administered 14 days following stereotactic body radiotherapy and every 2 weeks thereafter. Multi-variate Cox proportional hazard model was used to analyze the relationship between ORR per mRECIST and OS. The trial is registered with ClinicalTrials.gov (NCT03817736). **Results:** At the time of data cutoff (22 Mar 2023), total 15 surviving patients had been followed for 34.9 months (IQR, 30.8 to 43.4). The median sum of the largest diameters of lesions was 15.1cm (IQR: 8.3 to 14.9) and 21 (64%) patients had macrovascular invasion. For the entire cohort, the 3-year OS rate was 49% (95% CI: 31 to 67). The confirmed ORR was 67% (95% CI: 48-82) with CR 42%, PR 24%, SD 9%, and PD 24%. The 3-year OS rate of CR, PR, and SD + PD was 86% (95% CI: 67-100), 50% (95% CI: 15-85), and 10% (95% CI: 0-29) respectively (P<0.001). Multivariable analyses showed objective response had an independent predictive value of OS (hazard ratio [HR]: 2.6, 95% CI 1.5 to 6.5, P=0.004). **Conclusions:** START-FIT combination resulted in promising 3-year survival outcomes in patients with locally advanced unresectable HCC with 3-year OS rate of 86 % without surgery among CR patients. Radiological response by mRECIST was an independent predictor of OS. **Keywords:** Hepatocellular Carcinoma, TACE, SBRT, Immunotherapy, Checkpoint Inhibitors, Unresectable, Locally Advanced, START-FIT

Figure 1. Comparison of the overall survival (OS) of patients with CR vs. PR vs. SD + PD based on radiological response by mRECIST



OP-05

Integrative Multi-Omics Profiling for Resectable Hepatocellular Carcinoma Uncovers Clinically Available Serum Biomarkers to Predict Microvascular Invasion

Incheon Kang[1], Sunyoung Lee[2], Ju-Seog Lee[3], Sung Hwan Lee[1]

[1]Department of Surgery, CHA Bundang Medical Center, CHA University School of Medicine, Republic of Korea; [2]Department of Gastrointestinal Medical Oncology, Division of Cancer Medicine, University of Texas MD Anderson Cancer Center, USA; [3]Department of Systems Biology, Division of Basic Sciences, University of Texas MD Anderson Cancer Center, USA

Aims: Microvascular invasion (MVI) is a well-known prognostic factor to predict cancer relapse after curative resection of resectable hepatocellular carcinoma (HCC). It is mandatory to uncover clinically available serum biomarkers to predict the MVI feature at the initial diagnosis of HCC. **Methods:** Using gene expression profiling for resected human HCC (Discovery cohort, n=240), we identified transcriptomic signature predicting the MVI feature. Repeated validation for the MVI signature performed using the Bayesian covariate compound predictor method at the multiple independent cohorts (Six Validation cohorts, n=1,263). Serum biomarker dataset from the patients of TCGA-LIHC samples correlated with the MVI signature. **Results:** The MVI signature with 1028 genes was identified from robust statistical testing from the discovery cohort, and robust validation for the prediction performance of the MVI signature showed significant accuracy in the validation cohort (AUC=0.865, P<0.01). Multi-omics analysis revealed aggressive tumor biology associated with the MVI signature regarding FOXM1, CD24, and MYC downstream pathways. A diagnostic panel from integrating significant serum biomarkers to predict MVI was identified from stepwise regression (P<0.001). Comprehensive analysis of drug-sensitivity for the MVI signature was performed by integrative in-silico prediction methods using the dataset from Cancer Dependency Map project (Broad Institute). **Conclusions:** Integrative multi-omics profiling for resectable HCC uncovers clinically available serum biomarkers to predict MVI without a surgical specimen. A novel combination of serum biomarkers shows high performance in sorting out the tumor with aggressive tumor biology. Precision strategy to discover resectable tumors beneficial from surgical resection can be established from consecutive clinical trials based on this translational study. **Keywords:** Hepatocellular Carcinoma, Biomarker

OP-06

Landscape of T-Cell Exhaustion Heterogeneity in Hepatocellular Carcinoma Revealed by Integrating Whole Exome, Transcriptomes, and Single-Cell Sequencing

Soon Kyu Lee[1], Jinyeong Lim[2], Joo Yeon Jhun[3], Jong Young Choi[4], Ho Joong Choi[5], Young Kyoung You[5], Ji Won Han[4], Pil Soo Sung[4], Seung Kew Yoon[4], Mi-La Cho[3], Jeong Won Jang[4]*

[1]Division of gastroenterology and hepatology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Department of Health Sciences and Technology, Samsung Advanced Institute for Health Science and Technology, Sungkyunkwan University, Seoul, Republic of Korea; [3]The Rheumatism Research Center, Catholic Research Institute of Medical Science, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [4]Division of gastroenterology and hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [5]Department of Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Immune checkpoint inhibitors have revolutionized treatment strategy in unresectable hepatocellular carcinoma (HCC) and have also been explored as an adjuvant therapy after surgery. Thus, investigating the heterogeneity of T-cell exhaustion in resected HCC is mandatory to improve the understanding of tumor microenvironment (TME) in HCC. **Methods:** To delineate the heterogeneity of T-cell exhaustion and their developmental trajectory, we performed single-cell RNA sequencing coupled with TCR sequencing analyses in HCC patients (n=8) who underwent liver resection. Moreover, whole exome sequencing (WES) and whole transcriptome sequencing were also integrated with the results of single-cell sequencing. **Results:** We identified two distinctive patient groups based on the levels of $CD8^+$ T-cell exhaustion: high (n=2) or low (n=6), according to the expression scores of exhaustion markers including LAG3, PDCD1, TGIT, and CTLA4 (Figure 1A). We further revealed that the high exhaustion group showed higher clonal expansion in the $CCL5^+CD8^+$ T effector memory cells and cycling T cells with the higher expression of exhaustion genes than the low exhaustion group (Figure 1B). Results of trajectory analysis showed two distinct branches, one directed towards exhaustion and the other towards cytotoxic T cell lineages. The high exhaustion group was more likely to be directed towards the exhausted lineage, as evidenced by increased expression of $PDCD1^+$ or $TIGIT^+$ markers with clonal expansions (Figure 1C). The high exhaustion group also showed higher property of $CXCL13^+CD4^+$ T follicular hyper cells with the higher expression of PDCD1 compared to low exhaustion group. Moreover, higher expression of PDCD1 in the $FoxP3^+CD4^+$ regulatory T cells were also identified in the high exhaustion group. The high exhaustion group had the TP53 mutation identified by the WES analysis, while the low exhaustion group had mutations in the CTNNB1 and TERT promoter regions (Figure 1D). **Conclusions:** This study revealed the heterogeneity of T-cell exhaustion in the TME of resected HCC

with verifying their differences in the gene expression and clonal expansion. **Keywords:** Hepatocellular Carcinoma, Exhaustion, Tumor Microenvironment, Sequencing, PDCD1, LAG3, CTLA4

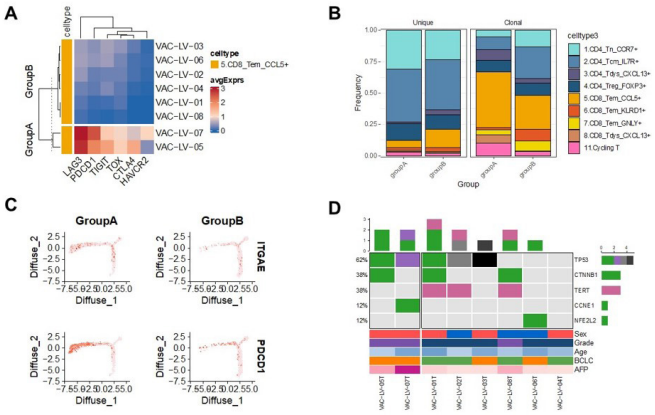


Figure. Heterogeneity of T-cell exhaustion in hepatocellular carcinoma. Group A, high exhaustion group; group B, low exhaustion group.

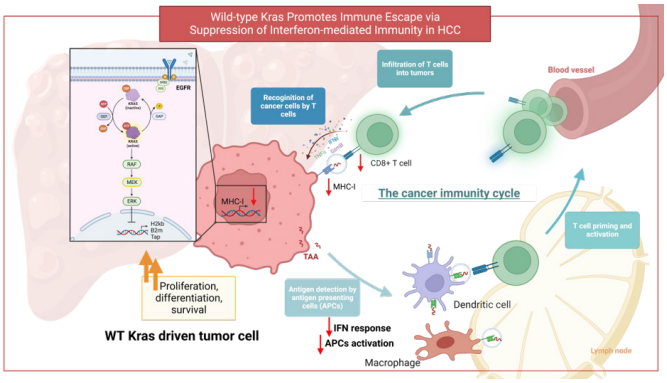
OP-07

Wild-Type Kirsten Rat Sarcoma (Kras) Promotes Immune Escape via Suppression of Interferon-Mediated Immunity in Hepatocellular Carcinoma

Martina Mang Leng Lei[1], Terence Kin Wah Lee[2]

[1]Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong; [2]State Key Laboratory of Chemical Biology and Drug Discovery, The Hong Kong Polytechnic University, Hong Kong

Aims: Although immune checkpoint inhibitors (ICIs) demonstrate tremendous promise for the treatment of hepatocellular carcinoma (HCC) patients, their response rates are modest (~15%). This unsatisfactory outcome can be attributed to the ability of HCC cells to evade immune surveillance. Therefore, understanding the immune evasive mechanism of HCC is urgently needed. **Methods:** Critical oncogenic signaling pathway in immune evasion was identified in an antigen-expressing C-Myc^{OE} /Tp53^{KO} HCC mouse model by data-independent acquisition mass spectrometry (DIA-MS) proteomics. In vivo functional characterization was performed using gene transduction via hydrodynamic tail vein injection. The clinical significance was evaluated in publicly available datasets as well as immunohistochemistry analysis. Potential downstream pathways were investigated by single cell RNA sequencing (scRNA-seq), immune profiling, western blot, and multiplexed immunofluorescence staining. **Results:** We identified that wild-type Kras was highly upregulated in immune-escaped tumors, with concurrent activation of its ligand-driven EGFR and its downstream MEK/ERK signaling. Likewise, endogenous Kras overexpression in this model led to increase in tumor burden with shorter survival time of mice, implicating the regulatory role of Kras signaling in immune evasion. Clinically, wild-type Kras was overexpressed in HCC at both mRNA and protein levels and associated with tumor recurrence and poorer patients' survival. Using scRNA-seq analysis, we demonstrated that Kras hampered the recruitment of dendritic cells, leading to defective T cell activity via suppression of the interferon signaling. Activation of Kras/MEK/ERK signaling impaired HCC recognition by T cells via the downregulation of MHC-I-driven antigen presentation. This data, together with the observation showing upregulation of this signaling pathway in PD1-treated tumors, suggest a rational therapeutic strategy with a combination of KRAS inhibitor with ICIs. **Conclusions:** This study uncovers a new role of wild-type Kras and its signaling pathway in immune evasion and potentially opens a novel therapeutic avenue for HCC treatment. **Keywords:** Wild-Type Kirsten Rat Sarcoma, Antigen Presentation, Immune Evasion, Interferon Signaling



OP-08

Differential T Cell and Monocyte Responses in Hepatocellular Carcinoma Treated with Regorafenib Plus Nivolumab: A Biomarker Analysis of the Phase 2 RENOBATE Trial

Hyung-Don Kim[1], Seyoung Jung[2], Baek-Yeol Ryoo[1], Min-Hee Ryu[1], Beodeul Kang[3], Hong Jae Chon[3], Jung Yong Hong[4], Ho Yeong Lim[4], Jeong Seok Lee[1,5], June-Young Koh[5], Changhoon Yoo[1]

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Republic of Korea; [3]Department of Medical Oncology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea; [4]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [5]Genome Insight, Inc., San Diego, La Jolla, California, USA

Aims: In the phase 2 REBNOBATE trial, we evaluated the efficacy and safety of regorafenib-nivolumab as a front-line treatment in patients with unresectable hepatocellular carcinoma (uHCC). We herein present the results of the comprehensive biomarker study. **Methods:** Patients received nivolumab 480 mg every 4 weeks and regorafenib 80 mg daily on a 3 weeks-

on/1 week-off schedule (n=42). Single-cell RNA sequencing was performed using peripheral blood mononuclear cells collected at baseline and early on-treatment from patients showing progressive increase in tumor burden (early progressors) and response or stable disease for at least 10 months (long-term responders). **Results:** Upon regorafenib-nivolumab, diversification of T-cell receptor repertoire and enrichment of genes representing immunotherapy-responsiveness and cytotoxicity in MKI67+ proliferating CD8+ T cells were noted in long-term responders. Relative abundance and prominent transcriptomic changes of classical monocytes were observed in long-term responders. Monocytic populations from long-term responders had a preferential M1-directed polarization as well as regorafenib-induced transcriptomic reprogramming. In contrast, those from early progressors were featured by M2-directed transcriptomic changes and insufficient up-regulation of inflammasome-related genes. Interaction through IFN-γ pathways between proliferating CD8+ T cells and classical monocytes was exclusively observed in long-term responders. **Conclusions:** Differential T cell and monocytes responses were associated with distinct clinical outcomes of HCC patients treated with regorafenib plus nivolumab, suggesting a potential to develop biomarkers associated with these cells or novel immunotherapies to overcome resistance in uHCC patients. **Keywords:** Hepatocellular Carcinoma, Immune Landscape, Biomarker, Nivolumab-Regorafenib

OP-09

Diagnostic Algorithm for Subcentimeter Hepatocellular Carcinoma Using Alpha-Fetoprotein and Imaging Features on Gadoxetic Acid-Enhanced MRI

Peng Huang[1,3], Kai Hou[1,3], Changwu Zhou[1,2,3], Fei Wu[1,3], Yuyao Xiao[1,3], Cheng Wang[1,3], Gengyun Miao[1,3], Chun Yang[1,3], Mengsu Zeng[1,2,3]

[1]Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai, China; [2]Shanghai Institute of Medical Imaging, Shanghai, China; [3]Department of Cancer Center, Zhongshan Hospital, Fudan University, Shanghai, China

Aims: To investigate whether serum alpha-fetoprotein (AFP) can help in imaging diagnosis of subcentimeter hepatocellular carcinoma (HCC) on gadoxetic acid-enhanced MRI (EOB-MRI). **Methods:** This study retrospectively enrolled 218 treatment-naïve patients with chronic hepatitis B who had a solitary subcentimeter observation on EOB-MRI. The final diagnoses of 218 observations were 107 HCC (all by pathology) and 111 non-HCC (47 by pathology and 64 by follow-up). Two board-certified radiologists independently evaluated MRI features. Youden's index was applied to determine the new cutoff value of AFP for subcentimeter HCC. Through logistic regression analyses based on AFP and imaging features, diagnostic criteria were developed according to different combinations of significant findings. The diagnostic performance of possible criteria was compared to the diagnostic hallmarks of HCC (arterial-phase hyperintensity and portal-phase hypointensity). **Results:** The optimal AFP cutoff value for HCC diagnosis was 13.7 ng/ml. Four findings (AFP >13.7 ng/mL, arterial-phase hyperintensity, portal-phase hypointensity, and transitional-phase hypointensity) were independently associated with HCC diagnosis. A new criterion (at least three of the four aforementioned findings) showed a significantly higher sensitivity than that of diagnostic hallmarks of HCC (72.0% vs. 53.3%, $P<0.001$) and comparable specificity (91.0% vs. 91.9%, $P>0.999$). Another criterion (all four significant findings) achieved a higher specificity than that of the diagnostic hallmark (99.1% vs. 91.9%, $P=0.008$). Subgroup analysis for hepatobiliary hypointense observations yielded similar results. **Conclusions:** Including AFP in the diagnostic algorithm (at least three of AFP >13.7 ng/mL, arterial-phase hyperintensity, portal-phase hypointensity, and transitional-phase hypointensity) may improve the diagnostic performance for subcentimeter HCC. **Keywords:** Carcinoma, Hepatocellular, Magnetic Resonance Imaging, Gadolinium Ethoxybenzyl DTPA, Alpha-Fetoproteins

OP-10

Non-Negligible Differences in Radio-Pathologic Characteristics and Prognosis between Subcentimeter and 1-2cm Hepatocellular Carcinoma

Peng Huang[1,3], Changwu Zhou[1,2,3], Fei Wu[1,3], Yuyao Xiao[1,3], Cheng Wang[1,3], Gengyun Miao[1,3], Chun Yang[1,3], Mengsu Zeng[1,2,3]

[1]Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai, China; [2]Shanghai Institute of Medical Imaging, Shanghai, China; [3]Department of Cancer Center, Zhongshan Hospital, Fudan University, Shanghai, China

Aims: To compare the imaging features, pathologic characteristics, and treatment outcomes between subcentimeter and 1-2 cm hepatocellular carcinoma (HCC). **Methods:** Enrolled were 243 patients (82 with subcentimeter HCC and 141 with 1-2 cm HCC) who underwent surgical resection with preoperative gadoxetic acid-enhanced MRI (EOB-MRI). Two radiologists independently assessed the MR imaging features. The incidence of imaging features and pathological characteristics were compared. Survival outcomes, including recurrence and overall survival, were compared by Kaplan-Meier analysis. Multivariable Cox regression analysis was utilized to identify recurrence-related prognostic factors. **Results:** Compared with 1-2 cm HCC, subcentimeter HCC had a lower incidence of restricted diffusion (87.8 vs. 95.7%, $P=0.027$), portal-phase washout (58.5% vs. 73.8%, $P=0.013$), typical enhancement pattern (50.0% vs. 66.7%, P =0.014), and microvascular invasion (4.9% vs. 14.9%, $P=0.022$). However, if washout was evaluated in portal-phase or transitional-phase, the incidence of typical enhancement pattern did not differ significantly. During a median follow-up period of 47.4 months, patients with subcentimeter HCC experienced less early and overall tumor recurrence and longer overall survival. Tumor size < 1cm was an independent protective factor of overall recurrence (HR: 0.466, $P=0.027$), and microvascular invasion was independently associated with early recurrence (HR: 2.815, $P=0.021$). **Conclusions:** Subcentimeter HCC had distinguished differences in imaging features, pathological characteristics, and survival outcomes than 1-2 cm HCC. It may be more appropriate to develop specialized diagnostic criteria and take an early treatment strategy. **Keywords:** Hepatocellular Carcinoma, Magnetic Resonance Imaging, Gadolinium Ethoxybenzyl DTPA,

Subcentimeter, Prognosis

OP-11

Non-Contrast Abbreviated MRI (NC-aMRI) VS Contrast-Enhanced (CE-aMRI) for Hepatocellular Carcinoma (HCC) Surveillance among High-Risk Populations-A Meta-Analysis

Soe Thiha Maung[1,2], Roongruedee Chaiteerakij[2]

[1]Mahar Myaing Hospital, Yangon, Myanmar; [2]Division of Gastroenterology, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Thailand

Aims: Magnetic resonance imaging (MRI) is a highly valuable clinical modality that is widely used for the detection and characterization of both benign and malignant liver and biliary diseases. MRI offers multiparametric capabilities and is superior to computed tomography (CT) in this regard. MRI is commonly used to characterize hepatic lesions and as a reference examination when results from CT or ultrasonography (US) examinations are inconclusive or incomplete. Liver MRI utilizes various sequences that generate images with unique information regarding the liver and biliary system. The use of MRI provides both anatomical and functional information about the liver through different contrast mechanisms. However, the use of full contrast MRI is limited by accessibility issues, high costs, long examination times, complex technology, and the risk of contrast-related side effects. Abbreviated MRI protocols have emerged as an alternative to full contrast MRI protocols. These abbreviated MRI protocols aim to reduce unnecessary and redundant MRI sequences, thereby improving patient comfort, reducing costs, examination time, and image interpretation time without compromising diagnostic accuracy. Abbreviated MRI protocols have been proposed as a screening method for hepatocellular carcinoma (HCC). Nonetheless, various applications of abbreviated MRI have been explored for the evaluation of liver diseases. The aim of this study is to evaluate the performance of non-contrast abbreviated MRI (NC-aMRI) for detecting HCC during surveillance and to compare it with contrast-enhanced abbreviated MRI (CE-aMRI). **Methods:** This study followed the PRISMA guideline and identified research studies on aMRI for detecting HCC in MEDLINE, EMBASE, and Cochrane databases. Pooled sensitivity and specificity were calculated using a hierarchical model, and the quality of the included articles was assessed using the QUADAS-2 tool. Sensitivity and specificity of NC-aMRI and CE-aMRI were compared using bivariate meta-regression. **Results:** The performance of non-contrast abbreviated MRI (NC-aMRI) for detecting hepatocellular carcinoma (HCC) in surveillance has been evaluated in 26 studies. The pooled sensitivity and specificity of NC-aMRI were 86% (95% confidence interval (CI), 84–88%; I^2 =67%) and 93% (95% CI, 92–95%; I^2 = 78%), respectively, which is comparable to contrast-enhanced aMRI (CE-aMRI) with a pooled sensitivity and specificity of 89% (95% confidence interval (CI), 87–91%; I^2 =69%) and 95% (95% CI, 94–96%; I^2 = 89%), respectively. Additionally, among the NC-aMRI protocols, diffusion-weighted imaging (DWI) alone showed a sensitivity and specificity of 84% (95% confidence interval (CI), 79–88%; I^2 =62%) and 95% (95% CI, 94–97%; I^2 = 77%), respectively, which is not significantly different from that of dynamic aMRI protocol. **Conclusions:** These findings suggest that NC-aMRI has good overall diagnostic performance for detecting HCC and may be a useful tool for future HCC surveillance. **Keywords:** HCC Surveillance, Abbreviated MRI

OP-12

Machine Learning Classification of Hepatocellular Carcinoma Based on CT Scan Image Using Probabilistic Neural Network Algorithm

Rifaldy Fajar, Efiany, Nana Kurnia

Computational Biology and Medicine Laboratory, Yogyakarta State University, Indonesia

Aims: The most common type of liver cancer is Hepatocellular carcinoma (HCC), which begins in the main type of liver cell (hepatocyte). Hepatocellular carcinoma occurs most often in people with chronic liver diseases, such as cirrhosis caused by hepatitis B or hepatitis C infection. Examinations carried out to determine the presence of HCC are by measuring the level of Alpha-Fetoprotein in the blood, radiographic diagnoses such as ultrasound examination, CT-Scan, and MRI, as well as performing a liver biopsy. HCC is often not identified because the symptoms of HCC are masked by the underlying disease. So we need a method to make it easier to identify HCC disease through CT-Scan images. In this study, an alternative machine learning algorithm is used, namely the Probabilistic Neural Network that works to classify HCC. **Methods:** The method used in this study is a Probabilistic Neural Network to identify HCC disease. The steps taken to identify HCC disease are starting with pre-processing using Gaussian filtering to improve image quality by reducing noise in the image, then segmentation using thresholding, morphology operators, and finding contour which aims to get image segmentation in the heart, as well as to feature extraction using a gray level co-occurrence matrix to analyze the texture of the image as input for the identification process. The image data used in this study were obtained from The Cancer Imaging Archive (TCIA) and Radiopedia.org. **Results:** The test results obtained indicate that the proposed method is able to identify HCC disease with an accuracy obtained of 94%. The use of the gray-level co-occurrence matrix method for the feature extraction process works well for recognizing objects so that they can identify HCC and normal categories. **Conclusions:** The Probabilistic Neural Network method can identify HCC disease quite well based on the accuracy obtained exceeding 90%. However, further research and development are needed to improve the accuracy of the classification system. **Keywords:** Classification, CT Scan, Hepatocellular Carcinoma, PNN Algorithm

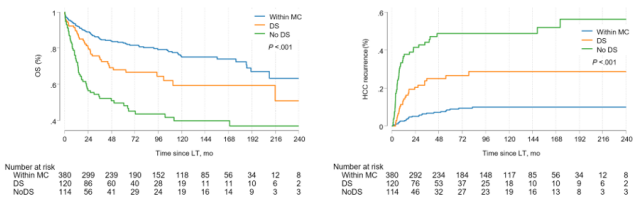
OP-13

Long-Term Outcomes of Liver Transplantation for Patients with Hepatocellular Carcinoma beyond Milan Criteria: A Multicenter Cohort Study

Heechul Nam[1,2], Ji won Han[1,2], Soon Kyu Lee[1,2], Hyun Yang[1,2], Hae Lim Lee[1,2], Pil Soo Sung[1,2], Hee Yeon Kim[1,2], Ho Joong Choi[3], Gun-Hyung Na[3], Young Chul Yoon[3], Jung Hyun Kwon[1,2], U Im Chang[1,2], Chang Wook Kim[1,2], Si Hyun Bae[1,2], Young Kyoung You[3], Jong Young Choi[1,2], Seung Kew Yoon[1,2], Jin Mo Yang[1,2], Jeong Won Jang[1,2]*

[1]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]The Catholic Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [3]Department of Surgery, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Recent guidelines recommend that liver transplantation (LT) can be considered for patients with hepatocellular carcinoma (HCC) that exceeds Milan criteria (MC) if they have been successfully downstaged to within MC. However, multi-center studies analyzing long-term outcomes are lacking. This study aims to identify prognostic factors for overall survival (OS) and recurrence after LT in downstaged patients with HCC beyond MC. **Methods:** This is a multi-center retrospective study on consecutive patients with HCC underwent LT at 6 academic centers from September 1995 to September 2022. The associations of factors on OS and recurrence rate were analyzed using Cox proportional hazards regression and multivariable logistic regression models. **Results:** The study included 614 HCC patients who underwent LT and were categorized into three groups: within MC (n=380), successfully down-staged (DS, n=120), and not down-staged (NoDS, n=114). The majority of the patients were male (509 [82.9%]), and the median age was 54 years (IQR, 50-60 years). The median follow-up after LT was 55.9 months (IQR 19.7-121.8 months). The OS rates at 1, 3, 5, 10, and 20 years were 92.5%, 85.4%, 82.9%, 75.1%, and 63.3% for patients within MC; 89.8%, 74.8%, 68.1%, 59.5%, and 51.0% for DS; and 72.9%, 52.1%, 50.8%, 39.7%, and 36.9% for NoDS, respectively (P<0.001). The recurrence rates at 1, 3, 5, 10, and 20 years were 2.5%, 6.7%, 8.8%, 9.8%, and 9.8% for patients within MC; 13.9%, 25.6%, 27.1%, 29.3%, and 29.3% for DS; and 36.3%, 43.9%, 48.5%, 48.5%, and 56.3% for NoDS, respectively (P<0.001). In the DS group, independent prognostic factors associated with recurrence after LT were neutrophil-to-lymphocyte ratio (NLR) >2 at LT (HR, 3.02; 95% CI, 1.51-6.06; P=0.002) and microvascular invasion (MVI) on explant pathology (HR, 3.94; 95% CI, 1.72-9.04; P=0.001). **Conclusions:** This multi-center retrospective cohort study with long-term follow-up demonstrated that patients with HCC who successfully downstaged to within MC had favorable post-LT outcomes. Based on our data, patients who achieved successful downstaging and had low NLR (below 2) or without MVI were associated with favorable outcomes following LT. **Keywords:** HCC, Liver Transplantation, Milan Criteria, Downstaging



OP-14

Translational Hepatectomy for Hepatocellular Carcinoma with Inadequate Future-Liver-Remnant after Portal Vein Ligation in Combination with Apatinib Plus Camrelizumab: A Single-Arm Prospective Pilot Study (PLACES) Compared with ALPPS Cohort

Zhiming Zeng, Huasheng Huang, Guangzhi Zhu, Yanfeng Jiang, Xinping Ye, Jie Zeng, Cuizhen Liu, Hao Su, Ming Su, Ning Mo, Xiwen Liao, Fuchao Ma, Chuangye Han, Jinyuan Liao, Wei Qin, Chengkun Yang, Minhao Peng, Jie Ma, Tao Peng

The First Affiliated Hospital of Guangxi Medical University, Guangxi Province, China

Aims: The purpose of this study was to evaluate the efficacy and safety of hepatic portal vein ligation (PVL) combined with Apatinib and Camrelizumab in conversion of HCC with insufficient FLR to resectable HCC. **Methods:** An open, single-arm, prospective phase II clinical trial (PLACES study) was conducted in our center: patients with HCC who met the enrollment criteria were first treated with PVL on the diseased side of the liver, and then given Apatinib 250 mg orally once daily, combined with Camrelizumab 200 mg drip intravenously every 2 weeks, starting 2 weeks after surgery. Stage-II resection indication was that FLR/standard liver volume (SLV) increased above 40% for cirrhotic liver or 30% for normal liver, without contralateral and extrahepatic metastasis. The TKI+PD1 medication continued for 1 year. The results of this study were also compared with propensity score matching (PSM) cases of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) at the same center. **Results:** From April 2020 to February 2023, the PLACES study completed PVL in 30 individuals, all men, with a median age of 46 years (31-71 years) and a median FLR/SLV of 32.9% (19.1%-39.9%). According to RECIST v1.1, the objective response rate (ORR) was 26.7% and the disease control rate (DCR) was 66.7% in the latest overall population. According to mRECIST, ORR was 40% and DCR was 66.7%. 23 patients (76.7%) achieved sufficient FLR/SLV, among which 20 patients (66.7%) completed the stage-II hepatectomy. The most common treatment-related adverse events included Hypoalbuminemia (56.7%) and aspartate transaminase elevation (53.3%). From 2012 to 2021, 76 HCC patients received ALPPS, and the baseline data of both groups were matched 1:1 using PSM, with 25 matched cases in each group. Compared with ALPPS group, PLACES group had higher minimally invasive rate (96% vs. 2%), shorter operative time (211.3±61.3 min vs. 327.6±67.6 min), less blood loss (40 [20.0 to 50.0] ml vs. 300[175.0 to 500.0] ml), and fewer postoperative complications in stage-I operation (P<0.05). After PSM, 19 patients (76%) in the ALPPS group and 17 patients (64%) in the PLACES group underwent secondary hepatectomy. Among patients who completed stage II surgery, the OS in the PLACES group was better (P<0.05) regardless of before and after PSM. **Conclusions:** PVL combined with Apatinib and Camrelizumab is an effective and safe treatment option for HCC with insufficient residual liver volume, with higher minimally invasive rates and less postoperative morbidities than the ALPPS approach.

Keywords: Hepatocellular Carcinoma, Translational Therapy, Immunotherapy, Targeted Therapy

OP-15

A MRI-Based Prognostic Stratification System for Medical Decision-Making of Multinodular Hepatocellular Carcinoma Patients: Optimization of the Milan Criteria

Fei Wu[*,1], *Haitao Sun*[1], *Chun Yang*[1], *Mengsu Zeng*[#,1]

Department of Radiology, Zhongshan Hospital, Fudan University, China

Aims: Whether hepatectomy should be performed among patients with multinodular hepatocellular carcinoma (MHCC) beyond the Milan criteria remains controversial. This study aimed to determine the clinicoradiological prognostic factors for patients with MHCC beyond the Milan criteria and further to develop a prognostic stratification system. **Methods:** Between January 2015 and January 2019, consecutive patients with pathologically confirmed MHCC who underwent preoperative contrast-enhanced MRI were retrospectively enrolled. Preoperative clinical data and MR features were collected and analyzed. The multivariable Cox regression was applied to select clinicoradiological variables for recurrence-free survival (RFS) and overall survival (OS) and construct a prediction model. The discrimination and calibration performance of the models were assessed with the C-index and calibration curve. Risk stratification systems based on the prediction models were further developed. **Results:** A total of 176 patients with 398 lesions were finally included in the study. AST > 40 U/L (hazard ratio [HR], 1.533, 95% confidence interval [CI], 1.028-2.289, *P*=0.036), increased tumor burden score (HR, 1.088, 95%CI, 1.010-1.172, *P*=0.026), radiological liver cirrhosis (HR, 1.465, 95%CI, 1.029-2.085, *P*=0.034) and non-smooth tumor margin (HR, 2.461, 95%CI, 1.454-4.165, *P*=0.001) were independent predictors for poor RFS, while AST > 40 U/L (HR, 1.796, 95%CI, 1.070-3.015, *P*=0.027), AFP>400 ng/mL (HR, 2.111, 95%CI, 1.129-3.945, *P*=0.019) and radiological liver cirrhosis (HR, 1.792, 95%CI, 1.058-3.035, *P*=0.030) were independent predictors for poor OS among MHCC patients beyond the Milan criteria treated with liver resection. Two nomograms were independently developed and demonstrated good discrimination performance with C-index of 0.653 (95%CI, 0.602-0.794) and 0.685 (95%CI, 0.623-0.747) for RFS and OS, respectively. Based on the models, MHCC patients beyond the Milan criteria were stratified into three groups with significantly different RFS and OS (both *P*<0.001). **Conclusions:** Two MRI-based prognostic models with good discrimination performance were developed and could preoperatively stratify MHCC patients into groups with different long-term outcomes.
Keywords: Hepatocellular Carcinoma, Multinodular, Milan criteria, Prognosis

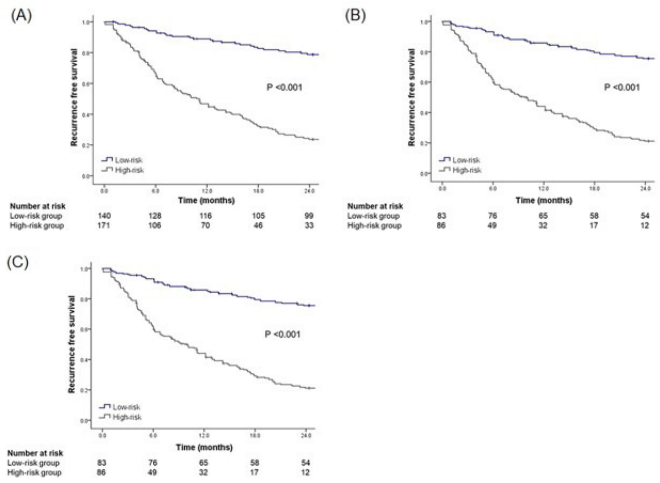
OP-16

Risk Stratification for Early Recurrence after Resection in Patients with Intermediate Stage Hepatocellular Carcinoma

Han Ah Lee[1,2], *Jeong-Ju Yoo*[3], *Minjong Lee*[1,2,4†], *Ho Soo Chun*[1,4], *Hwi Young Kim*[1], *Tae Hun Kim*[1,4], *Yeon Seok Seo*[5], *Dong Hyun Sinn*[6†]

[1]Departments of Internal Medicine, Ewha Womans University College of Medicine, Seoul, Korea; [2]The Korean Liver Cancer Association, Seoul, Republic of Korea; [3]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea; [4]Department of Internal Medicine, Ewha Womans University Medical Center, Seoul, Republic of Korea; [5]Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea [6]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Aims: It is unclear which patients will benefit from resection in patients with intermediate stage of hepatocellular carcinoma (HCC). We aimed to identify high-risk patients for early recurrence among patients with resectable intermediate-stage HCC. **Methods:** This multicenter retrospective study involved 1,686 patients who underwent resection or transarterial chemoembolization (TACE) for intermediate-stage HCC (2008–2019). Multivariate Cox proportional analysis was performed to identify high-risk patients who were treated with resection. A prediction model for 2-year recurrence-free survival (RFS) was developed using the training cohort and validated using the validation cohort. The 2-year RFS in each risk group was compared with that in patients treated with TACE after propensity score matching. **Results:** During a median follow-up of 31.4 months, the 2-year RFS was significantly higher in the resection group (28.5%, n=480) than in the TACE group (71.5% n=1,206) (adjusted hazard ratio [aHR]=1.471, 95% CI=1.199–1.803, *P*<0.001). Higher alpha-fetoprotein levels (aHR=0.202), ALBI grade (aHR=0.709), tumor number (aHR=0.404), and maximal tumor size (aHR=0.323) were significant risk factors for 2-year RFS in patients who underwent resection. The newly developed Surgery Risk score in BCLC-B (SR-B score) with four variables showed an area under the curve of 0.801 for the 2-year RFS and was externally validated. Based on risk stratification by SR-B score, low-risk patients had a significantly higher 2-year RFS (training: aHR=5.834; validation: aHR=5.675) than high-risk patients (all *P*<0.001) did. In a propensity score-matched cohort, low-risk patients treated with resection had a significantly higher 2-year RFS than those treated with TACE (aHR=3.891); high-risk patients had a comparable 2-year RFS to those treated with TACE (aHR=0.816). **Conclusions:** Resection may be beneficial for patients with resectable intermediate-stage HCC based on the SR-B score.
Keywords: BCLC B, Transarterial Chemoembolization, Early Recurrence



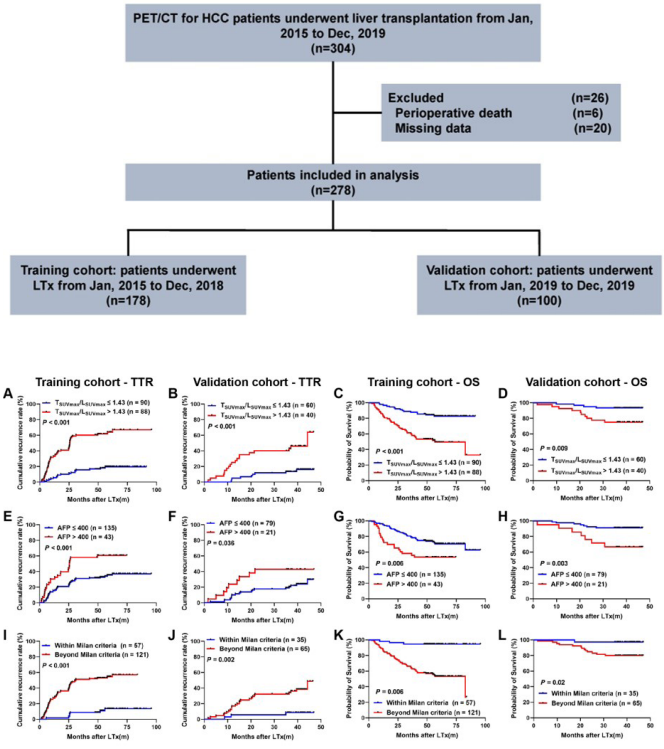
OP-17

Increased 18F-FDG Uptake of Tumor on PET/CT Predicts Tumor Recurrence in Hepatocellular Carcinoma Patients Undergoing Liver Transplantation

*Wen-jing Zheng[1‡], Yang Xu[1‡], Hui Tan[1‡], Peng-Xiang Wang[1], Jian Zhou[1], Jia Fan[1], Hong-Cheng Shi[1], Xin-Rong Yang[1]**

[1]Department of Liver Surgery, Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Key Laboratory of Carcinogenesis and Cancer Invasion, Ministry of Education, Shanghai, China

Aims: Besides radical resection, liver transplantation (LTx) is also an effective treatment for hepatocellular carcinoma (HCC). However, due to the tumor recurrence, some patients do not reach a satisfied outcome. This study aims to explore what role can ^{18}F-fludeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) play in predicting tumor recurrence after LTx in HCC patients. **Methods:** This analysis included 278 consecutive HCC cases underwent LTx at our center and accepted pre-operative ^{18}F-FDG PET/CT before LTx within 90 days, which were divided into a training cohort (n = 178) and a validation cohort (n = 100) according the time of LTx simply. We evaluated the predictive value of PET/CT for tumor recurrence after LTx in patients with HCC in both training and validation cohorts. In addition, we also included the analyses of immunohistochemistry and DNA sequencing of tumor tissues to reveal the molecular mechanism of the prognostic value of PET/CT. **Results:** Patients with tumor recurrence after LTx showed higher tumor SUV_{max} in preoperative PET/CT than patients without recurrence in the training cohort (6.73 ± 3.37 vs. 4.53± 2.80, P<0.001), and the similar results was observed in the validation cohort (6.11 ± 3.75 vs. 4.28 ± 2.61, P=0.007). Receiver operating characteristic curve analysis revealed that the ratio of tumor SUV_{max} to the liver SUV_{max} (T_{SUVmax}/L_{SUVmax}) was the most powerful predictor for post-LTx recurrence, with 1.43 as optimal cutoff. In training cohort, the patients with T_{SUVmax}/L_{SUVmax} > 1.43 showed significantly higher recurrence rate (63.6% vs. 18.9%, P<0.001) than patients with T_{SUVmax}/L_{SUVmax} ≤ 1.43 in Kaplan-Meier analysis; and the multivariate Cox regression analyses showed that T_{SUVmax}/L_{SUVmax} > 1.43 is the independent risk factor [Hazard ratio (HR): 2.421; 95% Confidence interval (CI): 1.304-4.494; P=0.005] of tumor recurrence. In validation cohort, results of analyses were similar: T_{SUVmax}/L_{SUVmax} > 1.43 indicated higher recurrence rate (47.5% vs. 15.0%, P=0.001) and was the independent risk factor (HR: 3.247; 95%CI: 1.16-9.087; P=0.025). In the subgroup analysis, T_{SUVmax}/L_{SUVmax} showed predictive value in both high and low recurrence risk subgroup (all P<0.05). Tumor tissue IHC showed that patients with T_{SUVmax}/L_{SUVmax} > 1.43 tended to have higher expression level of Ki67 and higher probability of CK19 positive expression. Meanwhile, DNA sequencing found that T_{SUVmax}/L_{SUVmax} > 1.43 was related to TP53, SDHC and B4GALT3 mutations, TP53, PI3K, WNT, Cell-cycle, Hippo and TGFβsignaling pathways alterations. **Conclusions:** T_{SUVmax}/L_{SUVmax} of perioperative ^{18}F-FDG PET/CT could serve as a potential predictor for HCC recurrence after LTx, which combined with criteria of LTx for HCC, like Milan criteria, can be more effective on LTx recipient choosing. **Keywords:** Hepatocellular Carcinoma, Positron Emission Tomography, Liver Transplantation, Tumor Recurrence, Prognosis



OP-18

The Impact of Dynamic Changes in Cachexia Index on the Outcomes after Hepatectomy for Hepatocellular Carcinoma

Munetoshi Akaoka, Koichiro Haruki, Shunta Ishizaki, Mitsuru Yanagaki, Masashi Tsunematsu, Norimitsu Okui, Michinori Matsumoto, Kenei Furukawa, Taro Sakamoto, Takeshi Gocho, Toru Ikegami

Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, The Jikei University School of Medicine, Tokyo, Japan

Aims: The cachexia index (CXI), which consists of skeletal muscle, inflammation, and nutritional status, has been associated with prognosis in patients with hepatocellular carcinoma (HCC). We hypothesized that dynamic changes in CXI might be associated with long-term outcomes in HCC. **Methods:** The study comprised 131 patients who had undergone primary hepatic resection for HCC between 2008 and 2019. Preoperative and postoperative CXI was calculated by the following formula: skeletal muscle index x serum albumin level / neutrophil-to-lymphocyte ratio. Pre- and post-CXI was classified into two groups (high vs. low). We retrospectively investigated the relationship between dynamic change in CXI from pre- to post-hepatectomy and disease-free and overall survival. **Results:** In multivariate analyses, negative HBs-antigen (P=0.02), preoperative high serum PIVKA-II level (P<0.01), poor tumor differentiation (P=0.02), multiple tumor (P<0.01), microvascular invasion (P<0.01), partial resection (P<0.01), postoperative complication (P<0.01), and preoperative low CXI (P<0.01) were significant predictors of disease-free survival, while high ICG_{R15} (P=0.01), poor tumor differentiation (P<0.01), multiple tumor (P=0.01), postoperative complication (P<0.01), preoperative low CXI (P<0.01), and postoperative low CXI (P<0.01) were significant predictors of overall survival. Postoperative low-CXI was positively associated with older age (P=0.045), larger tumor (P<0.01), longer operative time (P=0.047), greater intraoperative bleeding (P<0.01), and intraoperative blood transfusions (P<0.01). Moreover, the dynamic changes in CXI were associated with overall survival in each subgroup of patients with pre-low-CXI (P=0.02) or pre-high-CXI (P=0.03). **Conclusions:** Not only postoperative CXI but also dynamic changes in CXI from pre- to post-hepatectomy can be a prognostic indicator in patients with HCC, providing a compelling rationale for aggressive perioperative nutritional and physical interventions to improve long-term outcomes. **Keywords:** Hepatocellular Carcinoma, Cachexia, Hepatic Resection, Prognosis

OP-19

Four-Year Overall Survival (OS) Update from the Phase 3 HIMALAYA Study of Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma (uHCC)

Bruno Sangro[1], Stephen L. Chan[2], Robin Kate Kelley[3], George Lau[4], Masatoshi Kudo[5], Wattana Sukeepaisarnjaroen[6], Enrico N. De Toni[7], Junji Furuse[8], Yoon Koo Kang[9], Peter R. Galle[10], Lorenza Rimassa[11,12], Alexandra Heurgué[13], Vincent C. Tam[14], Tu Van Dao[15], Satheesh Chiradoni Thungappa[16], Valeriy Breder[17], Yuriy Ostapenko[18], Maria Reig[19], Mallory Makowsky[20], Charu Gupta[21], Alejandra Negro[20], Ghassan K. Abou-Alfa[22,23,24]

[1]Liver Unit and HPB Oncology Area, Clínica Universidad de Navarra and CIBEREHD, Pamplona, Spain; [2]State Key Laboratory of Translational Oncology, Department of Clinical Oncology, Sir Yue-Kong Pao Center for Cancer, The Chinese University of Hong Kong, Hong Kong; [3]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, California, USA; [4]Humanity and Health Clinical Trial Center, Humanity and Health Medical Group, Hong Kong; [5]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan; [6]Department of Medicine, Songklanagarind Hospital, Khon Kaen University, Khon Kaen, Thailand; [7]Department of Medicine II, University Hospital, LMU Munich, Munich, Germany; [8]Kanagawa Cancer Center, Yokohama, Japan; [9]Department of Oncology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea; [10]Department of Internal Medicine I, University Medical Center, Mainz, Germany; [11]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; [12]Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [13]Department of Hepato-Gastroenterology, Robert-Debré Hospital, Reims, France; [14]Tom Baker Cancer Centre, Department of Oncology, University of Calgary, Calgary, Alberta, Canada; [15]Cancer Research and Clinical Trials Center, Department of Optimal Therapy, National Cancer Hospital, Hanoi, Vietnam; [16]Health Care Global Enterprises Ltd, Bangalore, India; [17]N. N. Blokhin Russian Cancer Research Center, Chemotherapy Unit, Moscow, Russia; [18]Department of Minimally Invasive and Endoscopic Surgery, Interventional Radiology, National Cancer Institute, Kyiv, Ukraine; [19]Barcelona Clinic Liver Cancer (BCLC), Liver Unit, Hospital Clinic de Barcelona, IDIBAPS, CIBEREHD, University of Barcelona, Barcelona, Spain; [20]Oncology R&D, Late-Stage Development, AstraZeneca, Gaithersburg, Maryland, USA; [21]Oncology Biometrics, Late Oncology Statistics, AstraZeneca, Wilmington, Delaware, USA; [22]Department of Medicine, Memorial Sloan Kettering Cancer Center, Cornell University, New York, New York, USA; [23]Weill Medical College, Cornell University, New York, New York, USA; [24]Trinity College Dublin, Dublin, Ireland

Aims: In the primary analysis (data cut-off: 27 August 2021) of the phase 3 HIMALAYA study (NCT03298451) in uHCC, STRIDE (Single Tremelimumab Regular Interval Durvalumab) significantly improved OS and demonstrated a durable long-term survival benefit versus sorafenib; durvalumab monotherapy was noninferior to sorafenib (Abou-Alfa et al. NEJM Evid 2022). Here, we report an updated 4-year OS analysis of HIMALAYA. **Methods:** Participants with uHCC and no previous systemic treatment were randomized to STRIDE (tremelimumab 300 mg for one dose plus durvalumab 1500 mg every 4 weeks [Q4W]), durvalumab (1500 mg Q4W) or sorafenib (400 mg twice daily). Data-cut off was 23 January 2023 (STRIDE OS data maturity, 78%). OS and serious treatment-related adverse events (TRAEs) were assessed. In addition, baseline demographics and disease characteristics were assessed in long-term survivors (LTS; participants surviving ≥36 months beyond randomization). **Results:** Follow-up duration was approximately 4 years across treatment arms (Table). The OS HR versus sorafenib (0.78; 95% CI, 0.67–0.92) and estimated 36-month OS rate (30.7%) for STRIDE were consistent with the primary

analysis. The 48-month OS rate remained higher for STRIDE (25.2%) versus sorafenib (15.1%). No new serious TRAEs occurred after the primary analysis for STRIDE (17.5%). Durvalumab OS noninferiority to sorafenib and safety was consistent with the primary analysis. Baseline demographics, clinical characteristics and subsequent therapies, including tremelimumab rechallenge, for LTS in the STRIDE arm were generally consistent with the full analysis set, suggesting that LTS were not from any particular subgroup. **Conclusions:** These data reinforce the sustained, long-term OS benefit of STRIDE versus sorafenib in a diverse uHCC population, demonstrating unprecedented 3- and 4-year OS rates and longest follow-up to date in phase 3 uHCC studies. STRIDE maintained a tolerable safety profile, with no new serious safety events. **Keywords:** Durvalumab, Immunotherapy, Long-Term Survival, Long-Term Survivors, Survival, Tremelimumab, Unresectable Hepatocellular Carcinoma

Table: Updated analysis of HIMALAYA with 4 years of follow-up (data cut-off: 23 January 2023)

	STRIDE (n=393)	Sorafenib (n=389)
Median follow-up duration (95% CI)	49.12 (46.95–50.17)	47.31 (45.08–49.15)
OS HR (95% CI)*	0.78 (0.67–0.92)	
OS rates, % (95% CI)		
36 months	30.7 (26.1–35.3)	19.8 (15.9–24.1)
48 months	25.2 (20.8–29.7)	15.1 (11.5–19.2)
Serious TRAEs (including death), n/N (%)	68/388 (17.5)	36/374 (9.6)

*OS HRs and CIs were calculated using a Cox proportional hazards model.

OP-20

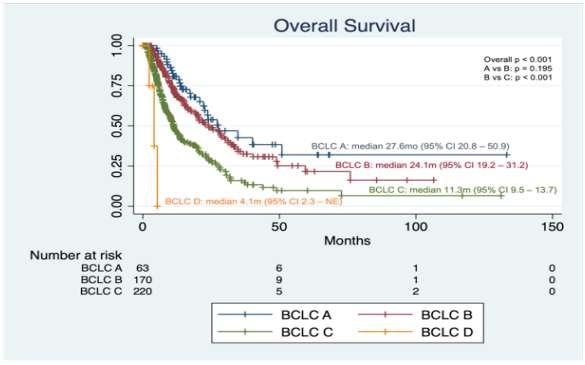
Survival Outcomes of Out-of-Milan Hepatocellular Carcinoma after Yttrium-90 Selective Internal Radiation Therapy in a Single Institution in Asia

Kaina Chen[1,2], Aaron Kian Ti Tong[4], Fiona Ni Ni Moe[3], Timothy Ong Sheng Khai[5], Yeo Eng Xuan[5], Daniel Peh Yang Yao[5], David Chee Eng Ng[4], Kelvin Siu Hoong Loke[4], Apoorva Gogna[6], Sean Xuexian Yan[4], Sue Ping Thang[4], Hian Liang Huang[4], Chow Wei Too[6], Weng Yan Ng[3], Pierce Chow[2,3,7]

[1]Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore; [2]Duke-NUS Medical School, Singapore; [3]Department of Surgical Oncology, National Cancer Centre Singapore, Singapore; [4]Department of Nuclear Medicine, Singapore General Hospital, Singapore; [5]Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [6]Department of Vascular and Interventional Radiology, Singapore General Hospital, Singapore; [7]Department of Hepato-pancreatico-biliary Surgery, Singapore General Hospital, Singapore

Aims: Selective internal radiation therapy (SIRT) or transarterial radioembolization (TARE) with yttrium-90 (Y90) has gained increasing popularity as a locoregional treatment for inoperable HCCs. Our study aims to evaluate the survival outcomes of HCC patients out of Milan Criteria, treated with resin-based SIRT Y90 in our institution. **Methods:** Patients above 18 years old treated with Y90 SIRT (SIR-Spheres®, Sirtex Medical, USA) between 1st January and 1st May 2019 at National Cancer Centre Singapore (NCCS) and Singapore General Hospital (SGH) were included. Important exclusion criteria were metastatic HCC, synchronous cancers, and significant missing data. All patients received Y90 SIRT within 4 weeks of ^{99m}Tc MAA study. Statistical analysis was performed with Stata/SE16.1 (StatCorp LLC). Ethical approval was granted by the Institutional Review Board. **Results:** A total of 457 patients with HCC out of Milan Criteria were included in the analysis. The majority of the HCCs were viral etiology (63.24%, 289/457), and 66.1% (302/457) were ALBI grade 2. Seventeen patients (4.2%, 17/399) developed radioembolization-induced liver disease (REILD), whereas 14 (3.5%) developed radiation pneumonitis (Table). Median overall survival was 20 months (95% CI 14.9 – 22.2) for the entire cohort. Survival by BCLC and further stratification with BCLC B subclassifications are shown in the figure. Survivals did not differ with age, gender, etiology, prothrombin time or multifocality. Multivariate analysis showed poor ECOG (HR 2.65, P<0.001), ALBI grade 2/3 (HR 1.5, P=0.004), AFP ≥ 400 ug/L (HR 1.5, P=0.001), Y90 absorbed dose <150 Grey (HR 2.0, P=0.004) and REILD (HR 3.2, P<0.001) were significant predictors of reduced survivals. **Conclusions:** We observed excellent clinical survival outcomes in HCC patients out of Milan Criteria treated with Y90 SIRT with a low complication rate. An absorbed dose of > 150 Gy is desired for better overall survival. **Keywords:** HCC, Y90-SIRT/TARE, Liver, Dosimetry

Figure 1. Kaplan-Meier survival curves of patients with HCC out of Milan criteria treated with Y90 SIRT, stratified by A) BCLC, B) BCLC B subclassification.



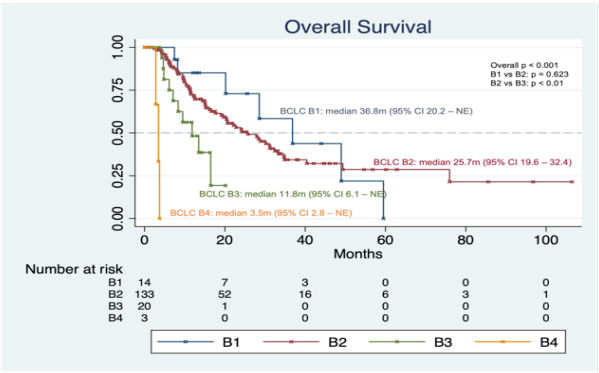


Table 1. Baseline Characters

Baseline Characters		N = 457	Proportions
Age	Mean (SD)	65.5 (11.2)	
	Median (IQR)	66.0 (59.5-72.5)	
	<65	199	43.50%
	>=65	258	56.50%
Gender	Male	384	84.00%
	Female	73	16.00%
ECOG	0 & 1	448	98.00%
	2 & 3	9	2.00%
Child Pugh	A	385	84.30%
	5	212	47.39%
	6	173	37.86%
	B	72	15.80%
	7	56	12.30%
	8	11	2.41%
	9	5	1.09%
ALBI	1	122	26.70%
	2	302	66.10%
	3	33	7.20%
Aetiology	HepB	226	49.50%
	HepC	58	12.70%
	HepB+C	5	1.10%
	Alcohol	29	6.40%
	NAFLD	89	19.50%
	Others	50	10.90%
Alpha-fetorotein (ug/L)	<400	246	66.50%
	>=400	124	33.50%
Tumour Burden	Solitary	129	28.35%
	Multifocal	326	71.65%
Tumour Size (cm)	<6cm	169	37.89%
	6-10cm	138	30.94%
	>10cm	139	31.17%
Tumour Location	Unilobar	229	50.33%
	Bilobar	226	49.67%
Portal Vein Invasion	No	263	57.55%
	Branch	135	29.54%
	Main and beyond	59	12.91%
BCLC	A	63	13.79%
	B	170	37.20%
	C	220	48.14%
	D	4	0.88%
BCLC SubB	B1	14	3.06%
	B2	133	29.10%
	B3	20	4.38%
	B4	3	0.66%
Y90 Injected Dose (GBq)	Mean (SD)	1.7 (1.0)	
	Median (IQR)	1.4 (1-2.3)	
Y90 Absorbed Dose (Grey)	Mean (SD)	151.5 (76.4)	
	Median (IQR)	130.6 (100.4-195)	
	<150	165	36.11%
	>=150	119	26.04%
	missing	173	37.86%
REILD	Yes	17	4.30%
	No	382	95.70%
Radiation Pneumonitis	Yes	14	3.50%
	No	385	96.50%

OP-21

Carbon Ion Radiation Therapy as a Local Salvage Treatment for Recurrent or Residual Hepatocellular Carcinoma Following Transarterial Chemoembolization

Kei Shibuya[1,2], Yoshihito Sekiguchi[2], Daijiro Kobayashi[1,2], Yuhei Miyasaka[1,2], Masahiko Okamoto[1,2], Tatsuya Ohno[1,2]

[1]Gunma University Heavy Ion Medical Center, Japan; [2]Department of Radiation Oncology, Gunma University Graduate School of Medicine, Japan

Aims: To clarify the usefulness of carbon-ion radiotherapy (C-ion RT) as a salvage treatment for recurrent or residual hepatocellular carcinoma (HCC) after TACE/TAE. **Methods:** Of all 300 cases treated with radical C-ion RT for hepatocellular carcinoma between September 2010 and September 2021. 106 cases with residual or recurrent HCC confirmed by imaging after prior TACE/TAE were retrospectively analyzed. The median age was 74.8 years (range: 45-91 years), and the median time from TACE/TAE to C-ion RT was 77 days (range: 14-734 days). Background liver diseases were hepatitis C/cirrhosis: 53, hepatitis B/cirrhosis: 12, combined hepatitis C/B: 2, alcoholic: 9, NASH/NAFLD: 13, normal liver: 14, other: 3. Liver function was Child-Pugh Grade A: 95 cases, B: 11 cases. Mean pretreatment ICG 15-minute retention rates was 23 (2.1-96.5)%. 96 cases had single lesions and 10 cases had multiple lesions treated in the same irradiated field. The mean tumor diameter of the largest lesion was 4.1 (0.9-10.4) cm. Patients received 52.8 Gy (RBE)/4 (22 patients), 60.0 Gy (RBE)/4 (83 patients), or 64.8 Gy (RBE)/12 (1 patient) of C-ion RT under respiratory synchronization. Local control and overall survival rates were calculated using the Kaplan-Meier method. Adverse events were evaluated by CTCAE ver. 4.0. **Results:** The median observation period was 30 months (1.0-12.9 months). The local control rates at 1 and 2 years were 95.8% and 93%, respectively, and the overall survival rates at 1 and 2 years were 88.3% and 76.3%, respectively. Acute adverse events of Grade 3 or higher, excluding transient laboratory abnormalities, were hepatic encephalopathy (Grade 3) in one patient; late adverse events of Grade 3 or higher were γGTP elevation (Grade 3) and radiation pneumonitis (Grade 3) in one patient and hepatic encephalopathy (Grade 3, difficult to distinguish from dementia) in one patient, respectively. There was no significant worsening of Child-Pugh Score at 3 and 6 months after treatment. **Conclusions:** C-ion RT can be an effective treatment for recurrent and residual HCC after TACE/TAE.
Keywords: Hepatocellular Carcinoma, Radiotherapy, Particle Radiotherapy, Carbon-Ion Radiotherapy

OP-22

Silencing of CircRNA-0033351 Represses Hepatic Stellate Cells Activation and Cytokine Storm Induced by Radiation Therapy for Primary Liver Cancer

Hao Niu, Li Zhang, Zhao-Chong Zeng

Zhongshan Hospital, Fudan University, Shanghai, China

Aims: Radiation-induced liver disease (RILD), also known as radiation hepatitis, is a serious side effect of radiotherapy (RT) for hepatocellular carcinoma. The activation of insubstantial hepatic stellate cells (HSCs) is the key process involved. This study was to explore the functions and mechanism of a new circular RNA, circRNA-0033351, in a human hepatic stellate cell line (LX-2) treated with radiation therapy for primary liver cancer. **Methods:** To explore the function of circRNA-0033351, small interfering RNAs targeting it were designed and a three-dimensional (3D) model of LX-2 cells was constructed. The viability of LX-2 cells was analyzed by cell proliferation assays, colony formation assays, and apoptosis assays. Enzyme-linked immunosorbent assay was used to detect the level of pro-inflammatory cytokines. Dual luciferase reporter assays, RNA pull-down assays, chromatin immunoprecipitation (known as ChIP), and a series of gain- or loss-of-function experiments were performed to explore the mechanism of circRNA-0033351. **Results:** The expression of circRNA-0033351 was significantly up-regulated in irradiated LX-2 cells compared with non-treated LX-2 cells. Interestingly, silencing of circRNA-0033351 inhibited LX-2 cell proliferation and significantly decreased the secretion of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α in irradiated LX-2 cells. Mechanistic analysis showed that circRNA-0033351 acted as the miR-708-5p sponge to regulate pro-inflammatory cytokine release through ZEB1/Wnt/β-catenin pathway. **Conclusions:** Silencing of circRNA-0033351 represses hepatic stellate cells activation and cytokine storm induced by radiation therapy through miR-708-5p/ZEB1/β-catenin pathway. These findings suggest that interference with circRNA-0033351 is a potential and critical therapeutic strategy for alleviating radiation hepatitis. **Keywords:** Circular RNA, Hepatic Stellate Cell Line, Radiation Therapy, Cytokine Storm

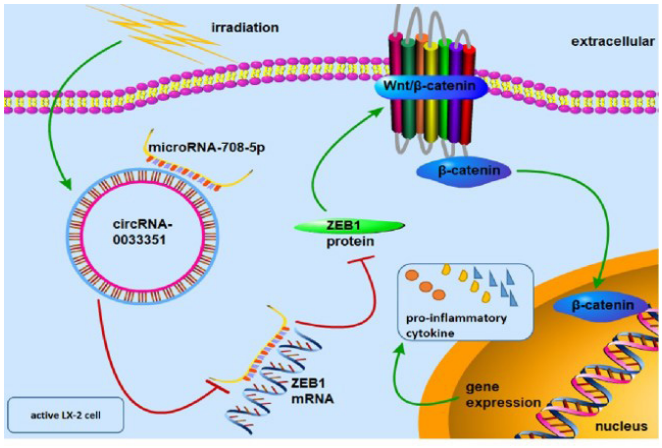


Figure1.Graphical abstract

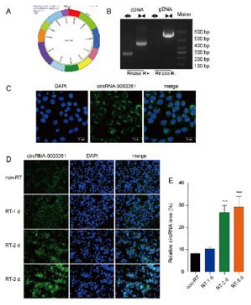


Figure 2. The expression of circRNA-0033351 was significantly up-regulated in irradiated-liver

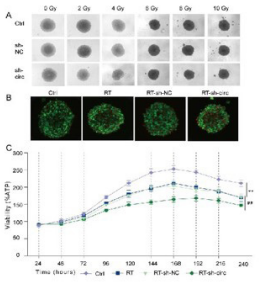


Figure 3.Knockdown of circRNA-003335 further reduced the proliferation of LX-2 cells activated by radiotherapy.

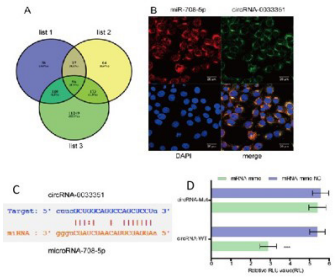


Figure 4. The interaction between circRNA-003335 and miR-708-5p

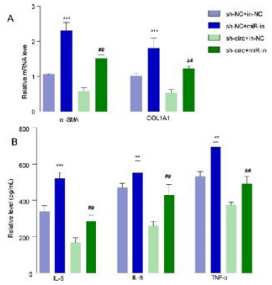


Figure 5. MiR-708-5p reverses the effect of circRNA-003335 on the activation and response of LX-2 cells treated with irradiation

OP-23

Performance and Effectiveness of Hepatocellular Carcinoma Screening in Individuals with HBsAg Seropositivity in China: A Multi-Center Population-Based Prospective Study

Hongmei Zeng, Maomao Cao, Changfa Xia, Dongmei Wang, Kun Chen, Zheng Zhu, Ruiying Fu, Chunfeng Qu, Wanqing Chen

National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China

Aims: The current guidelines recommend hepatocellular carcinoma (HCC) surveillance with ultrasonography (US) and/or serum alpha-fetoprotein (AFP) testing for at-risk individuals including those with hepatitis B virus (HBV) infection. However, the performance and survival benefits of annual screening have not yet been evaluated through a multi-center population-based prospective design in a Chinese population. Therefore, we aimed to systematically evaluate the performance and effectiveness of annual screening with US and AFP in individuals with HBV seropositivity using a multi-center prospective design. We further conducted an updated systematic review and meta-analysis to provide a comprehensive overview of the evidence on the association between screening and HCC survival additionally including the new results from this study. **Methods:** Between 2017 and 2021, we included 14,426 eligible participants in an organized annual HCC screening study in China using a multi-center prospective design. Selected persons were invited for each consecutive round at one-year interval. Until April 2021, we conducted four rounds of screening with US and AFP. Participants in whom HCC was

diagnosed were not offered subsequent screening tests. Local primary-care providers conducted active and passive follow-ups to track the HCC incidence as well as the vital status of all participants. We applied the Kaplan-Meier method to calculate HCC survival rate. Cox proportional hazard models were fitted to estimate the relationship between screening and survival, reported as HR and corresponding 95% CI. In the base case model, crude HRs were estimated without any adjustments. We further adjusted for lead-time and length-time biases. **Results:** After four rounds of screening and follow-up, we found 327 screen-detected cases overall. Compared with non-screened cancers (3-year survival: 25.7%), screen-detected cancers at incident rounds had the highest 3-year survival (50.8%), followed by screen-detected cancers at prevalent round (37.6%) and interval cancer (34.8%). The adjusted hazard ratios (HRs) of death after correction for lead-time bias and length-time bias for screen-detected cancers at the prevalent and incident rounds were 0.74 (95% confidence interval (CI): 0.60-0.91) and 0.52 (95% CI: 0.40-0.68), respectively. We further conducted a meta-analysis including 28 studies (244,827 participants) and demonstrated that HCC screening was associated with improved survival both before and after adjusting for lead-time bias. **Conclusions:** We demonstrated that both prevalent screening and incident screening are associated with survival benefits, and this survival advantage remained significant after correction for lead-time bias and length-time bias. The "real world" feasibility and effectiveness of annual HCC surveillance in community settings have important public health implications for HCC early detection and survival improvement, especially in resource-restricted regions with a high prevalence of HBV infection. **Keywords:** Hepatocellular Carcinoma, Screening, China, HBsAg Seropositivity

OP-24

Soluble Programmed Cell Death-1 as a Predictor of Hepatocellular Carcinoma Development during Nucleoside Analogue Treatment

Ritsuzo Kozuka, Masaru Enomoto, Minh Phuong Dong, Hoang Hai, Le Thi Thanh Thuy, Naoshi Odagiri, Kanako Yoshida, Kohei Kotani, Hiroyuki Motoyama, Etsushi Kawamura, Atsushi Hagihara, Hideki Fujii, Sawako Uchida-Kobayashi, Akihiro Tamori, Norifumi Kawada

Department of Hepatology, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan

Aims: Soluble immune checkpoint molecules are emerging novel mediators of immune regulation. However, it is unclear whether soluble immune checkpoint proteins affect the development of hepatocellular carcinoma (HCC) during nucleos(t)ide analogue (NA) treatment in patients with chronic hepatitis B virus infection. The aim of this study was to evaluate host immunological factors associated with HCC development, i.e., soluble immune checkpoint proteins, during NA treatment. **Methods:** This study included 122 NA-naïve patients (median age, 45 years old; 63.9% males and 85.2% with genotype C) who received NA therapy. We assessed the associations of clinical factors, including soluble immune checkpoint proteins, with HCC development during NA treatment. The baseline serum concentrations of 16 soluble immune checkpoint proteins were measured using multiplexed fluorescent bead-based immunoassay. **Results:** In total, 13 patients developed HCC during the follow-up period (median duration, 4.3 years). The fibrosis-4 index, platelet count, cirrhosis status, age, and α-fetoprotein were associated with HCC development during NA treatment in univariate analyses. Of the 16 proteins, soluble inducible T-cell co-stimulator (≥ 164.71 pg/mL; *P*=0.014), soluble programmed cell death-1 (sPD-1) (≤ 447.27 pg/mL; *P*=0.031), soluble CD40 (≤ 493.68 pg/mL; *P*=0.032), and soluble herpes virus entry mediator (≤ 2470.83 pg/mL; *P*=0.038) were significantly associated with HCC development (log-rank test). In multivariate analysis, an sPD-1 level ≤ 447.27 pg/mL (*P*=0.014; hazard ratio [HR], 4.537) and α-fetoprotein level ≥ 6.4 ng/mL (*P*=0.040; HR, 5.524) were independently and significantly associated with HCC development. The serum sPD-1 level at baseline was positively correlated with the ALT level ($p < 0.0001$, $r = 0.41$) and with the fibrosis-4 index ($p = 0.036$, $r = 0.19$). The serum sPD-1 level decreased rapidly after 6 ($p = 0.028$) and 12 ($p = 0.028$) months of NA treatment. **Conclusions:** Pre-treatment sPD-1 is a novel predictive biomarker for HCC development during NA treatment. **Keywords:** sPD-1, HCC, HBV, Hepatitis B

E-Poster Exhibition

Liver Cancer - Epidemiology and Surveillance

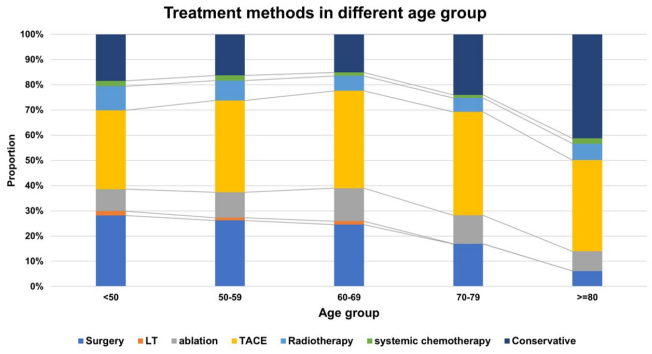
PE-01

Exploring Prognostic Disparities of HCC Treatment in the Elderly: An Analysis of the Korean Nationwide Cancer Registry Data

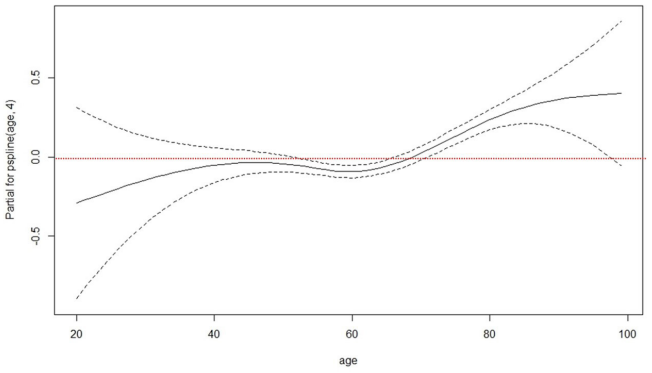
Ha Il Kim[1], Jihye Lim[2], Jihyun An[1], Joo Hyun Sohn[1]

[1]Department of Gastroenterology and Hepatology, Hanyang University College of Medicine, Guri, Republic of Korea; [2]Division of Gastroenterology and Hepatology, Department of Internal medicine, The Catholic University College of Medicine, Seoul, Republic of Korea

Aims: Although the incidence of hepatocellular carcinoma (HCC) is rising among the elderly population, there is a paucity of studies investigating the interplay between age and treatment diversity with respect to survival outcomes. **Methods:** The study population consisted of 7,014 individuals aged 20 years and older, who were identified through the Korea Primary Liver Cancer Registry for the years 2014 and 2017. Baseline characteristics, hepatocellular carcinoma (HCC) stage, treatment modalities, and overall survival (OS) were evaluated. Participants were stratified into five age groups (<50, 50-59, 60-69, 70-79, and ≥80 years), were stratified and compared by BCLC stage and treatment method. Cox regression model and restricted cubic spline (RCS) analysis were employed to establish the age cutoff at which the efficacy of curative and non-curative treatments diminished. Statistical significance was set at P<0.05 for all analyses. **Results:** The median age at the time of HCC diagnosis was 62 years with a male predominance (79.2%) and hepatitis B virus infection as the most common etiology (58.7%). The age distribution was 13.1% for <50 years, 30.2% for 50-59 years, 28.4% for 60-69 years, 21.5% for 70-79 years, and 6.7% for ≥80 years. Patients aged 70 years and above showed a decline in surgical treatment rate (28% to 14.3%) and a marked increase in conservative treatment rate (18% to 28%) compared to those under 70 years of age (Fig 1). This trend persisted in the analysis stratified by Barcelona Clinic Liver Cancer (BCLC) staging and comparable patterns was observed in the curative and non-curative treatment cohorts. Among patients who received only conservative treatment, no statistical differences in survival rate by stage were observed in age groups 70-79 and ≥80 years. Restricted cubic splines analysis using adjusted Cox regression results identified the age of 70 years as the threshold at which the potential treatment benefits began to diminish (Fig 2). **Conclusions:** For patients diagnosed with HCC after their mid-70s, the potential for prognostic benefit attributable to the cancer stage or treatment modalities may be diminished relative to the younger age group. Age-based risk stratification may be necessary in the context of individual clinical scenarios, and further research is required to assess the optimal timing for terminating HCC surveillance. **Keywords:** Hepatocellular Carcinoma, Elderly, Treatment, Prognosis



Restricted cubic spline by adjusted COX regression analysis



PE-02

Compliance of Screening of Hepatocellular Carcinoma in Patients with Chronic Viral Hepatitis

Won Sohn, Yong Kyun Cho, Byung Ik Kim

Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Republic of Korea

Aims: This study aimed to investigate the compliance of the screening for hepatocellular carcinoma (HCC) in patients with chronic viral hepatitis. **Methods:** A cross-sectional study was conducted based on nationally representative samples from the Korean National Health and Nutrition Examination Survey 2007-2012. Of 50,405 participants, a total of 1,275 patients with chronic hepatitis B or chronic hepatitis C were included in the final analysis. We investigated compliance of HCC screening using ultrasonography and serum alpha-protein. Univariable and multivariable logistic regression analyses were performed to evaluate the screening compliance associated risk factors such as age, sex, marital status, residential area, self-rated health status, education level, income status, private insurance for health care, alcohol and smoking. **Results:** The mean age of 1,275 patients was 49.4 years and male was 51% (n=618). The compliance of HCC screening was observed in 508 patients (40%): within 6 months

before the survey, 12 % (n=155); 6-12 months, 11% (n=134); >12 months, 17% (n=219). The multivariable analysis showed that compliance of HCC screening was significantly associated with age: 40-60 years (odds ratio [OR] 3.06 with 95% confidence interval [CI]: 2.26-4.15, *P*<0.001), age: >60 years (OR 2.92 with 95% CI: 1.93-4.42 *P*<0.001), self-rated health status: moderate (OR 1.42 with 95% CI: 1.07-1.89, *P*=0.016), self-rated health status: poor (OR 152 with 95% CI: 1.08-2.13, *P*=0.015), education: university or higher (OR 1.37 with 95% CI: 1.04-1.81, *P*=0.025), income: >50 percentile (OR 1.95 with 95% CI: 1.49-2.56, *P*<0.001) and private insurance for health care (OR 1.40 with 95% CI: 1.02-1.91, *P*=0.038). **Conclusions:** Compliance of HCC screening was favorable in patients with older age, poor health status, higher education level, high income and private insurance for health care in Korea. These findings may be helpful to increase HCC screening and surveillance rate in patients with chronic viral hepatitis. **Keywords:** Hepatocellular Carcinoma, Screening, Compliance, Chronic Hepatitis

PE-03

Impact of Newly Detected Diabetes by OGTT on Development of HCC

Seong Hee Kang[1,2], Moon Young Kim[1], Soon Koo Baik[1]*

[1]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea; [2]*Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea*

Aims: An association between diabetes mellitus (DM) and the development of hepatocellular carcinoma (HCC) in a study with infected HCV patients has been previously suggested. We aim to identify potential predictors of HCC, who were newly diagnosed with DM by oral glucose tolerance test (OGTT). **Methods:** This prospective observational study included 713 patients with either compensated or decompensated cirrhosis; these patients underwent a 75-g oral glucose tolerance test (OGTT). The patients were divided into three groups: patients with normal glucose tolerance (NGT), patients with IGT (100 ≤ fasting plasma glucose [FBG]< 126 mg/dL or 140 ≤ 2-h OGTT < 200 mg/dL), and patients with newly diagnosed DM (126 ≤ FBG or 200 mg/dL ≤ 2-h OGTT). **Results:** Among 713 patients, NGT was diagnosed in 139 (19.5%), IGT in 252 (35.3%), and DM in 322 (45.2%). HCC developed in 81 patients over a median follow-up period of 42.0 months (interquartile range, 20.5–66.5 months): NGT, 9.3%; IGT, 12.3%; and DM, 9.6%. In patients with compensated cirrhosis (CTP class A; n = 415), neither IGT (19/157; HR, 1.740; *P*=0.191) nor DM (22/173; HR, 1.784; *P*=0.163) conferred a higher risk for development of HCC. Among patients with decompensated cirrhosis (CTP class B and C; n = 298), both IGT (12/95; HR, 1.603; *P*=0.376) and DM (15/149; HR, 1.337; *P*=0.575) also did not have a significant impact on the development of HCC. However, a multivariate study in total patients showed that old age [adjusted hazard ratio (aHR) =1.043; 95% CI = 1.020–1.066; *P*<0.001], male (aHR, 3.959; 95% CI = 1.894–8.275; *P*<0.001), higher MELD score (aHR, 1.095; 95% CI = 1.033–1.161; *P*=0.002) and higher FBG by OGTT (aHR, 1.005; 95% CI = 1.001–1.010; *P*=0.018) were identified as independent predictors of the development of HCC. **Conclusions:** Although newly diagnosed IGT and DM by OGTT are not critical determinants for the development of HCC, higher FBG status carries an additional risk for HCC. These patients should also be carefully monitored for HCC. **Keywords:** HCC, Diabetes Mellitus, Oral Glucose Tolerance Test

PE-04

Do People with Liver Cancer Also Get a Financial Burden

Putri Ayu[1]

[1]Andalas University, West Sumatra, Indonesia

Aims: Analysis of the financial burden of liver cancer sufferers in the Sufi literature Liver cancer is the number three killer disease in the world. Patients with liver cancer are mostly caused by consuming cigarettes, alcohol, unhealthy lifestyles, and heredity. Liver cancer sufferers will have an impact on quality of life, among which the most impact is physical function, emotional function and financial function. This study analyzes how the finances of cancer sufferers are a burden or not. **Methods:** The method used is a systematic literature review. using reputable national and international journals. using Publish or Perish, filtering is done based on topics and keywords in the form of "liver cancer", "Financial Burden", and "Quality of Life". Then filtered using Mendeley for duplicate journals. The final step is in the form of filtering abstracts and titles. **Results:** The results show that the financial function is also included in the impact on the quality of life of patients with liver cancer. Sufferers have a large expenditure when Suffering Liver Cancer. A lot of costs are incurred from the treatment and treatment carried out. several journals show that Liver Cancer is a burden on state finances such as in Indonesia and China. in this country many sufferers are borne by the state. Even though the burden incurred is large, liver cancer patients can decrease, although the rate for full recovery is still high. **Conclusions:** So, Liver cancer places a valuable burden not only on patients but also on the healthcare system. Effective interventions within the health care system are needed to minimize the burden. However, prevention of this disease such as healthy lifestyle changes, early screening, and vaccination will help reduce the incidence of liver cancer, reduce mortality, and actually reduce the cost of the disease. **Keywords:** Liver Cancer, Financial Burden, Quality of Life, Literature

PE-05

Is It True That Religiosity Increases Survival Rate in Patients with Liver Failure?

Lintong Hottua Simbolon[1], Rosinta H P Purba[2]

[1]Law, Alumnus University of Lampung, Indonesia; [2]Department of Economics, Learning Up Institute, Indonesia

Aims: Recent research has established the multifaceted features

of religious involvement and evaluated how religious variables interact with diverse biobehavioral and psychosocial constructs to determine health status by suggested pathways linking religion and health. However, research on how the religiosity concept is associated with improved survival in liver failure patients remains unclear. This study aims to determine the characteristics of religiosity on the mental health quality of liver failure patients to increase survival rates. **Methods:** This study used a reputable published journal (PubMed/Medline, Scopus) with the following criteria, which were published in the last 10 years from 2011 to 2021, and using a questionnaire developed by Tix and Frazier (1998). Of several journals collected, 11 (eleven) articles were selected. **Results:** The study found that liver failure candidates with high religious coping (defined as having faith in God, trusting in God, seeking God's help, trying to perceive God's will in the disease, and worship or religious activities) have more pro-longed posttransplant survival than those with low religiosity. Patients with a negative score for the "seeking for God factor" were younger, but they had a three-fold increased risk of mortality from all causes compared to those with positive scores. Religiosity appears to be a coping mechanism for these people as they face the challenges of their new health problems. Further, it becomes median to mitigate mental health problems with lower levels of depression, higher rates of hope, and well-being. Further, it promotes lower patient mortality, including post-liver transplant patients, improved drug adherence, and better health behaviors. **Conclusions:** In conclusion, in patients with kidney failure, religion is attributed to prolonged survival rates. It's critical to emphasize how important it is for the care team to include religiosity as a disease-coping mechanism. Active coping, social support, and a multidisciplinary section may attempt transplanted patients to have an improved clinical outcome. **Keywords:** Religiosity, Mental Health, Prolonged Survival, Coping Mechanism

PE-06

Azathioprine on Risk of Extrahepatic Malignancy in Patients with Autoimmune Hepatitis: A Nationwide Claims Study in South Korea

Sung Hwan Yoo[1], Hyun Woong Lee[1], Jung Il Lee[1], Gi Hyeon Seo[2]*

[1]Department of Internal Medicine, Yonsei University College of Medicine, Gangnam Severance Hospital, Seoul, Republic of Korea; [2]Health Insurance Review and Assessment Service, Seoul, Republic of Korea

Aims: Long-term immunosuppressive therapy in patients with autoimmune hepatitis (AIH) increases the risk of extrahepatic malignancy in addition to hepatocellular carcinoma. However, the risk of extrahepatic malignancy is unknown in Korean AIH patients. We aimed to evaluate the impact of azathioprine (AZT) treatment on extrahepatic malignancy risks. **Methods:** We identified all persons diagnosed with AIH between 2008 and 2020. We included 8,280 patients with AIH, using the national claims data of the Health Insurance Review and Assessment Service (HIRA). The numbers of patients treated with and without AZT were 3,059 and 5,221, respectively. We estimated the cumulative risks of extrahepatic malignancy and hazard ratios (HRs) between patients treated with and without AZT. **Results:** Among 8,280 patients, the mean age was 56.7±13.5 years, 84.3% were women, and the follow-up period was 49.8±43.1 months. The mean age and sex are not different between patients treated with and without AZT. However, the number of patients with diabetes was higher in patients treated with AZT (31.3% vs. 28.0%). The number of patients with liver cirrhosis was higher in patients treated without AZT (36.0% vs. 38.9%). At the time of diagnosis, 85.5% of patients with AZT and 30.0% of patients without AZT were treated with steroids for more than 90 days (P<0.001). The incidence of extrahepatic malignancy was 1.36 and 1.23 per 100 person-years in the patients treated with AZT and without AZT, respectively (P=0.685). After we adjusted for confounding by age, sex, diabetes, and liver cirrhosis, the HR was 1.09 (95% confidence interval 0.79–1.51, P=0.600). **Conclusions:** The national claims data of HIRA did not show that AZT significantly increases the risk of extrahepatic malignancy among AIH patients. **Keywords:** Azathioprine, Risk, Malignancy, Autoimmune Hepatitis

PE-07

Utilization of Community-Based Health Centers (Puskesmas) to Improve Accessibility of Health Services for Liver Patients

Rosinta Hotmaida Pebrianti Purba

Department of Economics, Alumnus Universitas Gadjah Mada, Yogyakarta, Indonesia

Aims: More than 10% or 28 million of Indonesia's population are liver patients. Liver disease is the fifth most prominent cause of death for the elderly in Indonesia and is 3.3 times more likely to cause death due to infection with the Sars-Cov2 virus. The burden of government social insurance financing for liver disease in 2018 was one of the highest or reaching $235 million. Because the progression of fatty liver is very gradual (the silent killer) and new cases are known after an advanced stage. The Ministry of Health carries out a preventive program that reaches remote areas through various screenings. Utilizing Community-Based Health Centers (Puskesmas) as health facility that provides sub-district-based integrated services is expected to become early detection of liver disease. However, little is known about the effectiveness of Puskesmas in the framework of controlling liver disease. **Methods:** We utilize a longitudinal survey dataset from the 2014 Indonesia Family Life Survey (IFLS) to analyze and evaluate the effectiveness of the Puskesmas in improving the function of early liver disease detection. IFLS is a multi-level (individual, household, community, and facility levels), multi-topic, large-scale, and longitudinal survey that has been conducted in five waves since 1993. IFLS 2014 covers only 24 of all 34 Indonesian provinces. However, the covered provinces are also the most populated ones, so the survey is representative of 83% of the Indonesian population. **Results:** The analysis shows that the liver disease prevalence among observations is 1,9%. However, the percentage increases in senior citizens by two times or 3,8%, and 60% are men. The elderly with liver disease, whether they have

government social insurance or not, tend to access treatment at the Puskesmas. Given that Indonesia uses the Gate-Keeper system, the first-level health facilities are at the sub-district or community level. In addition to this, Posyandu Lansia, as an extension of Puskesmas, is also utilized by older people for routine health checks, obtaining food/supplements, and various meetings and counseling. Various integrated services can be accessed by the elderly from 80,353 Posyandu Lansia spread across 81,616 villages in Indonesia. The Posyandu Lansia is also a space for the elderly to access savings and loan financial services, religious activities, and political activities. Community-based health care is highly effective in improving the senior QoL in various aspects of life. However, 56% of older people who do not have insurance prefer traditional practitioners. **Conclusions:** The community-based health care outreach program is carried out by trained cadres whom the Ministry of Health jointly recruited, the Ministry of Social Affairs, and the Family Planning Agency. The Posyandu Lansia can be a forum that carries out early detection of liver disease and is very accessible in preventive programs and improving the elderly QoL through various health activities, hobbies, counseling, economics, religion, and politics. It also needs to address the covered social insurance for treatment and caregivers. **Keywords:** Integrated Care System, Liver Early Detection, Elderly with Liver Disease, Aging Market

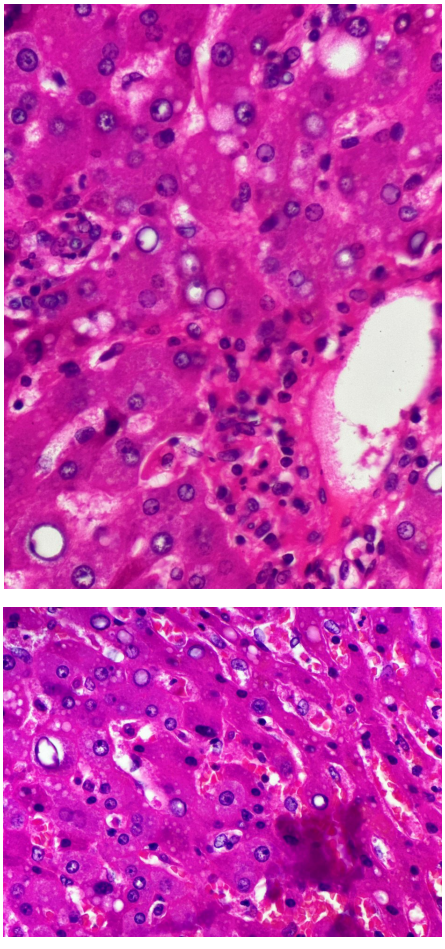
PE-08

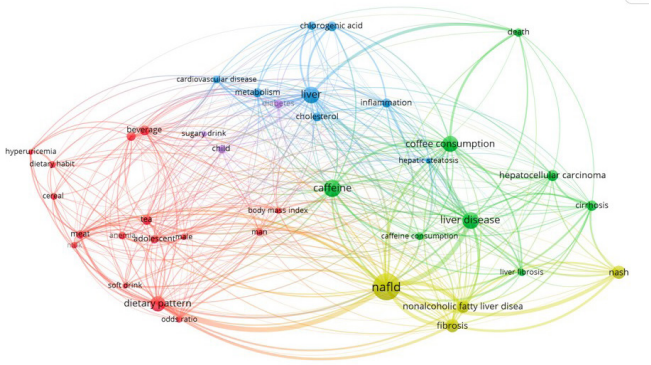
A Diagnosis of Intrahepatic Cholangiocarcinoma: A Case Report in the Philippines

Christian D. Jorge, Rouchelle D. Dela Cruz

Department of Pathology and Laboratories, Makati Medical Center, Philippines

Aims: 1. To report a rare case of intrahepatic cholangiocarcinoma with signet-ring cell subtype. 2. To be able to demonstrate key features of the rare subtype as the incidence increases worldwide. **Methods:** A 58 year-old male came in with a 1 month history of bloatedness and minimal weight loss. This prompted the patient to seek consult where ultrasound was done and showed a mass in the left lobe of the liver. The patient was then referred to a Gastroenterologist. Work-up and Computed tomography scan was done and showed lobulated and septated hypodense mass demonstrating heterogenous and peripheral enhancement with no discrete wash-out on delayed phase, located in segments II and III of the liver measuring 71.0 x 69.0 x 59.0 mm. Encasement of the left branch of the portal vein and resultant dilatation of the distal intrahepatic biliary ducts of segments II and III. The patient underwent laparoscopic converted to open left hepatectomy with caudate lobe showing the 1.0 cm hepatic mass occupying the left liver, which was hard and adherent anteriorly to the anterior peritoneum and the posterior aspect of the mass. The patient had no other lesions, especially from the rest of the gastrointestinal tract. On routine histopathology, submitted was the labelled "Left Liver" and collectively had the Segment II and III. The specimen weighted 504.5 grams and measured entirely at 15.0 x 11.0 x 7.0 cm. The liver capsule was smooth. Cut sections revealed an ill-defined, cream-tan to pink, soft to firm mass measuring 7.5 x 7.1 x 3.0 cm at segments II and III of the submitted specimen. There is a note of a milk-like fluid on dissection of the said mass. The mass was 0.3 cm from the nearest inked capsule. Representative sections were taken with the non-neoplastic liver. **Results:** Microscopic examination shows prominent mass effect with infiltration of the surrounding hepatic parenchyma. On higher magnification shows glandular forming cells with high nuclear to cytoplasmic ratio, marked pleomorphism and nuclear clearing. Striking features shows the scattered proliferation of the signet ring cell formations with intracellular mucin that displaces the nucleus to the periphery of the cell. Immunohistochemical staining for CK7, CK20, CK19, Ki67, Arginase-1, Heppar-1, Synaptophysin, Chromogranin, E-Cadherin and Moc-31 were done. The stains CK7 and CK19 turned out positive with a Ki67 of Low 8% proliferative index. The rest of the other immunohistochemical stains were negative. **Conclusions:** There are several international case reports of a signet ring cell subtype from intrahepatic cholangiocarcinoma that garnered recognition in the diagnosis of liver cancer as a whole and intrahepatic cholangiocarcinoma. This is the first reported case of Signet cell subtype in the Philippines. This is relevant as this diagnosis have implications in post-operative treatment and prognosis in these aggressive tumors especially in developing nations like the Philippines. Clinical data correlation and communication with the attending physician is necessary to be able to diagnose such rare tumor subtypes. **Keywords:** Liver Cancer, Intrahepatic Cholangiocarcinoma, Signet Ring, Cholangiocarcinoma





PE-09

Financial Burden of Liver Cancer: Problem and Solution for Liver Cancer Patient

Fitri Kurnia

Management Study Program, Economic Faculty, Universitas Muhammadiyah Sumatera Barat, Indonesia

Aims: Liver cancer is one of the deadliest cancers in Indonesia, therefore liver cancer is a health challenge that needs attention. In addition, liver cancer is a type of disease with high costs. This problem is certainly a challenge for cancer patients with low financial conditions, because they find it difficult to get treatment, especially those with severe liver cancer. Therefore, a solution is needed for liver cancer sufferers with financial difficulties, to get access to adequate health according to what they should get. **Methods:** Collected information from various articles, and made a selection with a focus category on financial solutions for liver cancer sufferers. **Results:** Identification of financial difficulties needs to start when someone is diagnosed with cancer, health care providers need to communicate proactively with patients about cancer treatment costs, other costs and potential disruption to the work of cancer sufferers. Health clinics also need to connect patients with financial assistance services (Government Assistance, Pharmaceutical Patient Assistance Programs, Nonprofit Programs for Co-Pay Relief, Cancer Organizations, General Organizations). Cancer patients who have received a diagnosis should budget for their daily needs. You can use the Money Advice and Budgeting Service. Patients should also begin to open up with the help of friends and family, this is very useful in difficult times and helps them deal with financial difficulties. Patients and families can take advantage of charitable institutions, for financial difficulties. **Conclusions:** There are several options that can be accessed by people with liver cancer in overcoming the problem of financial difficulties, these financial assistance services are in formal and informal forms. However, the most important is the financial identification performed by the patient after receiving a diagnosis of liver cancer, so that the financial condition and appropriate solutions can be mapped out. **Keywords:** Liver Cancer, Cancer Organizations, High Cost, Financial Difficulties

PE-10

The Changing Pathogenesis of Liver Cancer in Hawaii over Three Decades

Larry Hromalik, Linda L. Wong, Brenda Hernandez, Sandi A. Kwee

University of Hawaii, School of Medicine, USA; University of Hawaii, Cancer Center, USA

Aims: Worldwide trends support the increasing contribution of hepatic steatosis on the incidence of hepatocellular carcinoma (HCC). This study investigates if similar changes are seen in Hawaii, where the incidence of HCC is higher than most of the United States. **Methods:** This is a retrospective study of 1651 patients with HCC from an observational dataset 1991 to 2023 that includes 60-70% of Hawaii's liver cancer cases. Data collected included demographics, risk factors, disease etiology, treatment and outcome. We divided the database into various time intervals and compared the impact of each of these risk factors to evaluate for changes in risk factors over time. **Results:** From 1991-2023, there was an overall increase in the proportion of HCC cases presenting in patients with Nonalcoholic fatty liver disease/steatohepatitis (NAFLD/NASH) alone or NAFLD/NASH with accompanying cirrhosis. Conversely, HCC cases presenting with cirrhosis alone decreased. There were inconsistent fluctuations in the proportion of cases negative for both cirrhosis and NAFLD/NASH. From 1991-2023, there were significant increases in the proportion of HCC cases with NAFLD/NASH and metabolic risk factors including obesity, type 2 diabetes, hyperlipidemia, and hypertension. Cases with a history of smoking increased through 2020. HCV-associated cases increased through 2015 while HBV-associated cases decreased through 2020. There was no significant change in the proportion of alcohol-associated cases. **Conclusions:** While hepatitis B continues to be a major contributor to HCC in Hawaii, cases of Hepatitis C related HCC are declining. The data also supports increasing influence of metabolic risk factors and NAFLD/NASH on the incidence of HCC in Hawaii, paralleling trends observed elsewhere in the United States. Efforts will need to be made to manage these metabolic factors if we are to meaningfully decrease the impact these trends. **Keywords:** Hepatocellular Carcinoma, Nonalcoholic Steatosis, Hyperlipidemia, Diabetes

Diagnosis Year	NAFLD/NASH (p<0.0001)	Hyperlipidemia (p<0.0001)	Diabetes (p<0.0001)	Obesity (p<0.0001)	Excess Alcohol (p<0.0001)	HBV (p<0.0001)	HCV (p=0.009)	Smoking (p<0.0001)	Hypertension (p=0.0039)
1993-1997 (n=84)	3.6	6.6	32.9	6	35.7	51.2	28.2	41.1	40
1998-2002 (n=162)	8.6	10.3	26.5	8.6	38.3	42.6	31.5	52.9	58.1
2003-2007 (n=234)	5.6	18.9	25.2	17.1	46.2	40.6	42.7	59.4	49
2008-2012 (n=351)	12.8	26.5	35.3	23.1	43.6	38.6	40.5	63	59.4
2013-2017 (n=436)	15.3	32.8	42.7	27.5	43.5	28.6	46.7	67.2	62.4
2018-2022 (n=370)	29	51.6	45	27.3	43.4	32.2	34.3	65	65.4
Overall (n=1,613)	15.2	30.4	37	22.1	43	35.8	39.6	62.1	60.3

PE-11

Relationship between Coffee Consumption, Hepatic Cancers in Metro City Population

Sumit Rajput, Priya Tiwari

Department of Physiology, Bharati Vidyapeeth Deemed University, India

Aims: Carcinoma of the liver and gallbladder is a rare malignancy generally associated with a late presentation and a poor prognosis. Occupational exposures in the rubber, automobile, wood-finishing, oil, paper, chemical, textile, shoe, fiber and metal-fabricating industries lead to increased risk. To investigate the relationship between coffee consumption, hepatic cancers and gallstone disease in metro city population **Methods:** A population-based case-control study was conducted in urban Mumbai city from 15 July 2019 to 31 August 2020 involving interviews with 832 new cases of liver cancers (including 368 cases of gallbladder cancer, 191 cases of extrahepatic bile duct cancer and 68 cases of cancer of the ampulla of Vater) aged 35 to 74 years and 879 population controls frequency-matched to cases by gender and age in five-year group. 937 patients of gallstone disease were selected from the same hospital. All subjects were interviewed in person by trained interviewers by use of a structured questionnaire. Unconditional logistic regression analysis was used to calculate adjusted odds ratio (OR) and 95% confidence interval (CI). **Results:** Compared with coffee non-drinkers, current coffee consumption was inversely associated with risk of liver and gallbladder cancer, extrahepatic bile duct cancer and gallstone disease among females with OR of 0.57 (95% CI: 0.34-0.96), 0.53 (95% CI: 0.27-1.03) and 0.71 (95% CI: 0.51-0.99), respectively. OR declined with younger age at initiation of coffee drinking and with longer duration of coffee consumption (P for trend < 0.05). Among males, the corresponding OR were mostly below one, although not statistically significant. **Conclusions:** Coffee consumption may decrease the risk of liver cancers and extrahepatic bile duct among females. The protective effect appears to be independent of gallstone disease. **Keywords:** Hepatic Cancers, Coffee Consumption, Population

PE-12

Recurrence Rate-Based Strategy to Tailor Surveillance Scheduling in Single Hepatocellular Carcinoma ≤ 2cm after Curative Therapy: Analysis of 6,105 Global Patients

Ming Zhao[1,2,3], Qi-Feng Chen[1,2,3], Ning Lyu[1,2,3]

[1]Department of Minimally Invasive Interventional Therapy, Liver Cancer Study and Service Group, Sun Yat-sen University Cancer Center, Guangzhou, China; [2]State Key Laboratory of Oncology in South China, Guangzhou, Guangdong, China; [3]*Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China*

Aims: For initially diagnosed very early-stage hepatocellular carcinoma (HCC, VEH, i.e. single Hepatocellular Carcinoma ≤2 cm), surveillance after surgical resection (SR) or radiofrequency ablation (RFA) remains largely unclear. We conducted this multicenter study to explore optimal surveillance strategies and evaluate the current surveillance strategies for initially diagnosed VEH after SR/RFA to support the clinical follow-up schedule. **Methods:** A total of 6,105 initially diagnosed VEH patients who received SR/RFA from global centers were included. After the measurement of the recurrence rate of each month, delayed detection times for tumor recurrence of various follow-up strategies were calculated. The candidate strategies were evaluated according to the delayed detection times and the tumor volume doubling time (TVDT), and a preferable surveillance strategy was recommended. **Results:** The cumulative 1-, 2-, 3-, 4-, and 5-year recurrence probabilities were 12.7%, 25.9%, 35.7%, 43.7%, and 49.3%, respectively. Based on the monthly recurrence rate, programing surveillance schedules were tailored, which were more effective than current surveillance strategies under the same visits. When patients were followed up every 6 months, the delayed recurrence detection after curative treatment was expected to be 2.35 to 2.57 months. Given that 93.3% of patients would not have >TVDT with a rapid growth subtype when recurrent nodules were detected, a surveillance strategy with a 6-month interval was recommended. **Conclusions:** Six months of interval surveillance was conservatively supported in patients with VEH after curative therapy. **Keywords:** Very Early-Stage, Liver Cancer, Recurrence, Follow-Up

PE-13

Preventable Death from Liver Cancer

Lyazzat Kosherbayeva, Nazgul Akhtayeva, Kamshat Tolganbayeva

Asfendiyarov Kazakh National Medical University, Kazakhstan

Aims: Mortality from liver cancer is increasing every year and it is expected to rise by >55% by 2040 (H.Rumgay, 2022), Particularly in Kazakhstan can rise from 2020 to 2040 to +64.3% (Liu Y, Liu L. 2022). This study aimed to provide the trend of preventable mortality from liver cancer in Kazakhstan. **Methods:** Data collection was obtained from the Bureau of National Statistics of the Agency for Strategic Planning and Reforms of the Republic of Kazakhstan. The following data were obtained for the analysis of mortality rates: population by age categories in the Republic of Kazakhstan; mortality rates due to liver cancer from 2015 to 2021, by gender and 5-year age group (0, 1–4, 5–9, 10–14, . . . , 74 +). The selection of causes of death for the lists of preventable and treatable causes was taken from Organization for Economic Cooperation and Development (OECD)/Eurostat lists of preventable and treatable causes of death (January 2022 version). We used the age-standardized death rates given by OECD 2015 and corresponding 95% confidence intervals (95% CIs) were calculated for the age group 0–74 years and gender. **Results:** Preventable mortality from liver cancer decreased from 6.02 (95% CI: 5,51;6,53) to 4.02 (95% CI: 3,67;4,37) per 100000 populations during 2015-2021. The preventable mortality rates in male were three times higher in comparison to female. The number declined from 8,73(7,75;9,71) to 6,14(95% CI: 5,45;6,83) in males, whereas in females the preventable mortality decreased about two times over the period given (from 95% CI: 4,1(3,55;4,65) to 2,47(2,1;2,84)). **Conclusions:**

The introduction of screening programs for cancer and indicators for early detection make it possible to provide timely assistance, thereby reducing mortality. however, health policy makers need to take a closer look at the causes of death among the male population and develop specific interventions for this population. Funding: This research has been funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. AP09058136). **Keywords:** Preventable Mortality, Liver Cancer, Kazakhstan

PE-14

Surveillance of Hepatocellular Carcinoma Is Cost-Effective in Chronic Viral Hepatitis Patients in Korea

Young Youn Cho[1§], Hye-Lin Kim[2§], Eun Sun Jang[3], Dae Won Jun[4], Gi Hyeon Seo[5], Hyung Jun Kim[1*]*

[1]Department of Internal Medicine, Chung-Ang University Hospital, Republic of Korea; [2]College of Pharmacy, Sahmyook University, Republic of Korea; [3]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Republic of Korea; [4]Department of Internal Medicine, Hanyang University College of Medicine, Republic of Korea; [5]Health Insurance Review and Assessment Service, Republic of Korea
[§]These authors contributed equally to this work.
[*]Corresponding Author

Aims: Biannual hepatocellular carcinoma (HCC) surveillance of ultrasound (US) and alpha-fetoprotein (AFP) is recommended for chronic viral hepatitis and liver cirrhosis. However, there are little evidence supporting HCC surveillance in chronic hepatitis patients. In Korea, US was reimbursed in April 2018. After reimbursement, nationwide cost of the HCC surveillance program could be analyzed. This study aimed to check whether the HCC surveillance program was cost-effective using the nationwide cohort data. **Methods:** We designed a Markov model to compare the expected costs and quality-adjusted live-years (QALYs), between biannual and annual surveillance compared to no surveillance, with a 20-year time horizon. The starting age of the cohort was set to 40 or 50 years. Transition probabilities and costs were obtained mainly from the National Health Insurance database. An incremental cost-effectiveness ratio (ICER) was calculated. Early HCC was defined by treatment methods. **Results:** In liver cirrhosis patients, with starting age of 40, biannual and annual surveillance resulted in ICERs of $17,911 and $12,739 per QALY, respectively. When surveillance was restricted to chronic viral hepatitis patients without cirrhosis, with starting age of 40, biannual surveillance was marginally cost effective. Biannual and annual surveillance resulted with ICERs of $20,597 and $16,253 per QALY, respectively. After increasing the starting age to 50, both biannual and annual surveillance was cost effective, with ICERs of $12,288 and $9,742 per QALY respectively. **Conclusions:** In Korea, HCC surveillance program was cost effective in most clinical scenarios for liver cirrhosis and chronic viral hepatitis patients. **Keywords:** Hepatocellular Carcinoma, Surveillance, Chronic Hepatitis, Liver Cirrhosis, Cost-Effectiveness

Liver Cancer - Diagnosis and Liver Imaging

PE-15

The Relationship between Dental Health and Liver Cancer Risk

Syafri Suardi[1]

[1]Universitas Muslim Indonesia, Indonesia

Aims: Liver cancer is one of the deadliest diseases worldwide. Although there are some known risk factors such as exposure to chemicals and infection with hepatitis B and C viruses, other factors such as dental health may also contribute to a person's risk of developing liver cancer. However, the relationship between dental health and liver cancer is still not fully understood. **Methods:** To evaluate the relationship between dental health and liver cancer, we conducted a case-control study with liver cancer cases drawn from hospitalized patients and controls drawn from patients who did not have liver cancer. The data collected included information about dental and oral health history, such as the number of missing teeth, periodontal status, and history of dental treatment. We also collected information about other risk factors for liver cancer such as a history of alcohol and smoking, and a history of viral hepatitis infection. **Results:** Comparing data from 100 liver cancer cases and 100 controls, we found that people who had lost more teeth had a higher risk of developing liver cancer. People who have poor periodontal status also have a higher risk. However, we found no significant association between history of dental treatment and risk of liver cancer. After controlling for other risk factors, we found that oral health was still an independent risk factor for liver cancer. **Conclusions:** Our findings show that oral health can affect a person's risk of developing liver cancer. This shows that good dental and oral health care can help prevent liver cancer. However, further studies are needed to understand the mechanisms underlying this relationship and how better dental care can reduce the risk of liver cancer. **Keywords:** Liver Cancer, Dental Health, Risk Dental Health

PE-16

Assessment of Liver Function Test in Vegetarian and Non-Vegetarian

Santosh Kumar Gupta

School of Health and Allied Sciences, Pokhara University, Pokhara, Nepal

Aims: The aim of the study was to examine whether vegetarians had a lower risk of fatty liver disease and less severe liver fibrosis compared to non-vegetarians. This study will be carried out to evaluate different parameters of Liver Function Test in vegetarians and non-vegetarians. **Methods:** In this study, 174 vegetarian and non-vegetarian healthy people were included from Frontline Hospital, Old Baneshwor, Kathmandu, Nepal. In a vegetarian diet, the food intake of a person is confined to a large variety of

foods derived from plants along with milk and dairy. And any form of meat and products derived from animals are completely avoided. A non- vegetarian diet includes all forms of plant foods as well as foods and by-products that are derived from animals, such as poultry, fish, meat, etc. The results of Liver Function Test were performed using Fully automated analyzer (i.e.; Mindray BS-360E) during the year 2022In this study, 174 vegetarian and non-vegetarian healthy people were included from Frontline Hospital, Old Baneshwor, Kathmandu, Nepal. In a vegetarian diet, the food intake of a person is confined to a large variety of foods derived from plants along with milk and dairy. And any form of meat and products derived from animals are completely avoided. A non-vegetarian diet includes all forms of plant foods as well as foods and by-products that are derived from animals, such as poultry, fish, meat, etc. The results of Liver Function Test were performed using Fully automated analyzer (i.e.; Mindray BS-360E) during the year 2022. **Results:** In total of 174 vegetarian and non-vegetarian people, the mean ±SD of total bilirubin in vegetarian was 0.42 ± 0.18 and 0.83 ± 0.32 in non-vegetarian which was significant at $P<0.05$. Similarly, direct bilirubin was also significant at $P<0.05$ where its mean ± SD was calculated as 0.27± 0.17. Also, SGOT, Total protein were significant in non-vegetarian at $P<0.05$. but there was no significant change in SGPT, ALP and albumin in vegetarian and non-vegetarian. **Conclusions:** From this study, it can be concluded that dietary pattern is significantly associated with liver function test. And liver enzymes show a positive correlation with respect to the finding, it is necessary to follow vegetarian diet rather than non-vegetarian diet. **Keywords:** Vegetarian, Liver Function Test, Diet, Non-Vegetarian

Table 2: Baseline characteristics of study parameters (n=174)

Variables	Frequency (n)	Percentage (%)
Total bilirubin, gm/dL		
Normal	168	96.55
High	6	3.45
Direct bilirubin, gm/dL		
Normal	148	85.06
High	26	14.94
SGPT		
Normal	146	83.91
High	28	16.09
SGOT		
Normal	122	70.11
High	52	29.89
Alkaline phosphate		
Normal	151	86.78
High	23	13.22
Total protein		
Normal	12	6.90
High	162	93.10
Albumin		
Low	3	1.72
Normal	160	91.25
High	11	6.32

In the table no.2, the baseline characteristics of study parameters were taken. The parameters for liver function test are: Bilirubin (total &direct), SGPT, SGOT, ALP, Total protein and Albumin. In total study population ,168 normal and 6 high total bilirubin was measured. Direct bilirubin was normal in 85.06% of total study population and 14.94% was high in the study. Likewise,

Table 2: Baseline characteristics of study parameters (n=174)

Variables	Frequency (n)	Percentage (%)
Total bilirubin, gm/dL		
Normal	168	96.55
High	6	3.45
Direct bilirubin, gm/dL		
Normal	148	85.06
High	26	14.94
SGPT		
Normal	146	83.91
High	28	16.09
SGOT		
Normal	122	70.11
High	52	29.89
Alkaline phosphate		
Normal	151	86.78
High	23	13.22
Total protein		
Normal	12	6.90
High	162	93.10
Albumin		
Low	3	1.72
Normal	160	91.25
High	11	6.32

In the table no.2, the baseline characteristics of study parameters were taken. The parameters for liver function test are: Bilirubin (total &direct), SGPT, SGOT, ALP, Total protein and Albumin. In total study population ,168 normal and 6 high total bilirubin was measured. Direct bilirubin was normal in 85.06% of total study population and 14.94% was high in the study. Likewise,

PE-17

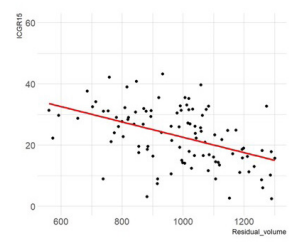
Gd-EOB-DTPA Binding T1 Mapping Phase Show Potential to Be a Way to Evaluate Per-Unit Liver Function

Yuchen Yang[1], Zhehan Shen[2], Huimin Lin[2], Di Ma[1], Yongjun Chen[2]

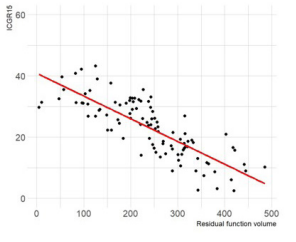
[1]Department of General Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, China; [2]Department of Radioloy, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, China

Aims: Liver function evaluation is an important clinical demand in the diagnosis and treatment for HCC patient. Quantification of per liver-unit function plays a decisive role in precise planning and navigation of hepatocellular carcinoma surgery. **Methods:** We enrolled 104 patients with pathologically diagnosed primary hepatocellular carcinoma. The correlation with ICG15 was calculated using residual liver volume, MR Elastography c value, and Gd-EOB-DTPA binding T1 mapping phase, respectively. **Results:** Gd-EOB-DTPA binding T1 mapping phase gets batter correlation with ICG15(Person_r = -0.8046) than residual liver volume (Person_r = -0.4631). The AUC which using T1-mapping phase data to detect patients with ICG15 greater than 14% is 0.93 **Conclusions:** T1-mapping show better efficiency when evaluating liver function than residual liver volume, and T1-mapping phase data may quantitatively evaluate per liver-unit function to optimize

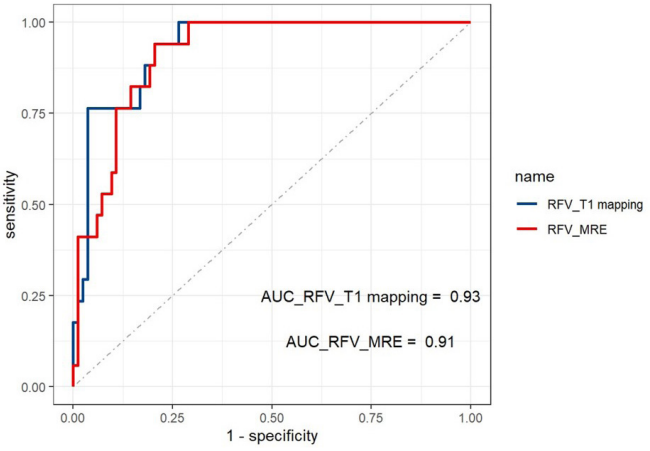
HCC surgical plan. **Keywords:** Gd-EOB-DTPA MR, T1 Mapping, Liver Function Evaluation, Surgical Planning



RV correlation with ICG15
(Person_r = -0.4631)



T1-mapping correlation with ICG15
(Person_r = -0.8046)



PE-18

Sociodemographic and Clinical Factors Associated with US LI-RADS Visualization Scores and Reasons for Limited Visualization among an Underserved Population at a Safety Net Healthcare System

Sera Kim[1], Mandana Khalili[2], Rena Fox[3], Stephanie Kim[4], Hailey Choi[1]

[1]Department of Radiology and Biomedical Imaging, University of San Francisco in California, USA; [2]Department of Internal Medicine, Zuckerberg San Francisco General Hospital, USA; [3]Department of Internal Medicine, University of San Francisco in California, USA; [4]University of San Francisco in California School of Medicine, USA

Aims: To identify sociodemographic and clinical factors associated with severely limited visualization score (VIS-C) on ultrasound (US) for hepatocellular carcinoma (HCC) screening. **Methods:** In this retrospective study, the radiology report database was queried for any patients who underwent US screening between 6/1/2020-2/28/2021; the initial and any follow-up US exams for interpreting radiologists' visualization scores and reasons were used. EMR was reviewed for sociodemographic and clinical factors. Univariate and multivariate analyses evaluated associations with VIS-C adjusted for age, sex, race. **Results:** Initial query yielded 937 patients; 10 without reported visualization scores were excluded. Final sample included 1873 US exams in 927 patients with following demographics: mean age 60; 57% male; 58% Asian, 16% White, 14% Hispanic, 9.7% Black, and 3.0% other; median BMI was 25.2 (range 14.1-52.88). Etiology of liver disease were: 61% hepatitis B (HBV), 21% hepatitis C (HCV), 19% non-alcoholic fatty liver disease (NAFLD), 13% alcohol-related liver disease (ALD), and 3.2% other. The rate of VIS-C was 2.3% (44/1873). Reasons were: sound attenuation (61%), parenchymal heterogeneity (32%), limited acoustic window (14%), bowel gas (4.5%), and body habitus (2.3%); 7/44 had multiple reasons. On univariate analysis, patients with VIS-C (vs no VIS-C) were more likely to be Hispanic and White race (11% and 13% vs 21% and 25%, P=0.003), have higher BMI (median 29.3 vs 25.2 kg/m2, P<0.001), use alcohol (34.1% vs 20.0%, P=0.036), be former smokers (45.5% vs 22.8%, P<0.001) have ALD (22.7% vs 10.4%, P=0.021) or NAFLD (36.4% vs 19.7%, P=0.006), or decompensated cirrhosis (11.4% vs 3.5%, P=0.021). Cirrhosis was not correlated (P=0.10). A lower proportion VIS-C (vs no VIS-C) had HBV (47.7% vs 69.1%, P=0.003). On adjusted multivariate analysis, higher BMI was positively associated with VIS-C (OR 1.12, 95CI 1.06-1.18, P<0.001). **Conclusions:** In this diverse, underserved patient population receiving HCC screening, higher BMI was predictive of poorer visualization scores. Sound attenuation was the most common reason for VIS-C exams. **Keywords:** Liver Reporting and Data System, Sociodemographics, Abdominal Ultrasound, Epidemiology and Surveillance

PE-19

Intraindividual Comparison of MRIs with Extracellular and Hepatobiliary Contrast Agents for the Noninvasive Diagnosis of Hepatocellular Carcinoma Using the Korean Liver Cancer Association-National Cancer Center 2022 Criteria

Sunyoung Lee[1]

[1]Department of Radiology, Severance Hospital, Yonsei University College of Medicine, Republic of Korea

Aims: The aim of the present study was to evaluate the per-lesion sensitivity and specificity of the Korean Liver Cancer Association-National Cancer Center (KLCA-NCC) 2022 criteria for the noninvasive diagnosis of hepatocellular carcinoma (HCC), with intraindividual comparison of the diagnostic performance of magnetic resonance imaging (MRI) with extracellular agents (ECA-MRI) and hepatobiliary agents (HBA-MRI). **Methods:** Patients at high risk for HCC who were referred to a tertiary academic institution for hepatic lesions with size ≥ 10 mm between July 2019 and June 2022 were enrolled. A total of 91 patients (mean age, 58.1 years; 76 men and 15 women) with 118 lesions who underwent both ECA-MRI and HBA-MRI were eligible for final analysis. The per-lesion sensitivities and specificities of the KLCA-NCC 2022 criteria using ECA-MRI and HBA-MRI were compared using McNemar's test. **Results:** The 119 lesions were 93 HCCs, 4 non-HCC malignancies, and 21 benign lesions. On HBA-MRI, the "definite" HCC category

showed significantly higher sensitivity than ECA-MRI (78.5% vs. 58.1%, $P<0.001$), with identical specificity (92.0% vs. 92.0%, $P> < 0.001$), with identical specificity (92.0% vs. 92.0%, $P>0.999$). For "probable" or "definite" HCC categories, there were no differences in the sensitivity (84.9% vs. 84.9%, $P>0.999$) and specificity (84.0% vs. 84.0%, $P>0.999$) between ECA-MRI and HBA-MRI. **Conclusions:** The "definite" HCC category of the KLCA-NCC 2022 criteria showed higher sensitivity in diagnosing HCC on HBA-MRI compared with ECA-MRI, without compromising specificity. There were no significant differences in the sensitivity and specificity of "probable" or "definite" HCC categories according to ECA-MRI and HBA-MRI. **Keywords:** Hepatocellular Carcinoma, Magnetic Resonance Imaging, Gadolinium, Radiology

PE-20

Mass-Forming Intrahepatic Cholangiocarcinoma: Preoperative Subcategorization Based on Magnetic Resonance Imaging

Yuyao Xiao[1], Mengsu Zeng[2]

Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai, China

Aims: To investigate the role of MR imaging features in preoperatively differentiating the iCCA subtype. **Methods:** The study retrospectively included 93 patients with mass-forming intrahepatic cholangiocarcinoma (iCCA; mean age, males vs. females: 60.66 ± 10.53 vs. 61.88 ± 12.82, 50 men). Uni- and multivariate logistic regression analyses were used to establish a predictive model for iCCA subcategorization based on significant imaging features. In addition, diagnostic performance parameters and corresponding receiver operating characteristic (ROC) curves of single significant imaging features and the predictive model were obtained. **Results:** The univariate analysis showed that visible vessel penetration, arterial phase hypoenhancement, peritumoral duct dilatation, lack of targetoid restriction and lack of T2 targetoid appearance were predictors of large duct type iCCA. In multivariate analysis, arterial phase hypoenhancement, peritumoral duct dilatation and lack of targetoid restriction were determined as independent predictors for large duct type iCCA. The regression-based predictive model achieved satisfactory preoperative prediction performance in iCCA subcategorization with the area under the ROC curve of 0.91 (95% CI: 0.85, 0.98), which performed much better than every single significant imaging feature. **Conclusions:** Arterial phase hypoenhancement, peritumoral duct dilatation and lack of targetoid restriction was valuable MR imaging indicators of large duct type iCCA. MR imaging characteristics can facilitate preoperative subcategorization of iCCA with satisfactory predictive performance. **Keywords:** Cholangiocarcinoma, Liver Neoplasms, Magnetic Resonance Imaging, Diagnosis Criteria

PE-21

Combined Hepatocellular Carcinoma-Cholangiocarcinoma: HCC Percentage Higher than 65% Predicted by Preoperative MR Features Is Prognostic

Yuyao Xiao[1], Mengsu Zeng[2]

Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai, China

Aims: To investigate the threshold value of HCC% for stratifying prognosis of patients with combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA), and to determine which preoperative MR characteristics have a role in predict the HCC% in cHCC-CCA. **Methods:** 107 patients with solitary pathologically confirmed cHCC-CCA were retrospectively included (mean age, males vs. females: 56.6 ± 10.7 years vs. 54.2 ± 12.8 years). The threshold value of HCC% for prognosis stratification was determined using receiver operating characteristic (ROC) curve and Youden Index with the reference of overall survival (OS), with which all enrolled patients were further divided into high- and low-HCC% groups. Uni- and multivariate logistic regression analysis were used to obtain significant predictors among preoperative MR imaging characteristics and clinicopathological information. **Results:** ROC curve and Youden Index suggested that the threshold value of HCC% was 65%, with which patients were divided into high- (51/47.7%) and low-HCC% (56/52.3%) groups. MRI-based LI-RADS categorization (OR = 3.657, P=0.006 vs. OR = 4.075, P=0.004) and serum carcinoembryonic antigen (CEA) >5ng/ml (OR = 0.348, P=0.089 vs. OR = 0.298, P=0.040) were significant predictors for HCC% in cHCC-CCA in both uni- and multivariate logistic regression analysis. **Conclusions:** HCC% was potentially a prognostic factor in cHCC-CCA patients, and patients with HCC% higher than 65% tend to show longer overall survival time. MRI-based LI-RADS categorization and serum CEA >5ng/ml are valuable for predicting HCC% in cHCC-CCA preoperatively. **Keywords:** Liver Neoplasms, Magnetic Resonance Imaging, Diagnosis Criteria, Prognosis

PE-22

Extra-Hepatic Feeding Artery: An Imaging Feature Predicts Prognosis of Hepatocellular Carcinoma

Cheng Wang[1,2], Mengsu Zeng[1,2]

[1]Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai, China; [2]Shanghai Institute of Medical Imaging, Shanghai, China

Aims: To identify imaging features that could predict prognosis after curative resection hepatocellular carcinoma (HCC) **Methods:** In this retrospective study, 99 patients with surgically resected HCC who underwent preoperative MR imaging within 1 month before surgery were enrolled between January 2017 and December 2018. Clinical-pathologic and MR imaging findings for predicting early

recurrence and overall survival (OS) were identified by using a Cox proportional hazards model. Important MR imaging features were compared with other findings, and multivariable logistic regression was performed to determine factors associated with the feature. The important MR imaging feature for predicting recurrence-free survival (RFS) and OS were identified by using a Cox proportional hazards model. **Results:** The size, TBIL, extra-hepatic feeding artery (EHFA) were associated with early recurrence (2.04 [95% CI: 1.15, 3.63], 0.86 [95% CI: 0.76, 0.97], 3.39 [95% CI: 1.18, 9.73], *P*<0.05, respectively), and TBIL, EHFA were associated with OS (1.11 [95% CI: 1.03, 31.21], *P*<0.05; 5.95 [95% CI: 1, 35.53], *P*=0.05). EHFA was associated with early recurrence and worse OS. HCC with EHFA showed a larger size compared to HCC without EHFA (*P*=0.001), and MVI positive, mosaic showed more common in HCC with EHFA (*P*<0.05, respectively). Non-rim APHE, peripheral washout, enhancing capsule, delayed enhancement and corona enhancement showed no significant difference in the two groups. MVI (0.23 [95% CI: 0.06, 0.87], *P*=0.03) and size (0.48 [95% CI: 0.27, 0.84], *P*=0.01) were the independent risk factor for EHFA. HCC with EHFA showed a significantly worse prognosis than those without EHFA. **Conclusions:** EHFA was associated with early recurrence, HCC with EHFA showed a significantly worse prognosis than those without EHFA. **Keywords:** Hepatocellular Carcinoma, Prognosis, MR, Image

PE-23

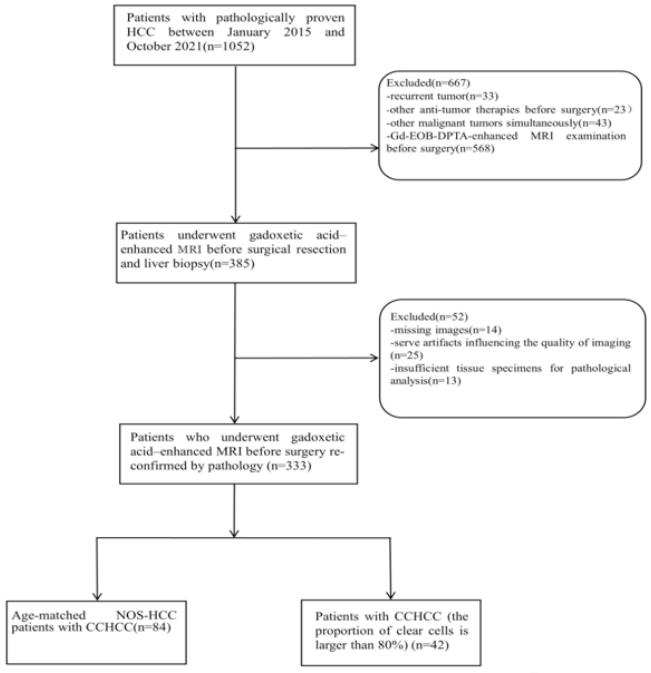
Clear Cell Hepatocellular Carcinoma: Gadoxetic Acid-Enhanced MR Imaging Features and Prognosis

Mingyue Song[1,2], Yuhao Tao[1,2], Kuang He[3], Mingzhan Du[3], Linchuan Guo[3], Chunhong Hu[2], Weiguo Zhang[1,2]

[1]Department of Radiology, Dushu Lake Hospital Affiliated to Soochow University, Medical Center of Soochow University, Suzhou, China; [2]Department of Radiology, The First Affiliated Hospital of Soochow University, Suzhou, China; [3]Department of Pathology, The First Affiliated Hospital of Soochow University, Suzhou, China

Aims: To investigate gadoxetic acid-enhanced MR imaging findings and prognosis of clear cell hepatocellular carcinoma (CCHCC) comparing with non-otherwise specified hepatocellular carcinoma (NOS-HCC). **Methods:** Forty-two patients with CCHCC and 84 age-matched patients with NOS-HCC were retrospectively enrolled. The clinical, pathological and MR imaging features were investigated in CCHCC and compared with NOS-HCC. Disease-free survival (DFS) and overall survival (OS) were determined by Kaplan-Meier analysis. Univariate and multivariate analyses were performed to examine factors that affected prognosis. **Results:** CCHCC showed fat content more frequently (*P*<0.001) and higher Edmondson tumor grade (*P*=0.001) compared with NOS-HCC. The lesion-to-muscle signal intensity ratio (LMR) and lesion-to-liver ratio (LLR) of CCHCC on pre-contrast T1WI (*P*=0.001,*P*=0.003) and hepatobiliary phase (HBP) (*P*=0.007, *P*=0.048) were significantly higher than those of NOS-HCC, while lesion-to-spleen ratio (LSR) of CCHCC on pre-contrast (*P*=0.339) and HBP (*P*=0.366) did not show statistically significance albeit higher than those of NOS-HCC. The 1- and 3-year overall survival (OS) and disease-free survival (DFS) for patients with CCHCC were 90.3%, 76.2%, 77.8% and 70% respectively. Log-rank analysis revealed no statistical discrepancy in clinical outcome between CCHCC and NOS-HCC. Multivariate Cox analysis confirmed that tumor diameter (hazard ratio=0.086; 95% CI:0.008,0.947; *P*=0.045) and pseudocapsule formation (hazard ratio=0.089; 95% CI:0.01,0.795; *P*=0.030) were independent prognostic factors for OS and DFS of CCHCC patients, which were different from NOS-HCC. **Conclusions:** Fat content and adjusted lesion signal intensity on pre-contrast T1WI and HBP could be used to differentiate CCHCC from NOS-HCC. CCHCC had similar prognosis with NOS-HCC and tumor size and pseudocapsule formation were independent predictive factor for survival of CCHCC patients. **Keywords:** Hepatocellular Carcinoma, Gd-EOB-DTPA, Magnetic Resonance Imaging

Figure 1 The flow chart of patient inclusion and exclusion



Flowchart of patients' enrollment. HCC, hepatocellular carcinoma; CT, computed tomography; MRI, magnetic resonance imaging.

PE-24

Distinct Radiological Features of Intrahepatic Lymphoepithelioma-Like Cholangiocarcinoma: Comparison with Classical Intrahepatic Cholangiocarcinoma

Geng-Yun Miao[1,2,3], Li-Heng Liu[1,2,3], Ming-Liang Wang[1,2,3], Meng-Su Zeng[1,2,3]

[1]Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai, China; [2]Shanghai Institute of Medical Imaging, Shanghai, China; [3]Department of Cancer Center, Zhongshan Hospital, Fudan University, Shanghai, China

Aims: Lymphoepithelioma-like cholangiocarcinoma (LEICC) has been recently introduced as a genetically distinct of intrahepatic cholangiocarcinoma (ICC). We aimed to investigate whether LEICC has distinct radiological characteristics in comparison with classical ICC, and to determine MRI features that can be used to differentiate LEICC from classical ICC. **Methods:** Five hundred and sixty-seven consecutive patients who underwent surgical resection or liver transplantation for ICC between 2014 and 2021 were retrospectively identified. Among them, 30 patients with LEICC (LEICC-cohort) and 116 with stage-matched classical ICC (control-cohort) were finally included. Pre-operative MRI data were compared between the two cohorts. Multivariable logistic regression analysis was performed to determine relevant imaging features suggesting the diagnosis of LEICC over classical ICC. **Results:** LEICCs showed significantly higher frequencies of a non-rim arterial phase hyperenhancement (APHE), washout on post-arterial images and a smooth margin, as well as less frequencies of perilesional enhancement and liver capsular retraction when compared with classical ICCs (P<0.05 for all). The multivariate analysis revealed that non-rim APHE (odds ratio, 10.863; 95% CI [3.295 – 35.821]; P<0.001) and the absence of perilesional enhancement (odds ratio, 3.350; 95% CI [1.167 – 9.619]; P=0.025) are significant independent imaging features that suggest the diagnosis of LEICCs over classical ICCs. **Conclusions:** Compared with classical ICCs, LEICCs does have distinct radiological characteristics. A smooth margin, non-rim APHE, washout on post-arterial images, absent perilesional enhancement and absent liver capsular retraction are useful MRI features that could help to differentiate LEICCs from classical ICCs. **Keywords:** Lymphoepithelioma-Like, Intrahepatic Cholangiocarcinoma, Magnetic Resonance Imaging, Diagnosis

PE-25

Is It Necessary to Distinguish between cHCC-CCA Cases with Less than 10% of CCA Components and HCC Cases?

Changwu Zhou[1,2,3], Chun Yang[2,3], Mengsu Zeng[1,2,3]

[1]Shanghai Institute of Medical Imaging, Shanghai, China; [2]Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai, China; [3]Department of Cancer Center, Zhongshan Hospital, Fudan University, Shanghai, China

Aims: To investigate the difference in RFS prognosis between cHCC-CCA cases with a small proportion of CCA components and HCC cases. **Methods:** Consecutive patients with malignant liver neoplasms who underwent MRI and surgery were prospectively recruited between January 2019 and September 2021. All cHCC-CCA patients were divided into different groups according to the ratio of CCA components. The primary end point was recurrence-free-survival. Cox regression analysis and Kaplan–Meier survival analysis was used to investigate and compare RFS prognosis. **Results:** One hundred sixty-four cHCC-CCA (mean age: 54.9 ± 12.6 years old) and 271 HCC cases (mean age: 53.7 ± 11.4 years old) were enrolled. During a median of 37 months (interquartile range, 27-41) of follow-up, 72 (43.9%) cHCC-CCAs and 51 (18.8%) HCCs experienced recurrences, respectively. There was no significant difference in RFS prognosis between cHCC-CCA cases with a CCA component of < 10% and HCC cases (log rank P=0.169). Moreover, there were no significant differences in some major HCC-favoring MR features, such as nonrim APHE (85.7% vs. 81.5%, P=0.546), nonperipheral washout (80.0% vs. 84.1%, P=0.534), and enhancing capsule (62.9% vs. 45.4%, P=0.051), between cHCC-CCAs with a CCA component of < 10% and HCCs. In addition, some clinicopathological findings had no significant differences between cHCC-CCAs with a CCA component of < 10% and HCCs (all P>0.05). **Conclusions:** There were no significant differences in RFS prognosis, major HCC-favoring MRI features, and clinicopathological findings between cHCC-CCAs with a CCA component of < 10% and HCCs. Therefore, we suggest that cHCC-CCAs with pathological diagnosis of less than 10% of CCA components should be treated as HCCs in clinical setting. **Keywords:** Liver Neoplasms, Magnetic Resonance Imaging, Prognosis

Liver Cancer - Staging and Prognosis

PE-26

Proper Position of Single and Large (≥ 5 cm) Hepatocellular Carcinoma in Barcelona Clinic Liver Cancer Classification

Sola Lee, Hyo-Sin Kim

Department of Surgery, Chonnam National University Medical School and Hospital, Gwangju, Republic of Korea

Aims: The purpose of this study was to evaluate the proper position of single large hepatocellular carcinoma (HCC) in the Barcelona Clinic Liver Cancer (BCLC) staging system. **Methods:** The data were collected from the nationwide multicenter database of the Korean Liver Cancer Association. Patients with single large (^{3} 5 cm) HCC were separated from BCLC stage A patients and designated as Group X. The remaining BCLC stage A and stage B patients were classified as Group A and Group B, respectively. The survival outcomes of propensity score-matched groups were compared. **Results:** Among the 3965 randomly selected patients, the number of patients in Group X, Group A, and Group B was 414, 2787, and 760, respectively. TriMatch analysis allowed us to obtain 116 well-balanced triplets. The 1-, 3-, and 5-year overall survival rates in Group X were worse than in Group A (91%, 71%, and 48% vs. 90%, 78%, and 64%, respectively; P<0.000). However, the rates were not different compared with those in Group B (91%, 71%, and 48% vs. 90%, 69%, and 48%, respectively; P<0.09). In multivariate analysis, Group X, Group B, age over 60 years, prothrombin time-international normalized ratio, and creatinine level were independent predictors of worse overall survival. **Conclusions:** Our findings suggest that Group X should be

relocated to BCLC stage B rather than BCLC stage A. **Keywords:** Hepatocellular Carcinoma, BCLC, Survival Outcome

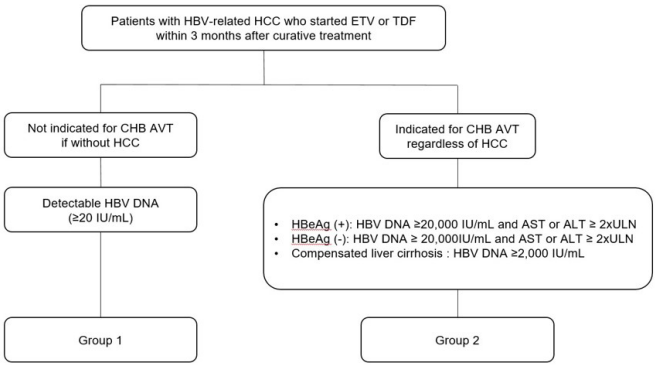
PE-27

Similar Recurrence after Curative Treatment of HBV-Related HCC Regardless of HBV Replication Activity

Mi Na Kim[1], Beom Kyung Kim[2,3,4*], Heejin Cho[5], Myung Ji Goh[6], Su Jong Yu[5], Dong Hyun Sinn[6], Soo Young Park[7], Seung Up Kim[2,3,4]*

[1]Division of Gastroenterology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea; [2]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea; [4]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea; [5]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [6]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [7]Department of Internal Medicine, Kyungpook National University Hospital, Daegu, Republic of Korea

Aims: Antiviral therapy (AVT) is required for patients with newly diagnosed hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC), if HBV DNA is detectable. We compared the risk of recurrence according to HBV replication activity at curative treatment of HBV-related HCC. **Methods:** Patients with HBV-related HCC who received surgical resection or radiofrequency ablation between 2013 and 2018 were enrolled in this retrospective cohort study. Patients were categorized into two groups according to HBV replication activity at curative treatment of HBV-related HCC (group 1: patients who met AVT indication for HBV-related HCC due to detectable HBV DNA but did not meet AVT indication for HBV if without HCC; group 2: patients who met AVT indication for HBV regardless of HCC). **Results:** In the entire cohort (n=911), HCC recurred in 303 (33.3%) patients during a median follow-up of 4.7 years. After multivariate adjustment for the covariates, group 2 showed a statistically similar risk of HCC recurrence (adjusted hazard ratio [aHR]=1.18, 95% confidence interval [CI]=0.85–1.64; *P*=0.332) compared to group 1. In addition, group 2 showed statistically similar risks of early (<2 years) (aHR=1.31, 95% CI=0.88–1.95), and late (≥2 years) (aHR=0.83, 95% CI=0.45–1.55) recurrence compared to group 1. Propensity score matching and inverse probability of treatment weighting analysis also yielded similar risks of HCC recurrence between the two groups (all *P*>0.05, log-rank tests). **Conclusions:** The risk of HCC recurrence in patients who received curative treatment for newly diagnosed HBV-related HCC was comparable, regardless of HBV replication activity at curative treatment of HCC. **Keywords:** Hepatocellular Carcinoma, Curative Treatment, Recurrence, Antiviral Therapy Indication



PE-28

The Efficacy of Biliary Drainage in HCC with Bile Duct Invasion: A Multicenter Retrospective Cohort Study

Keungmo Yang[1], Hyun Yang[1], Chang Wook Kim[1], Hee Chul Nam[1], Ji-Hoon Kim[1], U Im Chang[1], Jin Mo Yang[1], Ahlim Lee[1], Hae Lim Lee[1], Jung Hyun Kwon[1], Soon Woo Nam[1], Soon Kyu Lee[1], Pil Soo Sung[1], Ji Won Han[1], Jeong Won Jang[1], Si Hyun Bae[1], Jong Young Choi[1], Seung Kew Yoon[1], Hee Yeon Kim[1]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Bile duct invasion is a common occurrence in advanced hepatocellular carcinoma (HCC), often leading hyperbilirubinemia. However, the efficacy of pre-treatment biliary drainage in HCC patients with bile duct invasion and hyperbilirubinemia remains unclear. This study aimed to investigate the impact of biliary drainage on the prognosis in those patients. **Methods:** A total of 134 HCC patients with bile duct invasion were retrospectively analyzed form multicenter cohorts. Patients without hyperbilirubinemia (n = 75) or those who underwent biliary drainage for palliative purposes (n = 10) were excluded, and 49 patients with hyperbilirubinemia (23 with drainage and 26 without drainage) were involved in the final analysis. The modalities of biliary drainage included percutaneous transhepatic biliary drainage or endoscopic retrograde cholangiopancreatography, and hyperbilirubinemia was defined as a total bilirubin level of 2mg/dL or higher. **Results:** There were no significant differences in baseline clinical characteristics between the biliary drainage and non-biliary drainage groups in HCC patients with bile duct invasion and hyperbilirubinemia. The biliary drainage group had better overall survival (OS, *P*=0.02) and progression-free survival (PFS, *P*=0.07) than the non-drainage group (Median OS, 8.4 and 3.7 months; Median PFS, 4.0 and 2.0 months). Univariate and multivariate analyses demonstrated that biliary drainage was a significantly favorable prognostic factor for OS (hazard ratio 0.48 and 0.43, *P*=0.02 and *P*=0.01, respectively). Furthermore, the biliary drainage showed the favorable results in the first response evaluation of HCC treatment (*P*=0.03). **Conclusions:** Biliary drainage is an independent favorable prognostic factor for HCC

patients with bile duct invasion and hyperbilirubinemia. Therefore, this study suggests that biliary drainage should be considered in the treatment of advanced HCC patients with bile duct invasion for better survival outcomes. **Keywords:** Hepatocellular Carcinoma, Bile Duct Invasion, Hyperbilirubinemia, Biliary Drainage

PE-29

A Novel Nomogram for Prediction of Progression Free Survival after Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma

Qi-Qiao Wu[1], Yi-Xing Chen[2], Shi-Suo Du[2], Yong Hu[2], Ping Yang[2], Zhao-Chong Zeng[2]

[1]Radiation Oncology Department, Zhongshan Hospital, Fudan University (Xiamen Branch), Shanghai, China; [2]Radiation Oncology Department, Zhongshan Hospital, Fudan University, Shanghai, China

Aims: This study aimed to develop the combination of dose-volume features and clinical characteristics that can predict patient progression free survival (PFS) in hepatocellular carcinoma (HCC) treated with stereotactic body radiation therapy (SBRT). **Methods:** Sixty-nine HCC patients treated with SBRT during 2015-2020 were enrolled and divided into Progression and Non-progression Group. The dose-volume features were extracted from treatment plan system. Cox proportional hazards regression and least absolute shrinkage and selection operator analyses were performed to select relevant clinical parameters. The predictive performance of our model was evaluated by time-dependent receiver operating characteristic (ROC) curve and calibration curve analyses. **Results:** Three clinical features (Early response (complete response in 6 months), Age, Previous TACE treatment) and two dosimetric parameters (The relative volume of total liver treated with ≥5 Gy, Biological effective dose (BED)) were identified as the best progression free survival related predictors. Participants were divided into a high-risk group and a low-risk group based on the selected features. The areas under the ROC curve for our prognostic model were 0.79, 0.88, 0.87 for 1-, 2-, and 3- progression free survival, respectively. The calibration curve of the 5 independent PFS-related markers showed a good fit between nomogram-predicted PFS and actual PFS, suggesting that our model has good predictive value. **Conclusions:** This study demonstrated that a nomogram of combined dosimetric features and clinical characteristics can be conveniently used to assess individualized post-radiation prediction of PFS in HCC patients treated with SBRT. **Keywords:** Hepatocellular Carcinoma, Dosage, SBRT, Progression

PE-30

New Preoperative CT Staging of Intrahepatic Cholangiocarcinoma: Impact of Up-Staging of Tumor Multiplicity on Survival Outcomes

Yeun-Yoon Kim[1], Hye Jung Shin[2], Suk-Keu Yeom[3], Sang Hyun Choi[4], Hyungjin Rhee[1], Ji Hoon Park[5], Eun-Suk Cho[6], Sumi Park[7], Seung Soo Lee[4], Mi-Suk Park[1]

[1]Department of Radiology, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Biostatistics Collaboration Unit, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Department of Radiology, Korea University Ansan Hospital, Korea University College of Medicine, Republic of Korea; [4]Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea; [5]Department of Radiology, Seoul National University Bundang Hospital, Gyeonggi-do, Republic of Korea; [6]Department of Radiology, Gangnam Severance Hospital, Yonsei University College of Medicine Seoul, Republic of Korea; [7]Department of Radiology, National Health Insurance Service Ilsan Hospital, Goyang, Republic of Korea

Aims: To develop and validate a preoperative CT staging system for intrahepatic cholangiocarcinoma (iCCA), focusing on tumor multiplicity, adapted from American Joint Committee on Cancer (AJCC) staging system. **Methods:** Patients who underwent preoperative multiphasic CT and curative-intent R0 or R1 resection for mass-forming iCCA were retrospectively recruited from multiple institutions from January 2009 to December 2015. Based on Cox proportional hazards regression analysis of the 8th AJCC staging parameters, preoperative CT staging system was developed with subdivision of tumor multiplicity. Kaplan–Meier method was used to estimate overall survival (OS). Harrell's concordance indices (C-indices) of AJCC and modified systems were compared with bootstrap methods. Survival probabilities and C-indices were also examined in the temporally independent cohort sampled from January 2016 to May 2020 in one institution. **Results:** The development cohort included 319 patients (median age, 64 years; 208 men). In the modified staging system, multiple tumors (adjusted hazard ratio [HR]; satellitosis, 3.03, P <0.001; multifocal tumors, 3.92, P <0.001) was up-staged from T2 to T3; solitary tumor with intrahepatic vascular invasion (adjusted HR, 1.98, *P*=0.003) or solitary tumor perforating the visceral peritoneum (adjusted HR, 2.00, *P*=0.001) were designated as T2. AJCC T2 and T3 stages failed to discriminate the survival curves (log-rank P value for T2 vs. T3 = 0.812; 5-year OS, 23.4% vs. 26.8%), but new T2 stage showed better OS outcomes than T3 stage (log-rank P value for T2 vs. T3a [satellitosis] vs. T3b [multifocal tumors] = 0.003; 5-year OS, 33.8% vs. 8.4% vs. 4.8%). The C-indices of new staging system were higher than those of AJCC 8th staging system for predicting OS without statistical significance (T staging, 0.647 vs. 0.626, *P*=0.061; TNM staging, 0.636 vs. 0.614, *P*=0.069). In the validation cohort of 60 patients (median age, 68 years; 40 men), the new CT staging, instead of AJCC staging, showed significant differences in the survival probability. **Conclusions:** The new staging system which upstages tumor multiplicity provides better prognostic stratification

for OS than AJCC staging system using preoperative CT in patients with iCCA. **Keywords:** Intrahepatic Cholangiocarcinoma, Cancer Staging, TNM Staging System, Survival Analysis

PE-31

Development of a Prognostic Scoring System for Hepatic Vena Cava Budd-Chiari Syndrome with Hepatocellular Carcinoma

Xiaowei Dang, Shengan Liu, Luhao Li, Zhaochen Liu, Suxin Li

Department of Hepatopancreatobiliary Surgery, The First Affiliated Hospital of Zhengzhou University, China

Aims: Hepatocellular carcinoma (HCC) is a serious complication of hepatic vena cava Budd-Chiari syndrome (HVC-BCS) that significantly reduces the survival time of patients. Our study aimed to analyze the prognostic factors influencing the survival of HVC-BCS patients with HCC and to develop a prognostic scoring system. **Methods:** The clinical and follow-up data of 64 HVC-BCS patients with HCC who received invasive treatment at the First Affiliated Hospital of Zhengzhou University between January 2015 and December 2019 were retrospectively analyzed. Kaplan-Meier curves and log-rank tests were used to analyze the survival curve of patients and the difference in prognoses between the groups. Univariate and multivariate Cox regression analyses were performed to analyze the influence of biochemical, tumor, and etiological characteristics on the total survival time of patients, and a new prognostic scoring system was developed according to the regression coefficients of the independent predictors in the statistical model. The prediction efficiency was evaluated using the time-dependent receiver operating characteristics curve. **Results:** The analyses of the 64 patients, showed that serum albumin level < 34 g/L, maximum tumor diameter > 7 cm, and inferior vena cava stenosis (inferior vena cava stenosis was defined as a reduction of > 50% in the lumen diameter) were independent predictors of survival. Ultimately, 2 points were given for maximum tumor diameter > 7 cm, 1 point was given for serum albumin level < 34 g/L and inferior vena cava stenosis. The new prognostic scoring system was defined as the sum of three scores, and patients were classified as grades A, B, C and D with sum scores of 0, 1, 2, or > 2 points, respectively. Significant differences in survival were found among different groups. The time-ROC curve showed that the new prognostic scoring system had good prediction efficiency at different follow-up time points, the corresponding area under the curve values were all > 0.7 and higher than commonly used tumor staging. **Conclusions:** This study successfully developed a prognostic scoring system for HVC-BCS patients with HCC, which is helpful for clinical evaluation of patient prognosis. **Keywords:** Budd-Chiari Syndrome, Hepatocellular Carcinoma, Inferior Vena Cava Stenosis

PE-32

Study of New Methods for Analyzes and Monitor of Health Data in Relation to Hepatocellular Carcinoma Survivors Patients via Wearable Technology

Vikas Sharma, Madhu Gautam

Department of Internal Medicine, Sarojini Naidu Medical College, India

Aims: Hepatocellular carcinoma is the most common type of primary liver cancer in adults and is currently the most common cause of death in people with cirrhosis. New wearable sensor networks together with smartphone applications are being examined and tested for their potential to monitor and manage health goal in hepatocellular carcinoma survivors patients. To study effects of daily life routine activities on depression, anxiety, and weak immunity and CD4 counts data by wearable devices (MI band 8) that can obtain real-time data, processes them and provides assistance based on pre-determined specifications in hepatocellular carcinoma patients survivors in Mathura city, India. **Methods:** Total of 86 hepatocellular carcinoma survivors' patients were taken as subject with an equal ratio of male and female. Wearable monitoring devices (MI band 8) were put on the wrist of patients for 30 days and a questionnaire was filled out by each patient. Both obesity and lifestyle disorders in turn are known as important factors for developing cancer and aggravation toward once end-stage disease. In all subjects, blood glucose was measured on daily basis with day to day data of their monitoring of step count (deep sleep, light sleep, wake up time), blood pressure, calorie burnt, insulin dose, motion time i.e. every time when your body was in motion, sleep monitoring, monitoring heart rate, cardiac arrhythmias to know daily routines and recording them for health purpose. **Results:** Wearable device reading showed that there was a significant normal heart rate (P<0.05), increase calorie burnt with a significant decrease of blood glucose and blood pressure levels (P<0.01), and increased significantly (P<0.05) sleep duration in active physically workout, include walking in liver cancer survivors patients compared to less physically workout hepatocellular carcinoma survivors, identified by professional physiotherapists. There is significantly normalize in memory loss, wandering events and their CD 4 counts increase events normalize after one month with changing lifestyle routine among hepatocellular carcinoma survivors. Wearable device reading showed that after changing lifestyle routine among less physically active hepatocellular carcinoma patients, their CD 4 counts increase events normalize. **Conclusions:** With this study we show that, by using, wearable device ensured online assistive feedback for hepatocellular carcinoma survivor patients is possible with their health awareness, exercising and motivate further studies. Lifestyle modification through increased physical activity is beneficial in patients with hepatocellular carcinoma survivors. **Keywords:** Hepatocellular Carcinoma, Wearable Technology, Health Data

PE-33

Estimating Microvascular Invasion in Patients with Resectable Multinodular Hepatocellular Carcinoma by Using Preoperative Contrast-Enhanced MRI: Development and Validation of a Risk Score

Fei Wu[*,1], *Haitao Sun*[1], *Changwu Zhou*[1], *Chun Yang*[1], *Mengsu Zeng*[#,1]

[1]Department of Radiology, Zhongshan Hospital, Fudan University, China

Aims: The risk factors of microvascular invasion (MVI) in patients with multinodular hepatocellular carcinoma (mHCC) have been rarely investigated. This study aimed to identify the preoperative clinicoradiological factors for predicting MVI in patients with resectable mHCC, and further to develop and validate a stratified risk scoring system. **Methods:** 273 consecutive patients with pathologically confirmed mHCC (≥ 2 lesions) who underwent preoperative contrast-enhanced MRI were retrospectively enrolled (training/validation cohort:193/80). Preoperative clinicoradiological variables were collected and analyzed. In training cohort, the multivariable logistic regression with bootstrapping was used to select clinicoradiological variables associated with MVI and construct a risk scoring system. The performance of the risk score was assessed with the C-index, calibration curve and decision curve. A prognostic stratification based on the risk score was performed in mHCC patients. The risk score was verified in the validation cohort. **Results:** AFP>400 ng/mL, presence of satellite nodule, mosaic architecture and increased total tumor diameter were independent predictors of MVI while fat in mass was an independent protective factor of MVI in mHCC. Using the five clinicoradiological variables, a risk score was developed, demonstrating good discrimination performance in both training and validation cohort and fitting well in calibration curves. Decision curve analysis further confirmed its clinical usefulness. Based on the risk score, mHCC patients were stratified into high-risk and low-risk subgroups with significantly different recurrence-free survival. **Conclusions:** The presented risk score incorporating clinicoradiological parameters could stratify mHCC patients into high-risk and low-risk subgroups and predict prognosis in patients with resectable mHCC. **Keywords:** Hepatocellular Carcinoma, Prognosis, Magnetic Resonance Imaging, Statistical Model

Liver Cancer - Biomarkers

PE-34

Expression of Cancer Stem Cell Markers Cluster Differentiation 44 (CD44), CD90, CD133, Epithelial Cells Adhesion Molecule (EpCAM) and Alpha-Fetoprotein (AFP) Serum Level in Patients with Advanced Liver Disease

Syifa Mustika[1], *Supriono*[1], *Bogi Pratomo Wibowo*[1], *Cosmas Rinaldi A.Lesmana*[2]

[1]Department of Internal Medicine, Gastroenterohepatology Division, dr. Saiful Anwar General Hospital, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia; [2]Department of Internal Medicine, Hepatobiliary Division, Dr.Cipto Mangunkusumo National General Hospital, Universitas Indonesia, Jakarta, Indonesia

Aims: Serum alpha-fetoprotein (AFP) is a marker that is usually used to diagnose hepatocellular carcinoma (HCC) in advanced liver disease. Nowadays, cluster differentiation (CD)44, CD90, CD133, and Epithelial cell adhesion molecule (EpCAM) are cancer stem cells (CSCs) biomarkers that are predicted as an early marker for HCC and correlate with advanced liver disease progressiveness. Until now, none of the CSCs' research for HCC was conducted in Indonesia. This research aims to evaluate the role of CD44, CD90, CD133, EpCAM, and serum AFP levels in relation to advanced liver disease. **Methods:** An observational study was conducted from the 0^{th} to the 6^{th} month, on 41 patients with chronic hepatitis B or C, liver cirrhosis, and HCC in dr. Saiful Anwar General Hospital. Expression of CD44, CD90, CD133, and EpCAM serum was obtained using flow cytometry and serum AFP levels using ELISA. Patients' characteristic data were analyzed by bivariate and multivariate statistics. Data were also analyzed by correlative test (Pearson and Spearman) and comparative test (One-way ANOVA, unpaired T, Mann-Whitney, Chi-square, Kruskal-Wallis) with a significance value of $p < 0.05$. The prediction of factors influencing disease progression was analyzed using regression logistic tests. **Results:** There were 16 subjects with chronic hepatitis, 15 subjects of liver cirrhosis, and 10 subjects with HCC at the first observation. The expression of CSCs on early observation which significantly differed in all groups were $CD44^+/CD90^+$ (P=0,001), $CD133^+/EpCAM^-$ (P=0,004), and serum AFP (P=0,000). In 6 months of observation, there were 11 subjects of chronic hepatitis, 13 subjects of liver cirrhosis, and 4 subjects of HCC. In 6^{th} month, only AFP was significant in all groups (P=0,002). The expression of $CD44^+/CD90^+$ and $CD133^+/EpCAM^-$ had significant values at the first observation, but not in the regression logistic test. **Conclusions:** The expression of CD44+/CD90+, and CD133+/EpCAM- have role as detection markers in the initial observation of patients with advanced liver disease but both were inconsistent in 6^{th} month observation. Only serum AFP levels differed significantly in both periods. However, the correlation between CSC expression and disease progression is still unproven. **Keywords:** CD44, CD90, EpCAM, AFP, CD133, Advanced Liver Disease, Progressiveness

Parameter	Groups			p^
	Chronic Hepatitis (n = 16)	Liver Cirrhosis (n = 15)	HCC (n = 10)	
$CD44^+/CD90^-$ (% gated)	9.55 (IQR: 0.038-1.04)**	22.37 (IQR: 0.48-28.78)	8.68 (IQR: 0.26-17.67)	0.09‡
$CD44^+/CD90^+$(% gated)	11.86 (IQR: 5.97-22.04)	7.32 (IQR: 2.34-10.32)	5.45 (IQR: 1.85-6.36)	0.225‡
$CD44^+/CD90^+$(% gated)	0.73 (IQR: 0.28-1.19)	8.29 (IQR: 1.38-6.92) **	10.35 (IQR: 1.77-10.72)	0.001‡
$CD133^+/EpCAM^+$(% gated)	14.98 (IQR: 0.07-26.34)	11.57 (IQR: 0.11-24.65)	16.45 (IQR: 1.01-29.08)	0.647‡
$CD133^+/EpCAM^-$ (% gated)	18.76 (IQR: 13.98-22.87)	11.72 (IQR: 4.27-16.40)	7.17 (IQR: 0.77-7.62)	0.004‡
$CD133^+/EpCAM^+$(% gated)	7.91 (IQR: 2.30-13.78)	10.98 (IQR: 1.67-12.06)	10.39 (IQR: 3.33-8.51)**	0.807‡
AFP (ng/mL)	7.25 (IQR: 1.47-8.20)	27.00 (IQR: 3.20-30.00)	13088.55 (IQR: 216.25-23914.00)	0.000‡
• <200 ng/ml, n (%)	16 (100%)	15 (100%)	3 (30%)	
• >200 ng/ml, n (%)	0 (0%)	0 (0%)	7 (70%)	

Parameter	Groups			p^
	Chronic Hepatisis (n = 11)	Liver Cirrhosis (n = 13)	HCC (n = 4)	
$CD44^+/CD90^-$(% gated)	0.44 (IQR: 0.24-0.47)	0.58 (IQR: 0.10-0.58)	0.11 (IQR: 0.04-0.16)	0.166‡
$CD44^+/CD90^+$(% gated)	38.35 (IQR: 33.13-45.00)	33.45 (IQR: 27.71-37.07)	35.35 (IQR 32.67-36.36)	0.423*
$CD44^+/CD90^+$(% gated)	3.80 (IQR: 2.32-4.70)	5.58 (IQR: 2.13-5.22)**	3.53 (IQR: 3.01-4.16)	0.986‡
$CD133^+/EpCAM^+$(% gated)	6.16 (IQR: 2.76-7.08)	7.06 (IQR: 3.62-7.44)	5.58 (IQR: 5.00-6.04)	0.748‡
$CD133^+/EpCAM^-$ (% gated)	16.35 (IQR: 12.18-22.08)	14.91 (IQR: 9.62-14.36)**	12.44 (IQR: 10.98-13.94)	0.627‡
$CD133^+/EpCAM^+$(% gated)	25.80 (IQR: 22.67-27.36)	24.12 (IQR: 21.99-26.82)	26.44 (IQR: 24.23-28.65)	0.715*
AFP (ng/ml)	4.05 (IQR: 2.10-4.50)	20.34 (IQR: 3.70-11.70)**	16226.55 (IQR: 661.55-31762.50)	0.002‡
• < 200 ng/ml, n (%)	11 (100%)	13 (100%)	0 (0%)	
• > 200 ng/ml, n (%)	0%	0%	4 (100%)	

PE-35

Association of Circulating Lymphocyte with Progression-Free Survival for Patients with Recurrent Hepatocellular Carcinoma Who Received Stereotactic Body Radiotherapy Combined with Anti-PD-1 Therapy

Yuan Zhuang, Yi-Xing Chen, Bao-Ying Yuan, Shi-Suo Du, Zhao-Chong Zeng

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

Aims: Radiation-induced lymphopenia during therapy is associated with a poor prognosis. This study aimed to assess the relationship between peripheral lymphocyte levels and progression-free survival (PFS) in patients with recurrent hepatocellular carcinoma (HCC) who were treated with stereotactic body radiotherapy (SBRT) combined with anti-PD-1. **Methods:** This study prospectively enrolled patients who had recurrent or oligometastatic HCC and were treated with SBRT plus anti-PD-1 antibody (sintilimab) every 3 weeks for 12 months or until disease progression. Complete blood counts were obtained within 1 week before RT, 1 month and 4 months after RT, respectively. Absolute lymphocyte counts (ALCs), lymphocyte subset levels including CD3+, CD4+, CD8+ T, and NK cells were tested for their association with PFS. **Results:** From August 14, 2019, to August 23, 2021, Twenty-five patients were enrolled. The median treatment duration was 10.2 months. SBRT was administered at a median dose of 54 in six fractions. The median follow-up time was 21.9 months, and the median PFS was 19.7 months, with PFS rates of 68.0% and 45.3% at 12 and 24 months, respectively. The median levels of ALCs prior to the first treatment and 1 month after the treatment were 1368/μL and 851/μL, respectively. At the time of 4-month follow-up, the median ALCs returned to 1240/μL. In comparison with patients with PFS ≥19.7 months, the levels of ALCs, CD3+, CD4+, CD8+ T cells, and NK cells were significantly higher than those in patients with PFS < 19.7 months (P<0.05 for all). **Conclusions:** For patients with recurrent HCC, higher levels of circulating lymphocyte counts after the combined treatment of SBRT plus anti-PD-1 might indicate longer PFS time. **Keywords:** Hepatocellular Carcinoma, Radiotherapy, Anti-PD-1, Progression-Free Survival

PE-36

Some Clinical and Subclinical Characteristics on HCC Patients

Le Thi Thu Hien, Nguyen Khac Hung Manh

[1]Thai Nguyen University of Medicine and Pharmacy, Vietnam

Aims: Hepatocellular carcinoma (HCC) is currently the leading cancer in both incidence and mortality in Vietnam. To determine clinical and sub clinical characteristics on HCC patients. **Methods:** Prospective cross-sectional description, clinical and laboratory characteristics of 106 HCC patients hospitalized for treatment at Thai Nguyen Central Hospital from 2/2019 to 3/2023. **Results:** Male patients accounted for the majority, the incidence of HCC increased with age with 37.7% male patients aged 45-60 and 41.5% female patients over 60 years old. Most of the diseases are detected at stages A-B, in which women tend to detect the disease earlier (49.1% stage A) than men (52.8% stage B). The risk factors accounting for a high proportion are hepatitis (86.8%) (mainly hepatitis B accounting for 50.1%) and alcoholism (58.5%). The common tumor size is 3-5 cm (54.7%), tumor usually occurs in the right liver (56.6%). The mean values of liver damage tests (GOT, GPT, GGT) and liver cancer markers (AFP) were all higher than normal. However, there is still a certain percentage of patients with HCC but normal liver cancer markers. 47.2% detected tumor on ultrasound. **Conclusions:** There is a division of HCC patients by sex, age and disease stage. Hepatitis and alcohol are the two main risk factors for HCC. The tests reflect liver damage and some liver function is affected, but there are still some patients with HCC but liver cancer markers are normal. **Keywords:** Liver Cancer, Hepatocellular Carcinoma, Clinical Characteristics, Subclinical

PE-37

Comprehensive Analysis of Expression, Prognostic Value and Immune Infiltration for LMNB1 in Hepatocellular Carcinoma

Xiaowei Dang, Dute Gao, Huahu Guo, Liang Bao, Suxin Li, Zhaochen Liu, Yunchao Wang, Jiange Qiu, Binghua Jiang

Department of Hepatopancreatobiliary Surgery, The First Affiliated Hospital of Zhengzhou University, China

Aims: One of the deadliest cancers is HCC in the world, which seriously threatens human health. However, little is understood about the molecular processes that govern how HCC develops. Lamin B1(LMNB1), primarily component of the nuclear lamina, has been linked to the development of several malignancies. Thus, utilizing several open-source databases, we conduct a systematic analysis of the clinical importance and biological functions of LMNB1 in HCC. **Methods:** The Cancer Genome Atlas (TCGA), International Cancer Genome Consortium (ICGC), Kaplan–Meier Plotter, Metascape, the Kyoto Encyclopedia of Genes and Genomes (KEGG), CIBERSORT, and cBioPortal and bioinformatic analysis were used to investigate LMNB1 in patients with HCC. **Results:** LMNB1 was upregulated in HCC tissues and indicated HCC

patients had poor prognosis. The clinicopathological characteristics of HCC patients and the expression levels of LMNB1 were significantly correlated. Investigations on somatic mutations in high or low LMNB1 expression subgroups were also conducted. In samples with a higher expression of the LMNB1 group, TP53 mutations occurred more frequently, which may affect the clinical outcome of HCC patients. Moreover, immune infiltration analysis demonstrated that the Neutrophils and eosinophils were diminished in in the high-LMNB1 expression group. Biological function analysis suggested that LMNB1-silencing repressed HCC proliferation and cell migration abilities. Moreover, the functional prediction revealed that the LMNB1 participated in the Wnt/β-catenin pathway. **Conclusions:** LMNB1 is a reliable clinical prognostic biomarker and crucial effects on HCC tumor progression. **Keywords:** LMNB1, Prognostic Value, Hepatocellular Carcinoma, Immune Infiltration

Liver Cancer - Molecular Pathogenesis and Pathology

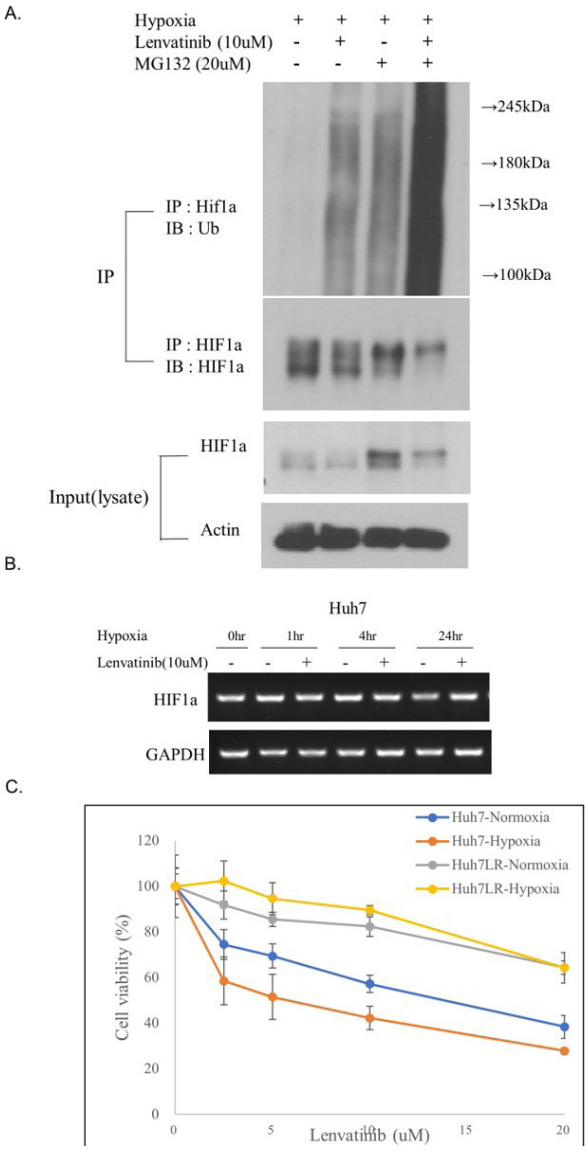
PE-38

Lenvatinib Induced Cell Death of Hepatocellular Carcinoma by Increasing HIF-α Degradation under Hypoxic Condition

Sung Won Chung, Kim Jin Sun, Won-Mook Choi, Kang Mo Kim

Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: A key contributing factor to inadequate treatment response in hepatocellular carcinoma (HCC) is the elevated expression of hypoxia-associated proteins, with hypoxia-inducible factor-1 alpha (HIF-1α) being the central protein. Although the connections between lenvatinib and downstream molecules of HIF-1α are recognized, no direct link has been verified. This study aimed to establish the relationship between Lenvatinib and HIF-1α, along with the underlying mechanisms. **Methods:** Lenvatinib or vehicle was treated to Huh-7 cell lines under either normoxia or hypoxia for 48 hours. Immunoblots, co-immunoprecipitation, quantitative polymerase chain reaction, and cell viability assays were performed. These experiments were replicated using the lenvatinib-resistant Huh-7 cell line. **Results:** Lenvatinib suppressed HIF-1α protein expression in Huh-7 cell lines under hypoxic conditions, without affecting mRNA levels, which were abrogated in the lenvatinib-resistant Huh-7 cell lines. Co-immunoprecipitation analysis demonstrated a substantial increase in ubiquitinated HIF-1α protein with lenvatinib treatment under hypoxic conditions, suggesting that lenvatinib may increase HIF-1α degradation in an ubiquitin-proteasome-dependent manner. Cell viability assays confirmed a reduction in the viability of Huh-7 cells when lenvatinib was administered under hypoxic conditions. **Conclusions:** Lenvatinib lowers HIF-1α expression in hypoxic HCC cells via degrading HIF-1α proteins via increasing the ubiquitination pathway. It may be a viable option to combine lenvatinib with hypoxia-inducing HCC treatments, such as transarterial chemoembolization. **Keywords:** Lenvatinib, HIF-1 Alpha



PE-39

Bile Acid-Mediated Induction of Hepatic Stellate Cell Activation Enhances the Invasion of Hepatocellular Carcinoma via Mcl-1 and COX-2

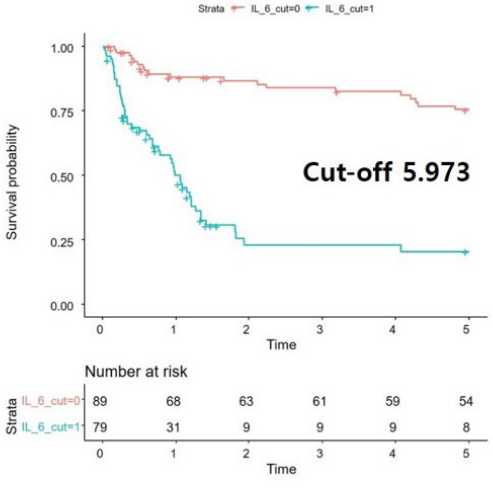
Yuri Cho[1], Minjong Lee[2], Min Ji Park[1], Narae Jung[1], Bo Hyun Kim[1], Joong-Won Park[1]

[1]Center for Liver and Pancreatobiliary Cancer, National Cancer Center, Goyang, Republic of Korea; [2]Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, Republic of Korea

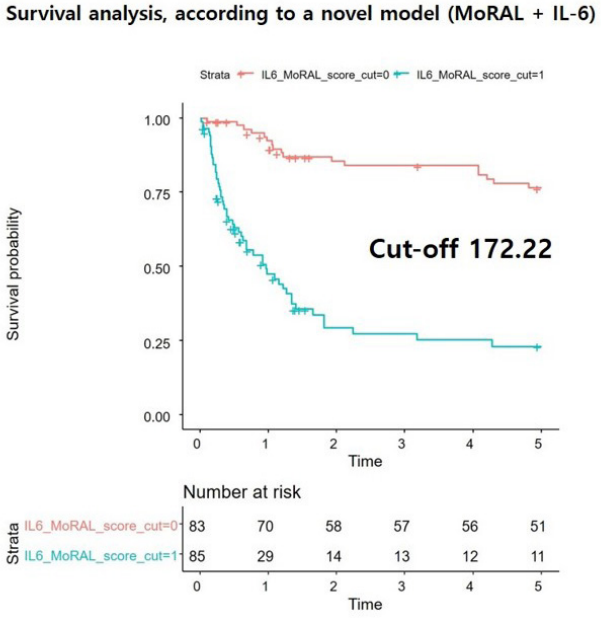
Aims: Activated hepatic stellate cells (HSCs) are the major

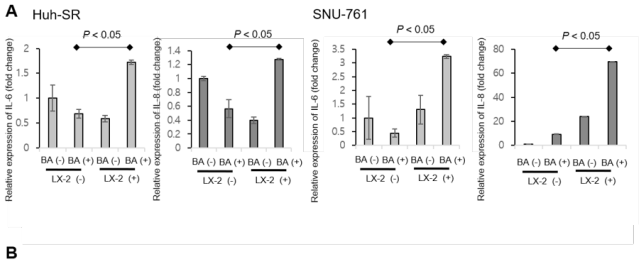
subtype of stromal cells in the liver tumor microenvironment which can promote the growth and migration of hepatocellular carcinoma (HCC) cells. Indeed, senescent and cancer-associated fibroblasts express numerous inflammatory and tumor promoting factors that are collectively referred to as the senescence-associated secretory phenotype (SASP). In the present study, we investigated the mechanisms of bile acid-mediated induction of HSC activation via the expression of the SASP in HCC cells. **Methods:** The immortalized human stellate cells (LX-2 cells) were used in this study. Invasion assay were done to evaluate the invasion of HCC cells (Huh-BAT, SNU-761, and Huh-SR) cocultured with HSCs. IL-6 and IL-8 mRNA was quantitated using real-time PCR. To investigate the mechanisms, western blot analyses were performed. A total of 168 serum samples from HCC patients were used for serum IL-6 levels and survival analysis. **Results:** Bile acid significantly increased the invasion of HCC cells when cocultured with HSCs as compared to monocultured HCC cells. Bile acid also increased protein expressions of the mesenchymal markers including α-SMA and vimentin in both HCC cells and HSCs. Moreover, bile acid increased the protein expressions of Mcl-1 and cyclooxygenase-2 (COX-2) in both HCC cells and HSCs. The inhibitors of either Mcl-1 induction by siRNA transfection or COX-2 activity by celecoxib decreased the bile acid-mediated HCC invasion. Mcl-1 and COX-2 induction was found to be due to transcriptional enhancement dependent on TGR-5 activation. Serum IL-6 level was a significant factor for overall survival of HCC patients. Moreover, a novel model, IL-6 + MoRAL score showed a significant discrimination function on overall survival with Harrell's c-index of 0.765 (95% confidence interval 0.719–0.808, P<0.0001). **Conclusions:** Bile acid-mediated induction of HSC activation enhances the invasion of HCC cells via the expression of the SASP. TGR-5 dependent overexpression of Mcl-1 and COX-2 may be the key factors which lead to HCC metastasis. SASP-induced increased IL-6 levels might be a significant factor for predicting overall survival of HCC patients. **Keywords:** Hepatocellular Carcinoma, Senescence-Associated Secretory Phenotype, Invasion, Survival

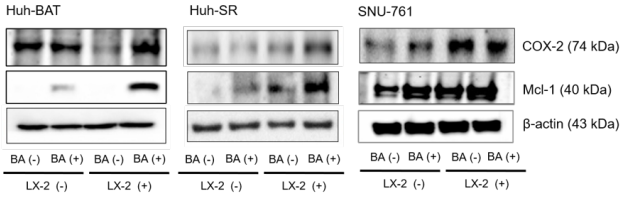
A

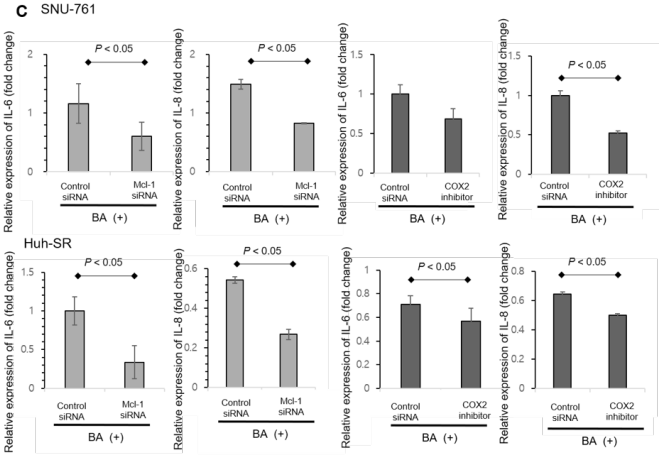


B









PE-40

Biological Potential and Therapeutic Effectiveness of Magnolin for the Treatment of Hepatocellular Carcinoma

Kanika Patel, Dinesh Kumar Patel

Faculty of Health Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, India

Aims: Lignans are an important class of phytocompounds mainly responsible for the defense mechanism of the plants. Magnolin also called 1-(3,4-dimethoxy-phenyl)-4-(3,4,5-trimethoxyphenyl)-tetrahydro-furo[3,4-c]furan, was found to be present in the volatile oil components of the Magnolia fargesii. Magnolin have anti-inflammatory, anti-oxidative, and vasodilatory effects and can protect against contrast-induced nephropathy. **Methods:** Biological potential of magnolin for their mechanism to treat hepatocellular carcinoma has been investigated in the present work through scientific data analysis of different scientific research work. In order to know the therapeutic potential of magnolin against liver carcinoma, detail scientific data of pharmacological activity of magnolin have been analyzed in the present work. **Results:** Present work signified the biological potential and therapeutic effectiveness of magnolin for the treatment of Hepatocellular carcinoma in medicine. Scientific data analysis signified that magnolin suppressed the proliferation and promoted cell cycle arrest and apoptosis in hepatocellular carcinoma cells Bel-7402 and SK-Hep1. Furthermore, combination of magnolin and with BRAF led to increased impaired proliferation through the inhibition of the ERK MAPK pathway, which signified its therapeutic potential for the improvement of hepatocellular carcinoma. **Conclusions:** Present work signified the therapeutic effectiveness of magnolin for the treatment of Hepatocellular carcinoma. **Keywords:** Magnolin, Hepatocellular Carcinoma, Proliferation, Cell Cycle Arrest

PE-41

Clinico-Pathological Characterization of hTERT-Telomere Abnormalities in Hepatocellular Carcinoma

Jeong Eun Jang[2], Jin Seoub Kim[2], Hye Seon Kim[2], Ji Min Kim[2], Jung Hyun Kwon[1], Ji Won Han[1], Pil Soo Sung[1], Si Hyun Bae[1], Jong Young Choi[1], Seung Kew Yoon[1], Jeong Won Jang[1]*

[1]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]The Catholic University Liver Research Center, Department of Biomedicine, Health Sciences, Department of Biomedicine, Health Sciences, Graduate School, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Human telomerase reverse transcriptase (TERT) genetic alterations play an essential role in hepatocarcinogenesis. However, the crosstalk of TERT promoter mutation, TERT expression, and telomere length (TL) in hepatocellular carcinoma (HCC) are not fully understood. The aim of the study is to investigate the association of TERT-telomere abnormalities with clinic-pathologic findings in patients with HCC. **Methods:** The study recruited a total of 222 HCC patients and 95 non-tumor patients with biopsied liver tissues. We detected TERT promoter mutation, TERT expression, and TL by Sanger sequencing and quantitative real-time PCR. The integrative analysis of TERT-telomere alterations and TL was performed in relation to the clinico-pathological findings of HCC. **Results:** TERT alterations were more frequently observed in tumors than in paired non-tumor tissues. Regarding the etiology of liver disease, TERT expression was highest in HBV-associated HCCs, TL was longest in HCV-associated HCCs, and TERT promoter mutations were more frequently present in non-HBV-associated HCCs than in HBV-associated HCCs. TERT overexpression was associated with high tumor burden, with its higher expression with a larger tumor, tumor multiplicity, and portal vein invasion or metastasis. Moreover, TERT expression positively correlated with grade of tumor differentiation and stage progression for both the mUICC and BCLC stages. In contrast, TL tended to be shortened with high tumor burden, with a negative correlation of TL with tumor differentiation and HCC stage progression. Unlike TERT expression or TL, there was no association between TERT promoter mutations and tumor stage or tumor grade. **Conclusions:** TERT genetic alterations and TL are tightly linked with HCC development and progression, with their respective roles in hepatocarcinogenesis. These data suggest that TERT-telomere abnormalities might serve as a feasible biomarker for cancer diagnostics and therapies in HCC patients. **Keywords:** Liver Cancer, Telomere, Biomarker, Pathology

PE-42

Therapeutic Benefit and Biological Potential of Tricetin on Liver Cancer: Biological Application in the Health Sectors

Dinesh Kumar Patel

Shalom Institute of Health and Allied Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Prayagraj, Uttar Pradesh, India

Aims: Flavonoidal compounds are the largest group of phenolic compounds isolated and separated in the nature and mainly found to be present in the higher plants. Flavonoidal compounds have been well known in the health sectors for their antimicrobials, anti-insect properties in the medicine. **Methods:** Flavonoid has been studied in the medicine and health sectors for their health beneficial aspects. Therapeutic benefit and biological potential of tricetin on liver cancer has been studied in the present investigation through scientific data analysis of various scientific research works. Pharmacological activities of tricetin have been investigated in the medicine through scientific data analysis of various scientific research works. **Results:** Scientific data analysis revealed the medicinal properties of tricetin in the medicine and other health sectors. Scientific data analysis revealed the therapeutic benefit and biological potential of tricetin on liver cancer as tricetin induced cancer cell death treatment by triggering mitochondrial and death receptor 5 apoptotic pathways and decrease of mean

tumor volume. **Conclusions:** Scientific data analysis revealed the therapeutic benefit and biological potential of tricetin on liver cancer. **Keywords:** Biological Potential, Tricetin, Liver Cancer

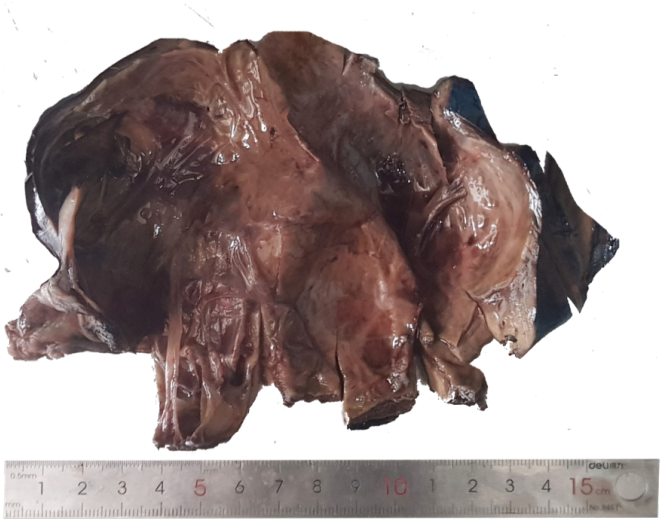
PE-43

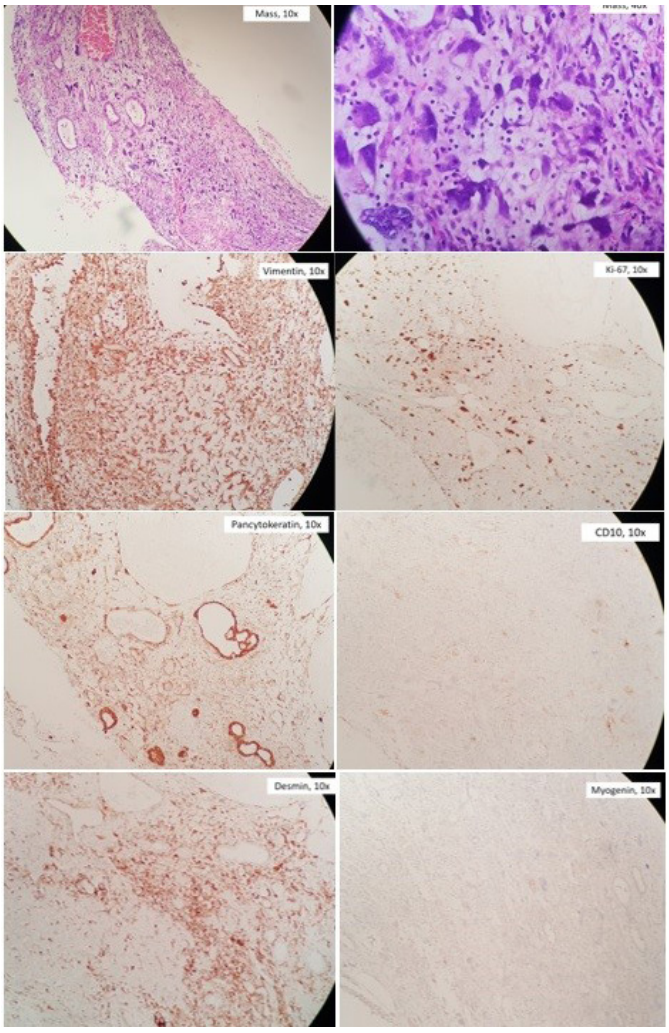
Mesenchymal Tumor of the Liver in an Eight-Year Old Filipino Child

Gladys Larissa V. Armada[1], Rouchelle D. Dela Cruz[1]

[1]Philippine Children's Medical Center, Philippine

Aims: Primary hepatic tumors are rare, accounting for less than two percent of neoplasms in the pediatric population. Only 30 cases of embryonal sarcoma of the liver have been reported locally over the past 15 years. **Methods:** This is a case of an 8-year-old female presenting with a two-week history of a non-tender, non-movable mass near the epigastrium initially managed as a case of parasitic infection. Imaging studies revealed a complex cystic mass in the left hepatic lobe. Given the age, the clinical considerations included hepatoblastoma, hepatocellular carcinoma, teratoma, and neuroblastoma. The patient then underwent left lateral hepatic segmentectomy. **Results:** On histologic examination, the unilocular septated cyst showed anaplastic spindle cells admixed with multinucleated giant cells and brisk mitosis set on a myxoid stroma. The morphologic and immunohistochemical studies were compatible with embryonal sarcoma of the liver. Embryonal sarcoma of the liver is the most common malignant hepatic mesenchymal tumor in the pediatric age group. There is no specific biochemical test to confirm this condition and tumor markers may often be normal. Definitive diagnosis is mainly based on histologic features as immunohistochemical stains are non-specific. **Conclusions:** Although this entity may pursue an aggressive clinical course, complete resection of the tumor is associated with a favorable outcome. The diagnosis of embryonal sarcoma of the liver lies on the histologic diagnosis, as clinical manifestations, laboratory, and imaging findings alone lack specificity. **Keywords:** Anaplastic, Embryonal Sarcoma, Liver





PE-44

Genomic and Histopathological Landscape of Premalignant Papillary Neoplasms of Human Biliary System

Taek Chung[1], Seungho Oh[2], Jeong Eun Yoo[1], Ho Kyoung Hwang[3], Sangwoo Kim[2], Young Nyun Park[1]

[1]Department of Pathology, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Department of Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea

Aims: Intraductal papillary neoplasm (IPN) of bile duct and intracholecystic papillary neoplasm (ICPN) are grossly visible premalignant lesions of biliary tract cancer that form exophytic masses. The purpose of this study is to elucidate the differences in carcinogenic sequence according to anatomical regions of biliary system and histopathological features. **Methods:** From the total of

166 cases composed of 33 intrahepatic / 44 extrahepatic IPNs and 89 ICPNs including 40 cases with associated invasive carcinoma, histopathological subtyping aided by immunohistochemistry was performed. Whole-exome sequencing on IPN/ICPNs, associated carcinoma and matched normal tissue was done. **Results:** Biliary subtype was the most common subtype in the entire cohort, with highest frequency observed in extrahepatic IPN (70%, *P*=0.016). Gastric subtype showed the highest incidence (40%, *P*=0.007) while intestinal subtype showed the lowest frequency (6%, *P*=0.025) in ICPN. Oncocytic subtype was found in only 2 cases of intrahepatic IPN. Somatic mutational analysis on IPN/ICPN revealed significantly mutated genes including CTNNB1, TP53, KRAS, APC and SMAD4. KRAS mutation was enriched in intrahepatic IPN (42%, *P*<0.001), whereas SMAD4 mutation was enriched in extrahepatic IPN (21%, *P*=0.005). ICPN had relatively higher CTNNB1 mutation rate compared to intra- and extrahepatic IPNs (23% versus 13% and 9%) (*P*=0.117). Intrahepatic IPN revealed no ERBB2 amplification, whereas it was found in 12% of extrahepatic IPN and 6% of ICPN, and there was no statistical significance (*P*=0.119). Intrahepatic IPN showed homogeneous mutational signature distribution of SBS1 and SBS5 compared to extrahepatic IPN and ICPN, which were characterized by heterogeneous mutational signature pattern and having APOBEC signatures. Genome-wide copy-number variation (CNV) assessment showed a gradual increase of copy-gain/loss with progression from low- and high-grade IPN/ICPN to invasive carcinoma. Phylogenetic tree analysis revealed that major driver mutations and CNVs were maintained during progression from low- and high-grade IPN/ICPN to invasive carcinoma. Gene ontology enrichment analysis on the mutations gained in the invasive carcinoma showed the enrichment of growth factor response signaling genes (adjusted *P*<0.001). **Conclusions:** This study discovered that mutational acquisition patterns in papillary neoplasm of biliary tract are different among intrahepatic IPN, extrahepatic IPN and ICPN. The mutational acquisition patterns in papillary neoplasms of biliary tract are characteristic according to their anatomical location, and mutational signature patterns showed more similarity between extrahepatic IPN and ICPN compared to intrahepatic IPN. Accumulation of significant CNV and mutations in growth factor response genes are responsible for the progression of IPN/ICPN from dysplasia into invasive carcinoma. **Keywords:** Bile Duct, Gallbladder, Papillary Neoplasm, Whole-Exome Sequencing, Carcinogenesis

PE-45

Expression Pattern of Fibronectin Correlates with Microvascular Invasion in Hepatocellular Carcinoma

Yoon Jung Hwang[1,2], Hyejung Lee[1], Haeryoung Kim[1,2]*

[1]Department of Pathology, Seoul National University College of Medicine, Seoul, Republic of Korea; [2]Department of Pathology, Seoul National University Hospital, Seoul, Republic of Korea

Aims: Fibronectin (FN), an extracellular matrix glycoprotein involved in cell adhesion and migration, has recently been shown to be overexpressed in hepatocellular carcinomas (HCCs) and suggested as a potential biomarker of vascular invasion. We aimed to evaluate the patterns of FN expression in HCCs, its clinicopathological implications, including vascular invasion status, and patterns of angiogenesis. **Methods:** Immunohistochemistry for FN was performed on tissue microarrays of comprising 258 surgically resected HCCs and their adjacent liver tissues. Three patterns of FN expression were seen in HCCs: cytoplasmic, membranous, sinusoidal pattern. Moderate or strong expression was regarded as FN-positive. **Results:** Cytoplasmic FN expression was seen significantly more frequently in the HCC (10.9%) than the adjacent parenchyme (1.1%, *P*<0.001). Membranous FN expression was only seen in the tumor cells (14.2%) and not in the non-neoplastic hepatocytes (*P*<0.001). Sinusoidal FN expression was seen significantly more frequently in the HCC (23.9%) compared to the adjacent parenchyme (0.6%, *P*<0.001). FN positivity in the membrane of tumor cells was significantly associated with high serum alpha-fetoprotein (AFP) and protein induced by vitamin K absence-II (PIVKA-II) levels, infiltrative gross type, poor Edmonson-Steiner (ES) grade, major vessel invasion, MVI, macrotrabecular massive (MTM) subtype, higher T stage, and vessels encapsulating tumor clusters (VETC) pattern. Sinusoidal FN expression in HCC was significantly associated with high serum AFP and PIVKA-II levels, infiltrative gross type, large tumor size MVI, MTM subtype and VETC pattern. **Conclusions:** FN expression in tumor cells and sinusoidal endothelial cells of HCC was associated with microvascular invasion and aggressive clinicopathological parameters, and sinusoidal FN expression was also associated with VETC pattern of angiogenesis. Evaluating FN expression in HCC may potentially be useful for identifying an aggressive group of HCCs with vascular invasion, especially in the biopsy setting. **Keywords:** Fibronectin, Microvascular Invasion, Hepatocellular Carcinoma

PE-46

Correlation between CTNNB1 Mutation Status and Tumor Phenotype in Hepatitis B Virus-Related Hepatocellular Carcinoma

Yoon Jung Hwang[1,2], Yangkyu Lee[1,3], Hyejung Lee[1], Haeryoung Kim[1,2]*

[1]Department of Pathology, Seoul National University College of Medicine, Seoul, Republic of Korea; [2]Department of Pathology, Seoul National University Hospital, Seoul, Republic of Korea; [3]Department of Pathology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

Aims: While CTNNB1 mutation is one of the most frequent genetic events in hepatocellular carcinoma (HCC), its frequency is lower in Asian countries and in hepatitis B virus (HBV)-related HCCs. In this study, we evaluated the frequency and types of CTNNB1-mutation in HBV-related HCC and correlated the molecular status with the histomorphological and immunohistochemical features. **Methods:** A total of 108 consecutive cases of treatment-naïve, surgically resected HBV-related HCCs were selected. Targeted sequencing for CTNNB1 exons 3, 7, and 8 was performed, and the results were correlated with the expression pattern of glutamine synthetase (GS), nuclear beta-catenin expression status, and the histomorphological characteristics of the tumor. **Results:** CTNNB1

mutations were identified in 14/108 (13%) HBV-related HCCs; of these cases, mutations were found in D32-S37 (n=8, 7%), T41 (n=4, 4%) and S45 (n=2, 2%) of exon 3. None of the HCCs demonstrated alterations in exons 7 and 8. CTNNB1 mutation was strongly associated with diffuse strong GS expression (P<0.001), nuclear beta-catenin expression (P<0.001) and the classic CTNNB1 morphology (P=0.038), defined by well-differentiated HCC showing a predominant microtrabecular pattern with pseudoglands. Diffuse strong GS expression was observed in 78.6% of the CTNNB1-mutated HCCs – 62.5% of the D32-S37-mutated HCCs, and in all of the T41 and S45-mutated HCCs. Nuclear beta-catenin expression was identified in 64.3% of the CTNNB1-mutated HCCs – 62.5% of the D32-37-mutated HCCs, 50% of the T41-mutated HCCs and all of the S45-mutated HCCs. All CTNNB1-mutated HCCs with nuclear beta-catenin expression showed diffuse strong GS expression. The classic CTNNB1 morphology was observed in 57% of all CTNNB1-mutated HCCs, 50% of the D32-S37-mutated HCCs, 75% of the T41-mutated HCCs, and 50% of the S45-mutated HCCs. **Conclusions:** CTNNB1 mutation was observed in 13% of HBV-related HCCs in this Korean cohort, and was associated with diffuse strong GS expression, nuclear beta-catenin expression and classic CTNNB1 morphology. **Keywords:** CTNNB1, Hepatocellular Carcinoma, Hepatitis B Virus

Liver Cancer - Treatment: Clinical Trials

PE-47

Clinical Trial in Asian Patients Liver Cancer: Systematic Review

Ferza Alfath

Department of Law, Alumnus Universitas Andalas, Indonesia

Aims: Liver cancer is cancer that originates from cells in the liver. This cancer can originate from liver cells or the spread of cancer cells from other organs, such as the intestine, skin, or breast (Halodoc, 2022). Primary liver cancer is a disease in which malignant (cancer) cells form in the liver tissue (National Cancer Institute, 2022). Clinical trials are experiments or observations in clinical research (Wiki, 2022). Clinical trials are also used in studying liver cancer in Asia. This study aim to development of liver cancer clinical trials in Asia. **Methods:** This research uses a systematic review method. We collected articles from 2010-2023 from an electronic database, lens.org. The keywords used are Autoimmune Liver Disease and Asian Children. Then as many as three selected articles were reviewed to answer the purpose of this study. **Results:** The Asian Liver Transplant Network (ALTN) is a strategic network of key opinion leaders in liver transplantation (LT) from Hong Kong, Japan, Indonesia, Singapore, South Korea, Taiwan, and the Philippines, which provides a platform for regular exchange to facilitate best clinical practice (Tan et al, 2019). Study from Chen et al. (2010) staging and treatment, clinical practice guidelines and recommendations for the design and conduct of clinical trials that have been developed primarily in the West cannot be used throughout the world without modification. Another study from Tan et al. (2019) there are notable differences in the indications and procedures for LT between Western and Asian settings. **Conclusions:** Clinical trials on Asian Liver Cancer Patients began to develop in Hong Kong, Japan, Indonesia, Singapore, South Korea, Taiwan and the Philippines. **Keywords:** Clinical Trial, Asia, Systematic Review, Liver Cancer

PE-48

Comparison of Background Characteristics of Patients Receiving Lenvatinib VS Atezolizumab Plus Bevacizumab in Unresectable Hepatocellular Carcinoma

Shinji Itoh[1], Masafumi Ikeda[2], Daisuke Onozuka[3], Ryosuke Tateishi[4], Tatsuya Yamashita[5], Takuji Okusaka[6], Naoya Kato[7], Junji Furuse[8], Masatoshi Kudo[9]

[1]Department of Surgery and Science, Kyushu University, Japan; [2]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Japan; [3]Department of Oral Microbe Control, Osaka University, Japan; [4]Department of Gastroenterology, The University of University, Japan; [5]Department of Gastroenterology, Kanazawa University Hospital, Japan; [6]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Japan; [7]Department of Gastroenterology, Chiba University, Japan; [8]Department of Gastroenterology, Kanagawa Cancer Center; [9]Department of Gastroenterology and Hepatology, Kindai University, Japan

Aims: In clinical practice, there are various background factors and patterns in the treatment sequence of systemic therapy for patients with unresectable hepatocellular carcinoma (HCC). Therefore, a prospective, observational, large-scale multicenter study of systemic therapy for HCC (PRISM) was conducted to establish real-world evidence from real-world data in Japan. Clinical trial registration: UMIN000040488. **Methods:** Patients with histologically or clinically diagnosed unresectable HCC who are receiving first-line systemic therapy and have provided written informed consent are eligible for this study. The primary endpoint is the overall survival of each regimen at each treatment line. The planned sample size is 1,000 patients with an enrollment and follow-up period of 2 years each. Herein, we compared the background factors in patients who received lenvatinib (LEN) and atezolizumab plus bevacizumab (ATZ/BEV) as first-line systemic therapy by using the Wilcoxon rank-sum test, chi-square test, or Fisher's exact test. The two-sided significance level for all tests was P<0.05. **Results:** The enrollment of 1,000 patients was completed in 40 Japanese participant hospitals between August 2020 and July 2022. Of these, 915 were included in this study, excluding those ineligible, untreated, mis-enrolled (i.e., sorafenib and other treatment as first line. Seven hundred seventy-four patients (84.6%) treated with ATZ/BEV and 141 (15.4%) treated with LEN as first-line systemic therapy were enrolled in this study. The LEN group had significantly worse performance status (P=0.007), lower serum albumin (P<0.001), worse Child-Pugh classification (P<0.001), and

worse ALBI grade (P<0.001) than the ATZ/BEV group. Moreover, the LEN group showed a significantly higher frequency of intrahepatic lesions than ATZ/BEV group (P=0.006). **Conclusions:** This study revealed that LEN was selected in cases with poor general condition and liver function. The PRISM study is a useful clinical study that can clarify the real-world data of systemic therapy for HCC in Japan. **Keywords:** Hepatocellular Carcinoma, Lenvatinib, Atezolizumab Plus Bevacizumab

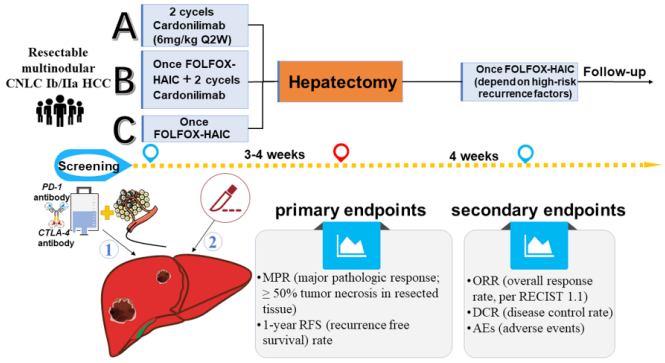
PE-49

Neoadjuvant Cadonilimab (PD-1/CTLA-4 Bispecific Antibody) Plus Transhepatic Arterial Infusion Chemotherapy (HAIC) with FOLFOX for Resectable Multinodular CNLC b/ a Hepatocellular Carcinoma

Yongguang Wei[1], Zhiming Zeng[2], Guangzhi Zhu[1], Zili Lv[3], Xinping Ye[1], Kaiyin Xiao[1], Liling Long[4], Hao Su[1], Ming Su[1], Ning Peng[1], Jilong Wang[1], Chuangye Han[1], Chenhui Li[4], Jie Ma[1], Tao Peng[1]

[1]Department of Hepatobiliary Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, China; [2]Department of Medical Oncology, The First Affiliated Hospital of Guangxi Medical University, Nanning, China; [3]Department of Pathology, The First Affiliated Hospital of Guangxi Medical University, Nanning, China; [4]Department of Radiology, The First Affiliated Hospital of Guangxi Medical University, Nanning, China

Aims: Cadonilimab is a bispecific, humanized IgG1 antibody (PD-1/CTLA-4). HAIC plus immunotherapy has synergistic antitumor effect. This trial is to evaluate the safety and efficacy of cadonilimab plus HAIC (FOLFOX) as a neoadjuvant intervention in resectable multinodular CNLC Ib/IIa HCC patients. **Methods:** In this phase 2, cohort clinical trial (ChiCTR2200067161), eligible patients (pts) were randomly assigned (1:1:1) to 3 arms: (A) 2 cycles of cadonilimab (6mg/kg Q2W); (B) once HAIC followed by 2 cycles of cadonilimab; (C) once HAIC. All pts receive scheduled surgery on day 21-28 and postoperative adjuvant HAIC (Fig). The primary endpoints were MPR rate defined as ≥50% tumor necrosis and 1-year RFS rate. Main secondary endpoints included ORR (RECIST 1.1), DCR, AEs. **Results:** From January 4 to March 30, 2023, 9 pts were enrolled (3 pts in each arm). All pts were ECOG PS 0-1 and Child-Pugh A. Five pts received scheming hepatectomy (2pts in Arm A, 2pts in Arm B, 1pt in Arm C). Pathologically, 2 pts in Arm B achieved MPR, which showed tumor heterogeneity with one lesion complete response and another partial response; 2 pts in Arm A were partial response. Tumor necrosis was not observed in Arm C, but inflammatory infiltrating and fibrosis area in the tumor accounted for 45%. All pts met SD and DCR was 100%. The most common TEAEs in Arm B and C were ALT, AST and bilirubin increase (60.0%), which mainly resulted from HAIC. TEAEs in Arm A were grade 1 bilirubin increase and triiodothyronine decrease (1/3). No grade 3 or worse TEAEs occurred. No pts delayed surgery. The most common surgical complications were ALT and AST increase (100%), bilirubin increase (60%) and serum amylase increase (40%). **Conclusions:** This study preliminarily demonstrated that neoadjuvant cadonilimab plus HAIC show promising antitumor activity with manageable safety for HCC. This trail is ongoing. **Keywords:** HCC, Immunotherapy, PD-1/CTLA-4, Bispecific Antibody, HAIC, Neoadjuvant Treatment



Liver Cancer - Treatment: Surgical Resection and Transplantation

PE-50

A Systematic Review on Live Donor Liver Transplantation (LDLT) in Asia

Devi Yulia Rahmi

Department of Management, Universitas Andalas, Indonesia

Aims: Live Donor Liver Transplantation (LDLT) is an essential life-saving procedure for patients with acute liver failure and hepatocellular carcinoma. In adults, the most common reason for LDLT is liver cirrhosis, which refers to liver scarring. In children, biliary atresia is the most common reason for LDLT. The success of liver transplantation worldwide has brought increased demand for liver grafts. In Asia, the focus has been on living donor liver transplantation (LDLT), as this procedure is more acceptable in most Asian cultures. LDLT, initially devised for pediatric liver transplant patients, has evolved from using a left lobe graft to a right lobe graft for an adult recipient. This study aims to see the development of LDLT in Asia. **Methods:** This research uses a systematic review method. We collected articles from 2010-2022 from an electronic database (pubmed.gov, springer, science direct, Gleneagles). The keywords used are LDLT and Asia. Then as many as ten selected articles were reviewed to answer the purpose of this study. **Results:** Asian liver transplant centers have been the world's pioneers, innovators, and technical advancement catalysts, especially concerning LDLT. Techniques to expand the living donor pool have also been adopted, like ABO-incompatible, paired exchange and dual lobe living donor liver transplants. The unique combination of demographic, social, economic and political factors in Asia will ensure that LDLT remains the predominant form of liver transplantation. In one of the sample

LDLT in Hongkong patients, 74.9% met the UCSF criteria, and 64.5% met the Milan criteria. A 5-year overall and disease-free survival rate of 78.9% and 76.3% were achieved (Mok et al., 2022). **Conclusions:** LDLT in Asia is starting to develop. The technique that is often used is ABO-incompatible, paired exchange and dual lobe living donor liver transplants **Keywords:** Live Donor Liver Transplantation, Asia, Systematic Review

PE-51

Comparison of Open versus Laparoscopic Approaches in Salvage Hepatectomy for Recurrent Hepatocellular Carcinoma after Radiofrequency Ablation

Yeshong Park[1], Jai Young Cho[1], Ho-Seong Han[1], Yoo-Seok Yoon[1], Hae Won Lee[1], Boram Lee[1], MeeYoung Kang[1], Jinju Kim[1]

[1]Department of Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Republic of Korea

Aims: Although radiofrequency ablation (RFA) is widely used as an effective local treatment for hepatocellular carcinoma (HCC), evidence on salvage hepatectomy for marginal recurrence after RFA is limited. This study aims to compare open and laparoscopic approaches in salvage hepatectomy for recurrent HCC after RFA. **Methods:** Among patients who underwent hepatectomy between January 2004 and August 2022 at a single tertiary referral center, 55 patients who underwent salvage hepatectomy for marginal recurrence after RFA were selected. Open approach was used in 23 (41.8%) patients, while 32 (58.2%) patients underwent laparoscopic surgery. Short-term and long-term outcomes were compared between the two groups. **Results:** Major hepatectomy was more often performed in the open group (9 [39.1%] vs. 4 [12.5%], *P*=0.022). Operation time, intraoperative blood loss, and postoperative morbidity rates were similar, and there was no postoperative mortality in either group. Postoperative hospital stay was significantly longer in the open group compared to the laparoscopy group (8 [6 – 11] days vs. 5 [4 – 7] days, *P*=0.028). The 1-, 3-, and 5-year disease-free survival rates showed no difference between the two groups (44.6% vs. 62.5%, 16.5% vs. 13.5%, and 8.3% vs. 13.5%, respectively; *P*=0.154). The 1-, 3-, and 5-year overall survival rates between the two groups were also similar (85.7% vs. 96.8%, 79.6% vs. 86.0%, and 79.6% vs. 79.4%, respectively; *P*=0.480). In Cox multivariate analysis for overall survival, tumor number (hazard ratio [HR] 8.34, *P*=0.009), tumor grade (HR 17.98, *P*=0.008), and vascular invasion (HR 8.19, *P*=0.014) were independent predictors. Operative approach was not a significant risk factor (HR 0.94, *P*=0.913). **Conclusions:** Laparoscopic salvage hepatectomy shows oncologic outcomes comparable to the open approach with faster postoperative recovery rates. Considering that recurrence rates are high after RFA, laparoscopic approach should be considered as a first-line option in selected patients. **Keywords:** Hepatocellular Carcinoma, Radiofrequence Ablation, Marginal Recurrence, Salvage Hepatectomy

PE-52

Immunosuppression after Liver Transplantation

Nurzhan Yerniyazov[1], Aidos Kulmaganbetov[1], Symbat Kulmaganbetova[1], Baigenzhin Abay[2], Doskaliyev Zhaksylyk[3]

[1]Department of Surgery, Kyzylorda City Oncology Center, Kyzylorda, Kazakhstan; [2]Department of Surgery, National Scientific Medical Center, Astana, Kazakhstan; [3]Department of Surgery and Liver Transplantation, National Scientific Oncology Center, Astana, Kazakhstan

Aims: Immunosuppressive medications have many negative effects. one way of solving this is to minimize immunosuppression. **Methods:** 30 liver transplantations were performed in our Medical Center between January 2013 and January 2016: 22 – from living donors, and 8 – from cadavers. Most liver transplants were performed with SNUH (Seoul, Korea). The indications for liver transplantation (LT) were as follows: primary biliary cirrhosis – 6, hepatitis C virus (HCV) cirrhosis – 3, hepatitis B virus (HBV) cirrhosis – 20, and autoimmune hepatitis – 1. **Results:** In 28 recipients at the beginning immunosuppression as based on 3 components: Tacrolimus – MMF – Corticosteroids. All patients discontinue steroids after 6-12 months after transplantations, depending on the etiology of liver cirrhosis. One patient finished receiving MMF 2 years after transplantation. Two patients (after living donor transplantation) received (and receive now) only Tacrolimus and had no rejection episodes. But they have appointed hormones for a week after transplantations. One patient had a conversion from Tacrolimus to Cyclosporine. She had hyperglycemia after conversion glucose levels returned to normal. **Conclusions:** Minimization of immunosuppression is a necessary goal for transplant patients. Many immunosuppressive drugs have side effects, which lead to undesirable consequences or death. Immunosuppression minimization regimes should be safe for rejection and infectious complications in liver transplant patients. **Keywords:** Liver Transplantation, Liver Cirrhosis, MELD, Immunosuppression

PE-53

Surgical Tactics of Treatment of Liver Hemangiomas

Rokiya Surova[1]

KSMA, Kyrgyzstan

Aims: To evaluate the results of diagnostics and surgical treatment of patients with liver hemangiomas. **Methods:** A retrospective analysis of the results of treatment of 31 patients was carried out, of which 23 were women and 8 were men. The age of the patients was in the range of 25-65 years (mean age was 45 years). The duration of the disease ranged from 2 weeks to 10 years from the onset of the first clinical manifestations of the disease. For a more accurate diagnosis of this pathology, all patients underwent the following methods of instrumental examination: ultrasound (29 patients) and CT (21 patients) of the liver, patients with giant hemangiomas underwent MSCT (8 patients) to detect compression of the vessels and bile ducts of the liver. **Results:** As a result of

the study, the right lobe of the liver was affected in 20 patients (64.5%), the left lobe was affected in 8 patients (25.8%) and giant hemangioma in 3 patients (9.6%), 3 or more affected segments were found in 12 (38.7%) patients, involvement of 2 segments in 13 (41.9%) patients and involvement of 1 segment in 6 (19.3%) patients. The volume of surgical intervention: in 5 patients (16.1%), right-sided hemihepatectomy (HRHE), left-sided hemihepatectomy (LHHE) was performed in 2 (6.4%) patients, 20 (64.5%) patients - atypical liver resection (AR), including lobectomy and 2 (6.4%) patients underwent exploratory laparotomy. The maximum blood loss was about 1.5 liters, the minimum blood loss was 200 ml, 30 (96.7%) patients had Tachocomb hemostatic sponges glued to the resected lobes of the liver. 8 (25.8%) patients underwent simultaneous operations. Subsequently, the result of histological examination confirmed cavernous hemangioma in 24 (77.4%) patients, 3 (9.6%) patients had concomitant diseases, as well as capillary hemangioma in 1 (3.2%) patient. **Conclusions:** Early detection of liver hemangiomas can prevent the development of such life-threatening complications as rupture of the formation with massive bleeding. Thus, liver resection is an effective and affordable treatment for liver hemangiomas. **Keywords:** Liver, Tumors, Resection, Surgery

PE-54

Laparoscopic Drainage Basin Hepatectomy Based on Cone Unit

Yu Cheng, Hongkai Niu, Shunzhong Zhang

Department of Hepatobiliary Surgery, Binzhou Medical University Yantai Hospital, Yantai City, Shandong Province, China

Aims: Laparoscopic anatomical hepatectomy is mainly for liver malignant tumors, most HCC has the basis of cirrhosis, does not allow large-scale hepatectomy, with the deepening of the understanding of liver anatomy and the application of Laennec capsule, for patients with small HCC and severe cirrhosis, according to the precise basin of liver blood supply, the liver resection reduces the volume of hepatectomy and achieves the purpose of anatomical hepatectomy. This study explores the application of single or combined Cone Unit resection in drainage basin hepatectomy. **Methods:** In this study, 12 patients with cirrhosis underlying liver cancer underwent Cone Unit-based resection in the watershed .After enhanced CT or MRI, 3D reconstruction constructs the Glisson pedicle composition of the area where the tumor is located, each small pedicle blood supply area acts as a Cone unit, two methods determine the cone unit resection range: (1) Hilar gate Laennec capsule free is applied, one or several cone unit blood supply pedicle is isolated and ligated, ICG injection reverse staining determines 1 or several cone unit ranges for resection; (2) Another method: ultrasound localization of cone unit Glisson pedicle and puncture portal vein injection of ICG, anatomical excision by puncture one or several cone unit blood supply pedicles according to preoperative planning. **Results:** In all 12 patients with small HCC based on cirrhosis, 8 cases were reverse stained and 4 cases were orthostained. The median duration of surgery was 89±15 minutes and the average estimated blood loss was 103 ml. All 12 recovered successfully. There was no liver failure, and the hospital stay is 6.83 days. Follow-up results showed that the mean disease-free survival (DFS) was 24.7m and OS 38.9 m. **Conclusions:** Drainage Basin Hepatectomy based on cone unit watershed is a safe and effective surgical method for small HCCs with severe cirrhosis, which reduces the incidence of postoperative liver failure and reduces bleeding, thereby increasing DFS and OS in patients. **Keywords:** Hepatectomy, Cone Unit, Drainage

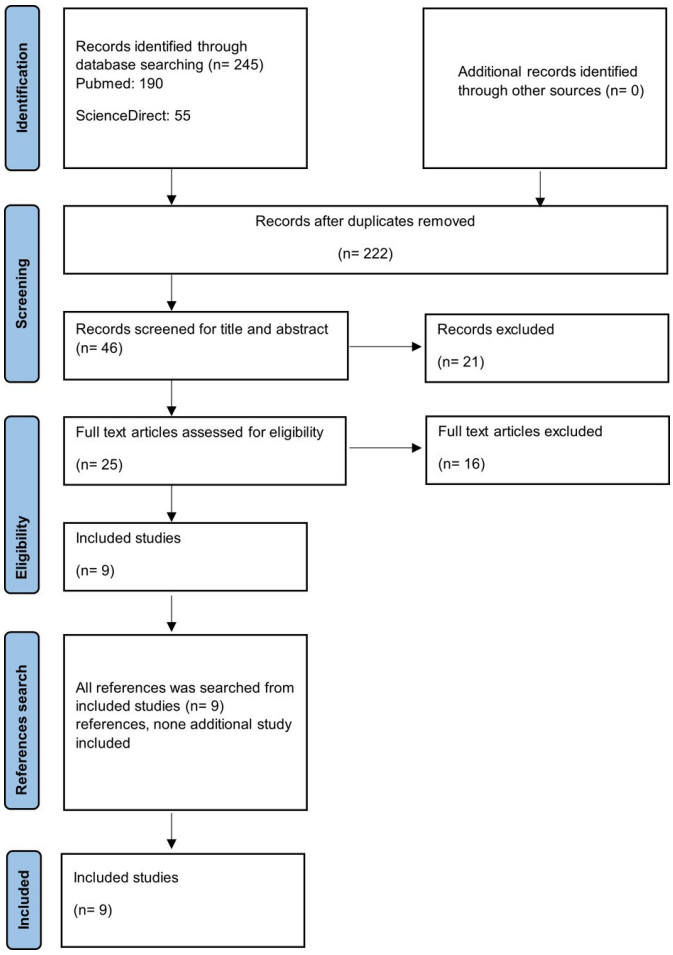
PE-55

Medical Tourism for Liver Transplantation in Patients with Hepatocellular Carcinoma: A Systematic Review of the Opportunity, Risks and Benefits

Nissa Larasati[1], Adika Zhulhi Arjana[2], Ninda Devita[3]

[1]Master of Tourism Programme, Universitas Gadjah Mada, Yogyakarta, Indonesia; [2]Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia; [3]Faculty of Medicine, Universitas Islam Indonesia, Yogyakarta, Indonesia

Aims: Liver transplantation is a treatment for liver cancer. However, organ shortage, high cost, and long waiting times drive some patients to travel abroad for transplants, a practice called transplant tourism. It may benefit some patients but also pose serious risks and complications. It may also harm the donors, the health systems, and the organ policies of both countries. This study aims to review the opportunity, risks, and benefits of transplant tourism for liver transplantation. **Methods:** We systematically reviewed the literature on medical tourism involving liver transplantation following the PRISMA guidelines. We searched PubMed and ScienceDirect databases for articles published in English from January 2013 to December 2023 using the following keywords: ("liver transplantation" OR "liver transplant" OR "hepatic transplantation" OR "hepatic transplant") AND ("medical tourism" OR "transplant tourism" OR "commercial transplant" OR "organ trade" OR "organ trafficking"). We included original research articles that reported data on the challenges and recommendations of medical tourism for liver transplantation. We excluded articles that did not focus on liver transplantation or did not provide sufficient information on medical tourism. **Results:** We included nine articles (1 cohort, two cross-sectional, and six qualitative) in the analysis. The primary diagnosis was hepatitis B or C infection. Medical tourists were driven by the long waiting times, high costs, and strict criteria for liver transplantation in their home countries. However, the five-year survival rates were lower for the medical tourist than domestic recipients (53%-86% vs. 72%-91%, respectively). **Conclusions:** Medical tourism for liver transplantation in patients with hepatocellular carcinoma has challenges, risks, and benefits. More research, regulation, and collaboration are needed to address ethical, legal, and medical issues. Patients, healthcare providers, and policymakers should be informed and responsible for transplant tourism. **Keywords:** Liver Transplantation, Medical Tourism, Hepatocellular Carcinoma



PE-56

Multidimensional Quality of Life after Pediatric Liver Transplantation: Luck or Measurable Achievement?

Hepri Ardianson Purba[1], Rosinta Hotmaida Pebrianti Purba[2]

[1]Economics, Alumnus of University of Lampung, Indonesia; [2]Department of Economics, Learning Up Institute, Indonesia

Aims: The field of pediatric liver transplantation (LT) has come a long way over the last 50 years. As short-term outcomes are excellent, the long-term effects of pediatric LT and its consequences on various aspects of quality of life have not been extensively examined. This is especially true for children who receive an LT while they are young, as infantile-onset liver disease, surgery, and immunosuppression can all have a negative impact on growth and neurodevelopment. The objective of this study was to use a validated measure for children to identify the status of physical health, mental well-being, and socioeconomic status in this cohort. **Methods:** A systemic review of the English literature was carried out from an electronic database, covering all papers addressing long-term outcomes in pediatric liver transplants from 2000 to 2021. **Results:** A physical summary score of the LT recipients was lower than the normal population, only 26% of our cohort achieved a composite outcome of 'meaningful survival'. Late outcomes after pediatric liver transplant affects the liver graft in the form of chronic liver dysfunction, humoral rejection, de novo autoimmune hepatitis, recurrent disease, metabolic syndrome, kidney dysfunction, and malignancy, worsened neurocognitive development, and shortages in allografts because of the cumulative exposure to the adverse effects of long-term immunosuppressive medications. The prevalence of common mental health problems is significantly higher than in the general population (26%): distress to fatigue, sleep difficulties, financial concerns, problems at work/school, worry, and low self-esteem. It worsened because the parents experienced more emotional stress and disruption of family activities. Sexual dysfunction only short-term impact post-transplant (3 months), but no long-term effect was found. **Conclusions:** Importantly, despite normal liver function, many patients did not demonstrate 'meaningful survival'. We must refocus our efforts toward better understanding the long-term outcomes of children's "meaningful survival". The importance of promoting psychosocial support and family-centered care as key contributors to delivering a model towards the overarching goal of optimizing durable outcomes. **Keywords:** Pediatric Liver Transplantation, Long-Term Effects, Meaningful Survival, Family-Centered Care

PE-57

Sexual Function Deterioration among Donor and Recipients of Living Donor Liver Transplantation (LDLT) a Systematic Review

Hepri Ardianson Purba[1], Rosinta H. P. Purba[2]

[1]Department of Economics, Alumnus University of Lampung, Indonesia; [2]Department of Economics, Learning Up Institute, Indonesia

Aims: Although sexual functioning is essential to a Liver Cancer patient's Quality of Life (QoL), risk factors for hypogonadism and erectile dysfunction are largely unknown. This is a problem that patients and health professionals are reluctant to discuss face-to-face. **Methods:** An integrative literature review from an electronic database was conducted to determine the incidence of sexual dysfunction among donors and recipients of LDLT patients. Inclusion criteria included 1) patients aged 18 or over, and 2) using the Female Sexual Function Index (FSFI) and International Index of Erectile Function (IIEF). **Results:** Sexual dysfunction is characterized by disturbances in sexual desire and the psychophysiological changes associated with the sexual response cycle in men and women. QoL LDLT patients remained similar to the general population except they had lower mental health scores. The result also shows that sex hormone disturbances are highly prevalent in patients after LT, even though the rate is higher in men. It indicates that mental health problems after LT are related to sexual function deterioration. On the Donor side, sexual functioning was lower at the evaluation phase and three months than at one-year post-donation: difficulty reaching orgasm, lower

sexual desire, and dissatisfaction with sexual life. However, there has been an improvement in sex hormone levels after LT in some instances, namely, normalization of estradiol levels and lowering of prolactin and progesterone levels. **Conclusions:** LT has been shown to increase the QoL of liver disease patients. However, it is vital to assess QoL level after LT in patients and donors to know their satisfaction to cope with the situation. Mainly including the topic of sexuality in the routine of care. Finally, it is crucial to maintain high therapeutic adherence, thus ensuring a good outcome of the care received before and after the transplantation process. It aims to prepare them for the early recovery phase may improve recovery and reduce distress regarding sexual functioning. **Keywords:** Perioperative Nursing, Sexuality, Liver Recipients, Liver Donors, Living Donor Liver Transplantation

PE-58

Analysis of Recurrence Pattern after Partial Hepatectomies for Hepatocellular Carcinoma

Ming-Chin Yu[1], Heng-Yuan Hsu[1], Chun-Wei Huang[1], Tsung-Han Wu[2], Chao-Wei Lee[2]

[1]New Taipei Municipal TuCheng Hospital (Built and Operated by Chang Gung Medical Foundation), Taiwan; [2]Chang-Gung memorial hospital, Linkou branch, Taiwan

Aims: The long-term outcome of HCC after resection were improved in these years but patients with recurrence should be treated with different strategies based on the regional recurrence or distant metastasis, The clinical relevance between the recurrence pattern and perioperative events were rarely studied. The aim of this study is to analysis the impact of recurrence pattern. **Methods:** Of 764 HCC patients enrolled Linkou and Tucheng from 2012 to 2021 March, 10(1.3%) developed hospital mortality. The demographic data was compatible with our previous studies; male 76.7%, diabetes 26.5%, HBV 59.3%, HCV 26.7%, Most were Child A patients. Overall, 49.7% developed recurrence and 31.5% were lost. Recurrent patterns were classified as section margin, adjacent segment, multiple intrahepatic and distant mets. Cox regression and log rank tests were performed for disease-free survival. **Results:** There were 13.8%, 39.7%, 30.1%, 5.6% and 10.9% for AJCC stage Ia, Ib, II, IIIa and IIIb, respectively. margin 17 (2.3%), adjacent sector 227 (30.1%), multiple intrahepatic 51 (6.8%) and distant 80 (10.6%). There was no difference of disease-free survival between narrow and wide resection margin. Distant recurrence is associated with aggressive tumor biology, whereas local recurrence is associated with satellite lesions and cirrhosis. Patients with distant metastasis had the shortest interval for disease-free and it was related to overall survival. (10.9 m vs. 24.4, $.P<0.05$). **Conclusions:** Distant metastasis in recurrence pattern was associated with early recurrence but local recurrence occurred later. Furthermore, aggressive tumor biology is still the most important one for prognosis and should be detected with novel imaging system and bioinformatics. **Keywords:** HCC, Recurrence, Tumor Biology, Outcome

PE-59

Immediate Results of Surgical Treatment Cholangiocellular Cancer

Surov Edir[1], Bebezov Bakhadyr[1]

Kyrgyz -Russian Slavic University, Kyrgyzstan

Aims: To evaluate the immediate results of surgical treatment of cholangiocellular carcinoma. **Methods:** The results of treatment of 25 patients with hepatic cholangiocellular carcinoma from 2010 to 2018 are analyzed. There were 14 men (56.0%), women-11 (44.0%). The average age of patients was 61 ± 9 years. In 9 patients, the formation is localized in the left lobe, in 13 in the right lobe and 3 patients with bilobar liver damage. **Results:** The following types of liver resection were performed: RHHE –13, LHHE - 9, LLE - 1, exploratory laparotomy - 2. Blood loss averaged 798 ± 256 ml., minimum 200 ml. According to the international classification of TNM, patients were distributed as follows: T2N0M0 (stage I) - 19, T3N0M0 (stage II) - 6, T4N1M0 (stage IV) - 1 patients, There were the following types of complications in the postoperative period: hepatic failure in 6th, received conservative therapy; in 2 patients, the formation of a biloma in the abdominal cavity, followed by drainage under local anesthesia, received conservative treatment. One patient has a biliary fistula, closed on the 14th day after the operation. Postoperative mortality was not observed. **Conclusions:** The presence of cirrhosis and hepatitis in patients with hepatic cholangiocellular carcinoma worsens the immediate and long-term results of treatment, but is not a contraindication to surgical treatment. Surgical treatment of cholangiocellular carcinoma requires an accurate preoperative assessment of the functional reserve of the liver. **Keywords:** Liver, Cancer, Cholangiocarcinoma, Treatment

PE-60

Laparoscopic Liver Echinococcectomy

Kulmaganbetov Aidos[1], Yerniyazov Nurzhan[2], Kulmaganbetova Symbat[2]

[1]General Surgery Department, Kyzylorda City Regional Medical Center, Kazakhstan; [2]Liver Surgery Department, Kyzylorda City Oncological Center, Kazakhstan

Aims: The treatment of parasitic liver cysts remains one of the most critical problems of surgical hepatology. Only surgical treatment is recognized as the main for liver echinococcosis. Drug therapy rarely using, because of its ineffectiveness. New perspectives in the treatment of echinococcosis using the possibilities of video endoscopic surgical interventions-laparoscopic echinococcectomies. The goal is to improve the results of surgical treatment of patients with liver echinococcosis by reducing the traumatism of operations, the frequency of postoperative complications, relapses, and the duration of rehabilitation of patients after surgical treatment. **Methods:** In the department of Liver surgery of our center, in the period from 2012 to 2022 32 laparoscopic operations were performed in patients with liver echinococcosis. Among them were 18 men and 14 women aged from 19 to 52 years. Usually used 3 trocars. A trocar with a diameter

of 10 mm was introduced into the navel. Additional trocars were administered under laparoscopic control in the subcostal area, at the point directly above the hepatic cyst (10 mm trocar) and along the anterior axillary line (5 mm trocar). After that gauze was injected into the abdominal cavity and moistened with a solution of povidone, which was used to cover the area around the cyst. The same gauzes isolated the subphrenic or subhepatic space depending on the localization of the cyst. The next step was the puncture of the cyst with a thick needle with complete suction of the cyst contents with a vacuum suction. Then, through the same needle (without removing it from the cyst cavity), a 1% povidone solution was injected into the residual cavity. After exposure for 5 minutes, the entire cyst was aspirated again. The treatment was repeated twice. Then the cyst wall in its most thinned place was opened with electrocoagulation scissors. Excess fibrous capsules with thinned hepatic parenchyma were excised. Shell parasites were removed from the cavity of the cyst using an end container. In the case of bile duct fissures, we coagulated them with an argon plasma coagulator. The walls of the fibrous capsule were treated with a povidone solution. The drainage of the residual cavity was performed by specialized silicone drains. Then gauze moistened with a solution of povidone was removed from the abdominal cavity and the subphrenic or subhepatic space was drained. **Results:** Laparoscopic surgery of echinococcal liver cysts was possible in all 34 patients without conversion. The average duration of the operation was 54 ± 10 minutes. No intraoperative complications. The average length of hospital stay was from 5 to 7 days. No complication after operations. **Conclusions:** In conclusion, laparoscopic echinococcectomy can be successfully used in the treatment of liver echinococcosis in patients with superficial echinococcal cysts. The absence of laparotomic incision significantly reduces the time of rehabilitation of patients after surgical treatment. **Keywords:** Liver Echinococcectomy, Laparoscopic, Parasitic, Liver Cyst

PE-61

Immediate Results of Surgical Treatment Hepatocellular Cancer

Begimai Murzalieva

Kyrgyz State Medical University, Kyrgyzstan

Aims: To evaluate the immediate results of surgical treatment of HCC. **Methods:** The results of treatment of 25 patients with hepatic HCC from 2018 to 2022 are analyzed. There were 14 men (56.0%), women-11 (44.0%). The average age of patients was 61 ± 9 years. In 9 patients, the formation is localized in the left lobe, in 13 in the right lobe and 3 patients with bilobar liver damage. **Results:** The following types of liver resection were performed: RHHE –13, LHHE - 9, LLE - 1, exploratory laparotomy - 2. Blood loss averaged 798 ± 256 ml., minimum 200 ml. According to the international classification of TNM, patients were distributed as follows: T2N0M0 (stage I) - 19, T3N0M0 (stage II) - 6, T4N1M0 (stage IV) - 1 patients, There were the following types of complications in the postoperative period: hepatic failure in 6th, received conservative therapy; in 2 patients, the formation of a biloma in the abdominal cavity, followed by drainage under local anesthesia, received conservative treatment. One patient has a biliary fistula, closed on the 14th day after the operation. Postoperative mortality was not observed. **Conclusions:** The presence of cirrhosis and hepatitis in patients with hepatic HCC worsens the immediate and long-term results of treatment, but is not a contraindication to surgical treatment. Surgical treatment of HCC requires an accurate preoperative assessment of the functional reserve of the liver. **Keywords:** Hepatocellular Cancer, Liver Cirrhosis, Liver Surgery, Liver Resection

PE-62

Surgical Tactics for Colorectal Cancer with Synchronous Liver Metastases

Erlan Murzaliev

Kyrgyz-Russian Slavic University, Kyrgyzstan

Aims: Comparative assessment of the immediate results of simultaneous removal of the primary colorectal tumor with liver resection and two-step operations. **Methods:** The results of treatment of 36 patients from 2018 to 2022 were analyzed. 15 simultaneous and 21 consecutive operations were performed for synchronous colorectal metastases in the liver. Of these, extensive liver resections were performed in 41.7% and 58.3% of cases, respectively. Clinical, intraoperative, postoperative data were analyzed to assess the immediate results of the treatment. **Results:** Simultaneous operations did not increase intraoperative blood loss (756 ± 76 against 835 ± 83 ml, P=0.4), the number of postoperative complications (6.6% against 3.8%) and mortality (0% against 2.9% (1 patient)) in comparison with sequential operations. During operations on the colon and rectum, the number of postoperative complications and mortality did not differ (P=0.61 and P=0.48, respectively). Comparative assessment of postoperative complications and mortality after extensive simultaneous and sequential operations also revealed no differences (P=0.93 and P=0.96, respectively). All patients received neoadjuvant and adjuvant chemotherapy according to the XELOX, FOLFOX scheme. **Conclusions:** If simultaneous intrahepatic metastases of colorectal cancer are detected and there are no marked associated diseases, it is advisable to perform simultaneous operations, regardless of the location of the primary tumor and the amount of liver resection. **Keywords:** Liver Cancer, Colorectal Cancer, Liver Metastasis, Liver Resection

PE-63

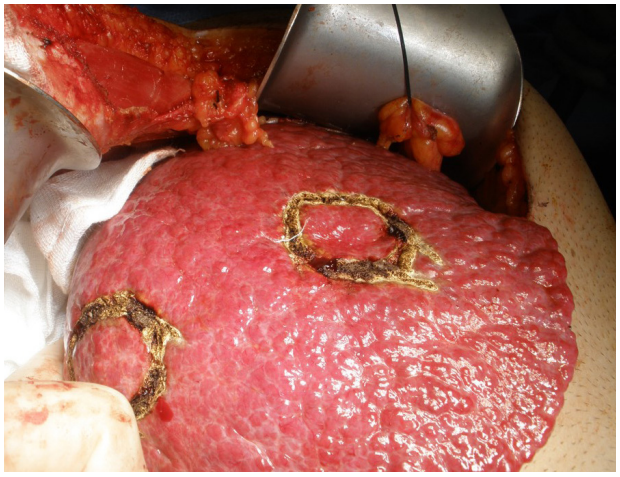
Enucleation of Dysplastic Nodule Segment 7 in Child B Liver Cirrhosis

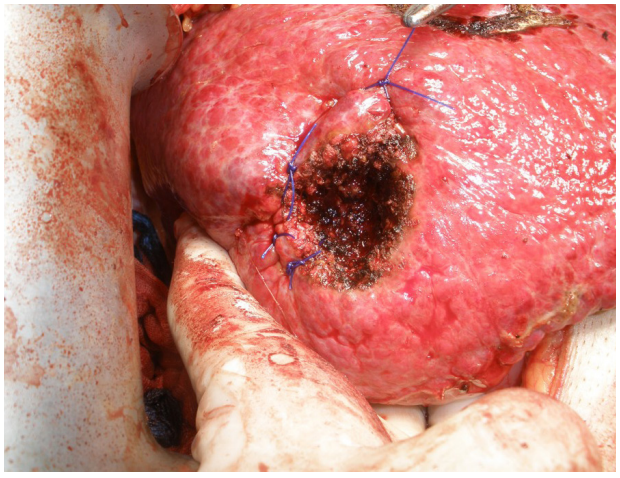
Muhammad Zakria[1]

Evercare Hospital, Lahore, Pakistan

Aims: To achieve zero margin clearance we have to remove the large portion of liver. This is acceptable in normal liver. But in case of cirrhotic liver, functional liver volume remains very small if large part of liver is removed. In some selected cases if there is dysplastic nodule in liver then we can proceed for enucleation of

dysplastic nodule. This will give enough residual functional liver volume. This can be applied in benign tumor of liver or low grade liver cancer. **Methods:** A 55 years old male patient was admitted in hospital. He was hepatitis B positive and PCR was negative. He was diabetic but blood sugar was controlled. He was cirrhotic with child B. CT scan was showing small dysplastic nodule in segment 7. His AFP was normal but PIVKA II was raised. There was no ascites. Patient was operated and dysplastic nodule in segment 7 was marked and removed. Biopsy was showing dysplastic nodule with few hepatocellular cancer cells. Patient was discharged on 4th postoperative day. **Results:** Enucleation was done satisfactory. **Conclusions:** Surgical treatment option where applicable is the best approach to treat the liver cancer. But in advanced liver tumor and in advanced liver disease it is not possible to opt this approach as a first option. But in selected cases in advanced liver disease, a small size nodule showing the characters of liver cancer can be removed locally specially if the size is about 2 to 3 cm. More research is required in such cases. **Keywords:** Dysplastic, Enucleation





PE-64

Living Donor Liver Transplantation in Children

Nuraliah, MPH

West Sulawesi Research and Empowerment Center, Indonesia

Aims: The prevalence of liver disease in Indonesia is relatively high. Based on data from the Ministry of Health, the number of people with chronic liver disease reaches 20 million people, of which 20-40% develop liver cirrhosis. This condition certainly interferes with liver function. Currently, pediatric patients who have liver disease and require treatment with transplants are also increasing. The purpose of this study is to describe the development of live donor liver transplantation in pediatric patients in Indonesia. **Methods:** A comprehensive search of some journals was conducted in the following databases such as MEDLINE. Studies were selected based on predefined inclusion/exclusion criteria and were critically appraised. Extracted data were tabulated to summarize key findings. Some of the journals we used were from 2012 to 2023. **Results:** Developments in liver transplantation in children have been carried out since 2010 in Indonesia. To date, the number of patients who have undergone liver transplantation from living donors is 41 pediatric patients and 6 adult patients. The survival success rate of this method is 87%. Five hospitals in Indonesia have carried out Living transfers and 2 are currently active. Dr Cipto Mangunkusumo Hospital (CMH) is one of 2 active centers conducting LT for children and adults. Another pediatric liver transplant center is Dr Sardjito General Hospital, which started its program in November 2015 with 4 pediatric LT done so far. First living donor child liver transplant (LDLT) in December 2010, in cooperation with Zhejiang University, Hangzhou, China, 2 years partnership. Further transplantation activities were continued in collaboration with the National University Hospital Singapore. Progress was slow during that time (2010-2014), with a total of 3 transplants. One of the reasons for the slow progress is the tight selection of recipients; during this period we only accept recipients weighing > 10 kg. In the process of liver transplantation with living donors there are a series of tests that must be carried out. The process is necessary to ensure the success of the transplant, both because of the risk of the donor and the recipient, so it must be very complete from the start. The examination includes laboratory examinations, imaging examinations, and physical examinations, and medical consultations. **Conclusions:** In conclusion, pediatric LDLT has made great strides in Indonesia. It already has one hospital, a national referral center, which has carried out the procedure independently. This program continually enhances surgical and medical management skills. A deceased donor program will be needed to address donor scarcity. **Keywords:** Living Donor, Transplantation, Children, Indonesia

PE-65

Effects of Livact Granule on Liver Function Recovery after Donor Right Hemi-Hepatectomy

Ho Joong Choi, Jin Ha Chun, Yoonyoung Choi, Sung Eun Park, Tae Ho Hong, Young Kyoung You

Department of Surgery, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Living donor liver transplantation (LDLT) is currently widespread due to organ shortage. LDLT is basically a high-risk surgery for the donor. Therefore, the safety of the donor is the most important issue in LDLT. In adult LDLT, right lobe grafts are usually used, which pose a greater risk for the donor than using a left lobe. There have been reports that taking branched chain amino acids (BCAAs) helps patients recover after hepatectomy. This study is performed to evaluate effect of Livact granule for donor safety and recovery. **Methods:** From January 2016 to December 2021, LDLT was performed on 258 patients at our center. Among them, 148 were in the non-Livact group and 110 were in the Livact group. Six of 110 patients in the Livact group stopped taking Livact due to nausea and vomiting, so 104 patients in the Livact group were analyzed. To assess the donor safeties and recovery, various preoperative and postoperative factors were evaluated. **Results:** The donor age was 35.8 years in the non-Livact group and 40.0 years in the Livact group. Other than that, there was no difference between the two groups in preoperative liver function tests, and there was no difference in future liver remnant or steatosis. There was no difference in total bilirubin level between the two groups at 5 days postoperatively, but PT INR was lower in the Livact group and albumin was higher in the Livact group. The days taken for total bilirubin to normalize were the same in both groups, but the Livact group took less days for INR to normalize. More patients in the non-Livact group were discharged with Jackson-Pratt (JP) drain because JP drainage did not decrease. **Conclusions:** In donor right hepatectomy patients, taking Livact granules, BCAAs, helps donor recovery. For donor safety, administration of Livact granules during the perioperative period may be considered. **Keywords:** Donor Right Hemi-Hepatectomy, Branched Chain Amino Acids, Livact Granule

PE-66

Economical Analysis of the Routine Use of Thromboelastography (TEG) to Analyze Blood Component Needed in Liver Transplant Patients

Ninda Devita[1], Adika Zhulhi Arjana[2]*

[1]Faculty of Medicine, Universitas Islam Indonesia, Indonesia; [2]Clinical Pathology and Laboratory Medicine Department, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Indonesia

Aims: Bleeding is a common complication for people who undergo liver transplants. This is because the liver's ability to regulate blood clotting is impaired during and after the surgery, leading to excessive breakdown of clots and trapping of platelets. Thromboelastography (TEG) is a test that can help identify what kind of blood products are needed. However, this test is often too expensive to use regularly. This study aims to evaluate the cost-effectiveness of TEG for bleeding cases in liver transplant patients**. Methods:** This study uses a cost-benefit analysis model based on data from a Tertiary Hospital in Indonesia on the expenses of liver transplant patients from 2018 to 2022. The model included all the costs from admission to discharge or death of the patients. The cost of thromboelastography (TEG) was obtained from the hospital's billing system. A benefit-to-cost ratio was computed by dividing the total benefits of using TEG for hospital savings by the total costs of using TEG for all liver transplant patients. **Results:** From 2018 to 2022, four liver transplants were performed. On average, each patient had five bleeding episodes. The hospital spent 267292 USD or 66823 USD per patient. The cost of TEG per patient was 79.38 USD, with a 25% retest rate. The total cost of using TEG for every bleeding case was 1587.5 USD. The hospital saved 2004.6 USD by using TEG. The benefit-to-cost ratio was 1.26, which shows that TEG can significantly lower hospital costs. **Conclusions:** Using TEG regularly reduces hospital costs by giving the correct blood products, avoiding unnecessary transfusions, and shortening the hospital stay. The benefit-to-cost ratio is above 1, which means the project is worth more than it costs. This study only looks at the direct economic impact. There are also many indirect economic benefits of using TEG for all bleeding cases of liver transplant patients, such as lower infection risk, lower hospitalization cost, and lower personal cost for the shorter hospital stay. However, this project may not apply to other hospitals without considering some differences in the assumptions used in this study. **Keywords:** TEG, Liver Transplant, Cost Benefit Ratio

Table 1. Cost-benefit analysis of TEG use

Components	Cost (USD)
Total hospital cost before intervention	267,292.00
TEG examination	63.50
Retest Rate	25%
retest cost, with a 25% retest rate	15.88
Bleeding event	5.00
Total hospital cost for intervention	1,587.50
Transfusion cost per event	33.41
Transfusion saving	2,004.60
The benefit-to-cost ratio	1.26274016

PE-67

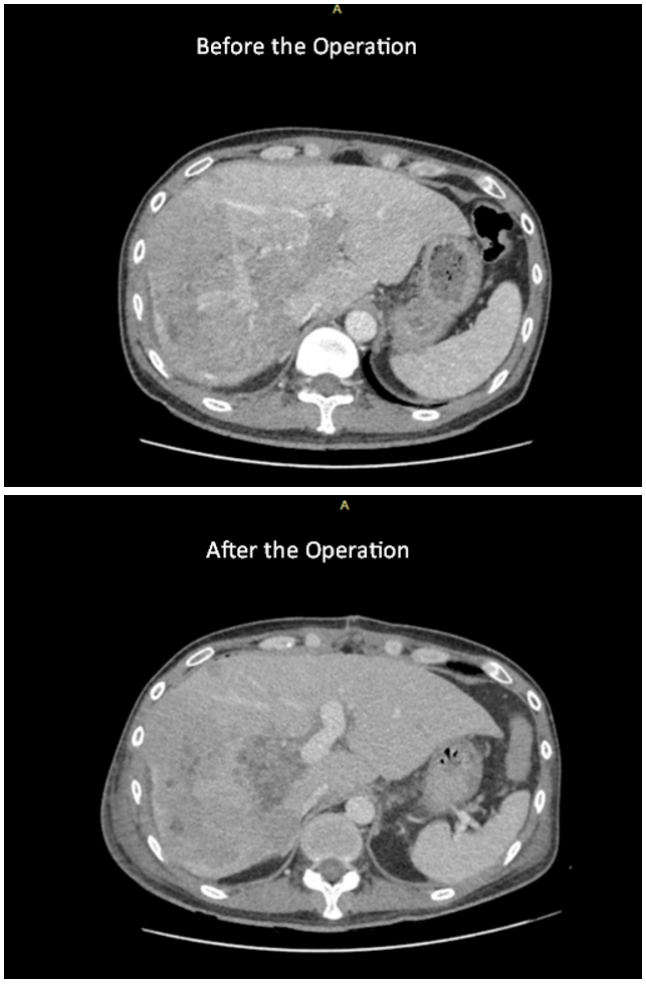
Tumor Thrombectomy via Surgically Reopened Umbilical Vein as a Palliative Treatment for Patient with Advanced Hepatocellular Carcinoma

Nguyen Truong Giang, Nguyen Minh Trong, Nguyen Kieu Hung

National Hospital of Tropical Diseases, Vietnam

Aims: Portal vein tumor thrombosis is an ominous prognosis factor in patients with HCC. It can cause deadly complications such as liver failure, GI bleeding due to portal hypertension. There are some reports of hepatectomy with tumor thrombectomy with good results. But we couldn't find any report of thrombectomy without

liver resection for advanced HCC. **Methods:** We present a case of a patient with huge right liver tumor and multinodular in the left with an extensive portal venous tumor thrombus extending into the main trunk and left portal branch. He had already been resistance to immunotherapy (Atezolizumab plus Bevacizumab) and HAIC. The CT Scanner showed that the tumor thrombosis increased rapidly, to prevent the complications, we performed the surgical tumor thrombectomy using a balloon catheter push to push the thrombus via reopened umbilical vein and ligated the right portal vein. **Results:** The operated time was 200 minutes with estimated blood loss 550ml. The patient recovered well with no complication. The post-operation CT Scanner show no thrombus in the main portal trunk and the left branch, with the left liver volume increase from 552ml to 705ml after 17 days. He was continued to treat with Lenvatinib and Radiotherapy. **Conclusions:** Tumor thrombectomy via the umbilical vein is safe and can be apply as a palliative treatment for patients with advanced HCC. **Keywords:** Tumor Thrombectomy, Portal Vein Tumor Thrombosis, Umbilical Vein



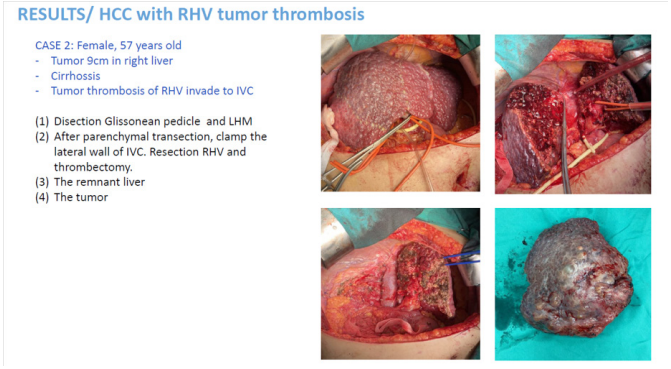
PE-68

Short Term Result of Parenchymal Sparing Anatomical Liver Resection Based on Portal Ramification of the Right Anterior Section: A Surgical Team's Experience

Nguyen Truong Giang, Nguyen Minh Trong, Nguyen Kieu Hung

National Hospital of Tropical Diseases, Vietnam

Aims: Anatomical liver resection is the treatment of choice for primary liver cancer. However, the remnant liver volume is equally important in patient selection for operation. Recent appreciation of the liver segmentation could divide the right anterior section (RAS) into ventral-dorsal segment or segment 5-segment 8. Thus, we aim to evaluate the short term results of parenchymal sparing liver resection based on portal ramification of the right anterior section. **Methods:** From July 1,2018 to December 30, 2022, 25 patients with hepatocellular carcinoma underwent ventral or dorsal segment sparing hepatectomy. The portal ramification of RAS was analyzed using the Multidetector Computed Tomography scan. The procedures were performed by 3 liver surgeons. **Results:** Among 24 patients with ventro-dorsal type of the RAS, there were 22 men and 2 women. The mean age was 59.8 ± 11.5 years. The ventral-segment preserving right hepatectomy was performed in 16 patients, the dorsal-segment mesohepatectomy in 2 patients and the dorsal-segment trisectionectomy in 3 patients. The mean operative time was 244.7 ± 44.1 minutes with a mean estimated blood loss of 277.4 ± 275.6 ml. Post-operative morbidity was reported in 7 cases (29.2%). The mean length of hospital stay was 13.3 ± 9.1 days. There was one operative death due to acute portal vein thrombosis. **Conclusions:** The pre-operative evaluation of RAS's anatomy is very important to decide the method of parenchymal sparing liver resection. This procedure is technically safe and feasible. **Keywords:** Parenchymal Saving Liver Resection, Ventral Dorsal



PE-69

Impact of Frailty on Long-Term Outcomes after Liver Resection for Hepatocellular Carcinoma in Elderly Patients

Shogo Tanaka[1,2], Takuma Okada[1,2], Hiroji Shinkawa[2], Go Ohira[2], Masahiko Kinoshita[2], Kenjiro Kimura[2], Kohei Nishio[2], Jun Tauchi[2], Takeaki Ishizawa[2]

[1]Department of Hepato-Biliary-Pancreatic Surgery, Izumi City General Hospital, Izumi City, Osaka, Japan; [2]Department of Hepato-Biliary-Pancreatic Surgery, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan

Aims: Frailty affects short-term outcomes after liver resection in elderly patients. However, frailty's effects on long-term outcomes after liver resection in elderly patients with hepatocellular carcinoma (HCC) are unknown. **Methods:** This prospective, single-center study included 81 independently living patients aged ≥65 years scheduled to undergo liver resection for initial HCC. Frailty was evaluated according to the Kihon Checklist, a phenotypic frailty index." We investigated and compared postoperative long-term outcomes after liver resection between patients with and without frailty. **Results:** Of the 81 patients, 25 (30.9%) were frail. The proportion of patients with cirrhosis, high serum alpha-fetoprotein level (≥200 ng/mL), and poorly differentiated HCC was higher in the frail group than in the nonfrail group (n = 56). Among the patients with postoperative recurrence, the incidence of extrahepatic recurrence was higher in the frail group than in the nonfrail group (30.8% vs. 3.6%, *P*=0.028). Moreover, the proportion of patients who underwent repeat liver resection and ablation for recurrence who met the Milan criteria tended to be lower in the frail group than in the nonfrail group. Although there was no difference in disease-free survival between the two groups, the overall survival rate in the frail group was significantly worse than that in the nonfrail group (5-year overall survival: 42.7% vs. 77.2%, *P*=0.005). Results of the multivariate analysis indicated that frailty and blood loss were independent prognostic factors for postoperative survival. **Conclusions:** Frailty is associated with unfavorable long-term outcomes after liver resection in elderly patients with HCC. **Keywords:** Elderly, Frailty, Hepatocellular Carcinoma, Kihon Checklist, Postoperative Survival

PE-70

Anatomic versus Non-Anatomic Resection for Early-Stage Intrahepatic Cholangiocarcinoma: A Multicentric Case-Matched Study from China

Qiao Ke[1,2], Lei Wang[3], Ziguo Lin[1], Hongzhi Liu[1], Jianying Lou[4], Shuguo Zheng[5], Xinyu Bi[6], Jianming Wang[7], Wei Guo[8], Fuyu Li[9], Jian Wang[10], Yamin Zheng[11], Jingdong Li[12], Shi Cheng[13], Weiping Zhou[14], Jingfeng Liu[1,2], Yongyi Zeng[1]*

[1]Department of Hepatobiliary Surgery, Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, China; [2]Department of Hepatobiliary Surgery, Clinical Oncology School of Fujian Medical University, Fuzhou, China; [3]Department of Radiation Oncology, Clinical Oncology School of Fujian Medical University, Fuzhou, China; [4]Department of hepatobiliary surgery, the Second Hospital affiliated to Zhejiang University, Hangzhou, China; [5]Department of hepatobiliary surgery, the Southwest Hospital affiliated to the Army Medical University, Chongqing, China; [6]Department of Hepatobiliary Surgery, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; [7]Department of hepatobiliary surgery, Tongji Hospital affiliated to affiliated to Tongji Medical College, Huazhong University of Science &Technology, Wuhan, Hubei, China; [8]Department of Hepatobiliary Surgery, Beijing Friendship Hospital affiliated to Capital Medical University, Beijing, China; [9]Department of Hepatobiliary Surgery, the West China Hospital of Sichuan University, Chengdu, China; [10]Department of hepatobiliary surgery, Renji Hospital affiliated to Shanghai Jiaotong University, Shanghai, China; [11]Department of Hepatobiliary Surgery, Xuanwu Hospital affiliated to Capital Medical University, Beijing, China; [12]Department of Hepatobiliary Surgery, the affiliated Hospital of Chuanbei Medical University, Nanchong, China; [13]Department of Hepatobiliary Surgery, Tiantan Hospital affiliated to Capital Medical University, Beijing, China; [14]Department of Hepatobiliary Surgery III, Eastern Hepatobiliary Surgery Hospital, Secondary Military Medical University, Shanghai China

Aims: Radical resection is still the most cost-effectiveness curative strategy for intrahepatic cholangiocarcinoma (ICC), but it remains controversial on the survival benefit of anatomic resection (AR). In this study, we sought to compare the oncologic outcomes between AR versus non-AR (NAR) as the primary treatment for early-stage ICC patients. **Methods:** Data of ICC patients who underwent hepatectomy and staged at AJCC I were retrospectively collected from 12 hepatobiliary centers in China between Dec 2012 and Dec 2015. Propensity score matching (PSM) was performed to minimize the effect of potential confounders, and disease-free survival (DFS) and overall survival (OS) were compared between AR group and NAR group with hazard ratio and 95% confidence interval (CI). **Results:** A total of 278 ICC patients staged at AJCC I were eligible for this study, including 126 patients (45.3%) receiving AR and 152 patients (54.7%) receiving NAR. After 1:1 PSM, there were 58 patients in each group. Significant differences were not observed in median DFS and OS before (median DFS: 20 months vs. 16 months, *P*=0.320; median OS: 36 months vs. 36 months, *P*=0.610; respectively) and after PSM (median DFS: 20 months vs. 17 months, *P*=0.340; median OS: 40 months vs. 36 months, *P*=0.770; respectively). Further analysis showed that the survival benefit of AR was not found in any subgroup stratified by Child-Pugh grade (A or B), surgical margin (<1 cm or ≥1 cm) and tumor diameter (≤5 cm or >5 cm) with all *P*>0.05. **Conclusions:** Patients with stage I primary ICC have not shown benefit from AR, and future research should focus on screening for potential beneficiaries of AR. **Keywords:** Intrahepatic Cholangiocarcinoma, Anatomic Resection, Prognosis, Propensity Score Matching

PE-71

Narrow Surgical Margin Does Not Influence the Prognosis of Solitary Hepatocellular Carcinoma: A Real-World Study from China

Qiao Ke[1], Jingfeng Liu[1]

[1]Department of Hepatopancreatobiliary Surgery, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, Fujian, China

Aims: The influence of surgical margin (SM) width on the prognosis of hepatocellular carcinoma (HCC) remains undetermined. Hence, we performed a real-world study in two tertiary specialized HPB centers from China to identify the

optimal SM width and evaluate its effect on solitary HCC patients receiving R0 resection. **Methods:** Data of patients with solitary HCC who underwent R0 resection between December 2012 and December 2015 from two tertiaries specialized HPB centers were retrospectively collected. The optimal cut-off value of SM width was determined by the X-tile software, and then the cases were divided into narrow and wide SM groups. Disease-free survival (DFS) and overall survival (OS) between the two groups were compared by the Kaplan-Meier method, and propensity score matching (PSM) was conducted to minimize the potential bias. **Results:** Totally, 1915 patients were eligible for this study. Based on X-tile software, 1mm was chosen as an optimal value for determining the prognosis of solitary HCC, and 968 cases (50.5%) had narrow SM (≤1 mm), 947 cases (49.5%) had wide SM (> 1mm). The wide SM had an apparent survival advantage over narrow SM both in terms of DFS and OS (both $P<0.05$), but these advantages disappeared in the matched cohort (both $P>0.05$). A multivariate analysis demonstrated that SM width was not an independent risk factor for DFS and OS both before and after PSM (all $P>0.05$). **Conclusions:** SM width does not influence the prognosis of solitary HCC, and narrow SM might be acceptable and oncologically safe in selected population. **Keywords:** Hepatocellular Carcinoma, R0 Resection, Surgical Margin, Prognosis

PE-72

Anatomic versus Non-Anatomic Resection for Patients with Hepatocellular Carcinoma and Microvascular Invasion: A Systematic Review and Meta-Analysis

Qiao Ke[1], Jingfeng Liu[1]

[1]Department of Hepatopancreatobiliary Surgery, Clinical Oncology School of Fujian Medical University, Fuzhou, Fujian, China

Aims: To evaluate the efficacy and safety comparing Anatomic resection (AR) versus Non-anatomic resection (NAR) for patients with hepatocellular carcinoma (HCC) and microvascular invasion (MVI). **Methods:** PubMed, MedLine, Embase, the Cochrane Library, Web of Science, Wanfang, and CNKI were used to identified eligible studies comparing AR versus NAR for patients with HCC and MVI. Primary endpoints including overall survival (OS) and disease-free survival (DFS) were evaluated using hazard ratio (HR) with 95% confidence interval (CI), and secondary endpoints including procedure time and the incidence of transfusion and severe postoperative complication were evaluated using mean difference (MD) and odds ratio (OR) with 95%CI, respectively. **Results:** Ten studies with 1732 patients including 742 patients in the AR group and 990 patients in the NAR group were eligible. The pooled HR for the OS and DFS were in favor of AR comparing with NAR (HR=0.64, 95%CI 0.54-0.75; HR=0.67, 95%CI 0.58-0.76; respectively). Subgroup analysis of single small HCC (<5cm) showed that the pooled HR for the OS and DFS were also in favor of AR (HR=0.59, 95%CI 0.47-0.75; HR=0.74, 95%CI 0.60-0.92; respectively). In addition, AR was found to be associated with prolonged procedure time (MD=23.14, 95%CI 15.15-31.13) and decreased incidence of transfusion (OR=0.45, 95%CI 0.25-0.80), but no significant difference was observed in the incidence of severe postoperative complications between groups of AR and NAR ($P>0.05$). **Conclusions:** For HCC with MVI, AR was superior to NAR in terms of both in OS, DFS and transfusion without increased risk of severe postoperative complications, although AR prolonged the procedure time. Hence, AR should be recommended for patients with MVI when feasible, especially those with single small HCC(<5cm). However, the conclusion needs to be furtherly verified. **Keywords:** Hepatocellular Carcinoma, Microvascular Invasion, Anatomic Resection, Meta-Analysis

PE-73

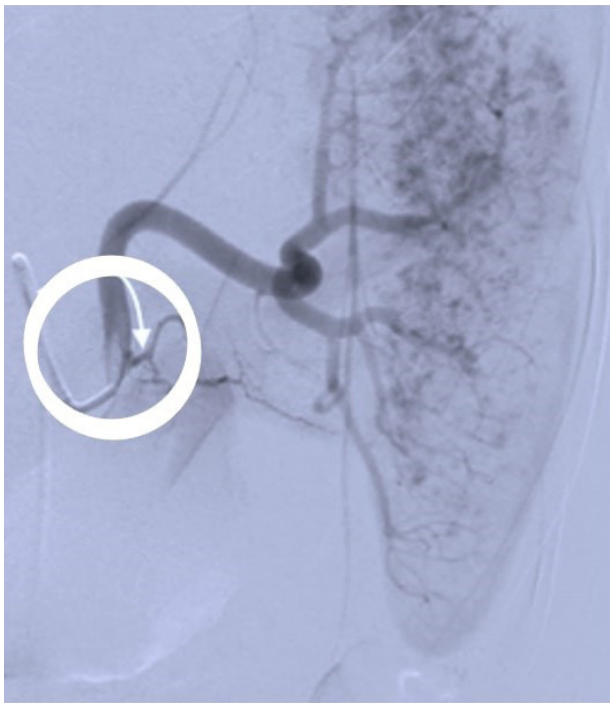
JSC National Scientific Center of Oncology and Transplantology

Aidar Zulkharnay[1], Azat Chinaliyev[1], Akhmet Seidakhmetov[2], Myltykbay Rysmakhanov[2]

[1]Interventional Surgery Department, JSC National Scientific Center of Oncology and Transplantology, Kazakhstan; [2]Department of the Liver Transplantation, Republic Transplant-coordinator Center, Kazakhstan; [3]Hepatobiliary Surgery and Liver Transplantation Department, Aqtobe City Regional Hospital, Kazakhstan

Aims: Syndrome of hypersplenism with the following thrombocytopenia, leukopenia, anemia, and ascites occur after orthotopic liver transplantation. These conditions might be treated by splenectomy. In our hospital, splenic artery intravascular embolization has been practiced as an alternative surgical method. **Methods:** Between January 2013 and June 2022, fifty-six orthotopic liver transplants were performed at the National Scientific Medical Research Center, Astana, Kazakhstan. Of these patients, 7 subsequently received splenic artery embolization 12 and 6 months after transplant: 4 patients who had been diagnosed with primary biliary cirrhosis and 3 patients with hepatitis B virus-related liver cirrhosis. Five patients received a right-lobe living orthotopic liver transplant, and 2 patients received a deceased donor transplant. Indications for splenic artery embolization (ascites, splenomegaly) were based on clinical and ultrasonographic investigation and laboratory findings (thrombocytopenia, platelet count < 60 × 109/L, leukocytopenia, and white blood cell count < 2 × 109/L). Two recipients had leukothrombocytopenia and refractory ascites, and 1 had only thrombocytopenia. Splenic artery embolization was performed via a percutaneous femoral artery approach under local anesthesia. Transcatheter splenic artery branch occlusion was performed by deploying occlusion material. Preoperative spleen size ranged from 17.5 × 8.0 cm to 22.0 × 12.5 cm; ascites volumes were > 1000 mL. **Results:** In all patients, ascites and platelet levels decreased after splenic artery embolization. In 3 patients with leukopenia, the white blood cell count normalized. After embolization, 4 patients had severe abdominal pain requiring analgesia medication, and 2 patients had a fever that lasted 3 days. Patients were discharged 6 to 9 days after embolization. Two patients developed a perisplenic abscess without fever 1 month after discharge, and the abscess was drained using an ultrasound-guided percutaneous procedure. **Conclusions:** Splenic artery embolization is a safe and effective minimally invasive method for treating hypersplenism and ascites in orthotopic liver transplant recipients and an alternative to open splenectomy. **Keywords:** Embolization,

Splenic Artery, LDLT, Hypersplenism



PE-74

Portal Vein Thrombosis in Patients with End-Stage Liver Disease on the Waiting List

Seidakhmetova Nazerke[1], Rysmakhanov Myltykbay[1], Seidakhmetov Akhmet[2]

[1]Department of Liver Surgery and Transplantation, Aqtobe City Regional Hospital, Kazakhstan; [2]Liver Transplantation Department, Republic transplant-coordinating Center, Kazakhstan

Aims: Among the patients with end-stage liver diseases on the waiting list, portal vein thrombosis (PVT) complicates the liver transplant operation and theoretically disturbs survival. The aim of this research is to find the consequence of PVT on the survival benefit of liver transplantation. **Methods:** From January 2015 to January 2022 patients with end-stage liver diseases were treated electively by liver transplantation performance AqtobeMedical Center. Data collection involved the review of age, body mass index (BMI), smoking, the presence of additional medical disorders, operative complications, postoperative care, surgical infections (SI), and duration of follow-up. Appropriate statistical tests were used. Also, by sequential stratification, we estimated the liver transplant survival benefit by MELD score and PVT status. **Results:** The occurrence of described PVT among liver transplant recipients was not a predictor of waiting list mortality but was a forecaster of posttransplant mortality. With all of this, transplant advantage was not significantly different for patients with PVT vs. those without PVT. **Conclusions:** PVT does not disturb waiting list mortality, but it is related to meaningfully advanced posttransplant mortality. Transplant surgeons should sensibly reflect on the risks of liver transplantation in clinically stable patients who have PVT.

Keywords: Liver Cirrhosis, Portal Vein, Liver Transplantation, Waiting List

Variables	PVT(+) n=19	(PVT-) n=81	P-value
Male/ Female	17/2	60/21	0.1511
Age (years) >78/≤78	7/12	14/67	0.0596
BMI (kg/m^2) >19.3/≤19.3	13/6	71/10	0.0747
Diabetes Y/N	6/10	20/51	0.4614
Preoperative biliary drainage Y/N	7/12	17/64	0.1453
Cholangitis in medical history Y/N	2/17	3/78	0.2398
Benign Y/N	0/19	5/76	0.5801
Preoperative blood test			
T-bil (mg/dL) >1.2/≤1.2	5/14	10/71	0.1539
AST (U/L) >35/≤35	14/5	25/56	0.0006
ALT (U/L) >45≤/45	12/7	19/62	0.0008
ALP (U/L) >257/≤257	16/3	48/33	0.0414
Albumin (mg/dL) >4.5/≤4.5	4/15	21/60	0.7749
CRP (mg/dL) >2.67/ ≤2.67	1/18	13/68	0.2957
WBC (/μL) >6250/ ≤6250	4/15	35/46	0.0747
Hemoglobin (mg/dL) >12.0/ ≤12.0	12/7	61/20	0.2830
Platelet (×10^3/μL) >262/≤262	7/12	12/69	0.0468
PT-INR (%) >1.14/≤1.14	7/12	10/71	0.0177

PE-75

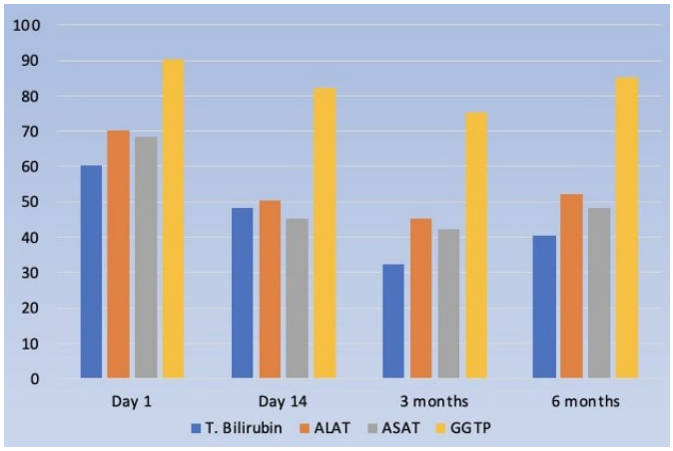
Human Fetal Liver Cells as a Bridge to the Liver Transplantation in Patients Waiting for Donors

Akhmet Seidakhmetov[1], Samat Saparbayev[2]

[1]Department of Liver Transplantation, Republic Coordination Center for Transplantation and Hi-tech Services, Kazakhstan; [2]Department of Surgery and Liver Transplantation, Aqtobe Medical Center, Kazakhstan

Aims: Liver transplantation (LT) is a method for treating liver cirrhosis. With a great increase in the death rate of patients with liver disorders, there is a necessity to pursue alternative therapeutic implementation as a supportive therapy. Recent studies show outstanding results in therapy using human fetal liver-derived stem cells (FLSC) which can deliver the potential to conservatively manage end-stage liver diseases. The present investigation aimed to study the safety and efficacy of FLSC transplantation. **Methods:** 132 patients with liver cirrhosis of different etiologies were included in this study. All patients were on the waiting list and they were divided into 2 groups: received FLSC therapy and no treatment.

FLSCs were obtained from the fetus after abortion by medical indications and were infused into the periphery. Liver function scores were chosen as endpoints to assess efficacy. **Results:** Child–Pugh score improved in 90 days in the cell therapy group. The model for end-stage liver disease score remained stable in the treated patients, whereas it increased during follow-up in the control group. Bilirubin levels increased among controls, whereas they decreased in the therapy arm during the first 60 days; INR RC differences between groups reached up to 10%. The changes observed did not persist beyond 90 days. There was marked clinical improvement observed in terms of all clinical and biochemical parameters. Further, there was a decrease in mean MELD score observed in 6 months follow-up in all patients. **Conclusions:** Transplantation of human FLSC into the periphery improved liver function in patients with advanced cirrhosis in the first 90 days. However, larger studies are necessary to define the role of human FLSC therapy in cirrhotic patients. Treatment by means of human FLSC proposes a potentially helpful modality to liver transplantation in the management of such diseases. **Keywords:** Fetal Cell, Liver Cirrhosis, Liver Transplantation, Waiting List



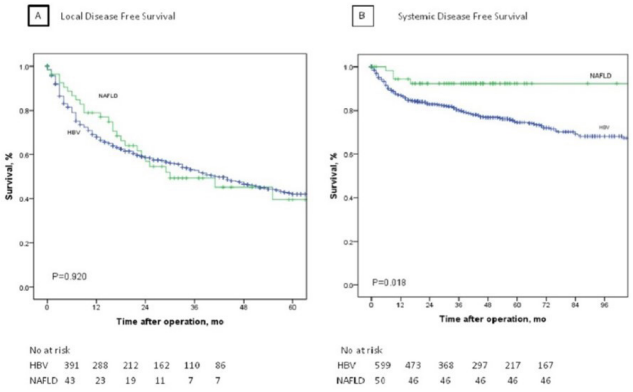
PE-76

Long-Term Surgical Outcomes for Non-Alcoholic Fatty Liver Disease Associated Hepatocellular Carcinoma

Jai Young Cho, Ho-Seong Han, Yoo-Seok Yoon, Hae Won Lee, Boram Lee

Department of Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Republic of Korea

Aims: The global burden of non- alcoholic fatty liver disease (NAFLD) and NAFLD-associated hepatocellular carcinoma (HCC) is steadily rising. We investigated the results after liver resection for NAFLD-HCC versus hepatitis B virus (HBV)-HCC. **Methods:** Patients who underwent liver resection for HCC between January 2004 and December 2018 were included. The outcomes of NAFLD-associated HCC were analyzed. Kaplan Meier method, log-rank test and uni/multivariate analysis with the logistic regression models were performed. **Results:** The prevalence of NAFLD-associated HCC was 8.4%. A significant number of NAFLD patients had no cirrhosis (21 patients; 38.8%). Although NAFLD patients had a significantly better 5-year survival (P=0.033), NAFLD was not significantly associated with overall survival in multivariate analysis (P=0.287). However, survival after 5 years declined in NAFLD patients and was similar to HBV. NAFLD was protective against systemic recurrence compared with HBV (P=0.018), and this was confirmed in multivariate analysis (P=0.044). Five-year systemic recurrence (P=0.044) was significantly lower in NAFLD patients and decreased with time from surgery. Multivariate analysis revealed that anatomical liver resection was independently associated with decreased recurrence in NAFLD patients (HR = 0.337; P=0.033). **Conclusions:** Overall survival is similar between NAFLD-associated HCC and HBV-associated HCC. NAFLD-associated HCC shows lower systemic recurrence compared to HBV-associated HCC. **Keywords:** NAFLD, NASH, Prognosis, Hepatectomy



Liver Cancer - Treatment: Transarterial Approach/ Percutaneous Ablative Therapy/Radiation Therapy

PE-77

Feasibility and Efficacy of Repeated Stereotactic Body Radiotherapy for Recurrent Hepatocellular Carcinoma

Won Il Jang[1], Mi-Sook Kim[1], Chul Ju Han[2], Jin Kim[2], Su Cheol Park[2], Sang Bum Kim[3], Eung-Ho Cho[3]

[1]Department of Radiation Oncology, Korea Institute of Radiological and Medical Sciences, Seoul, Republic of Korea; [2]Department of Internal Medicine, Korea Institute of Radiological and Medical Sciences, Seoul, Republic of Korea; [3]Department of Surgery, Korea Institute of Radiological and Medical Sciences, Seoul, Republic of Korea

Aims: The aim of this study is to evaluate the feasibility and efficacy of repeated stereotactic body radiotherapy (SBRT)

for inoperable recurrent hepatocellular carcinoma (HCC). **Methods:** We retrospectively reviewed medical record of 548 recurrent HCC patients who were treated with SBRT at Korea Cancer Center Hospital between January 2004 and May 2014. All patients were unsuitable for surgery or local ablation and had incomplete response to transarterial chemoembolization. Twenty-seven patients received repeated SBRT and 26 patients (96%) underwent the repeated SBRT for intrahepatic recurrence other than the lesion with the 1st SBRT. Only one patient underwent re-irradiation for the same lesion with the 1st SBRT. Twenty-five patients (93%) had Child-Turcotte-Pugh (CTP) class A (A5 in 20 and A6 in 5, respectively). Hepatitis B virus (HBV) infection was the predominant cause of liver disease (67%). The median dose was 51 Gy (range, 30-60 Gy in 3–5 fractions) and 45 Gy (range, 30–60 Gy in 3-4 fractions) in the 1st and the repeated SBRT, respectively. **Results:** The median follow-up duration was 16 months (range, 3–115 months). The median interval between the first and the repeated SBRT was 11 months (range, 2–48 months). The 2-year intrahepatic in-field progression-free, intrahepatic out-field progression-free, extrahepatic progression-free and overall survival rates were 85%, 19%, 54%, and 83%, respectively. Three patients (11%) experienced deteriorating of CTP score by greater than or equal to 2 within 3 months of SBRT without disease progression. The total mean normal liver biologically equivalent dose (BED) was the most significant predictor for hepatic deterioration after the repeated SBRT. **Conclusions:** This study demonstrated that repeated SBRT can be safely and effectively administered to the patients with inoperable recurrent HCC for salvage treatment. We suggest total mean normal liver BED constraint of 31 Gy3 or less for patients who treated with repeated SBRT. **Keywords:** Hepatocellular Carcinoma, Radiotherapy, Stereotactic, Re-Irradiation

PE-78

Trends of Radiotherapy for HCC in Elderly Patients

Bong Kyung Bae[1], Jeong Il Yu[1], Hee Chul Park[1], Myung Ji Goh[2], Yong-Han Paik[2]

[1]Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [2]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Aims: To report the trends of radiotherapy in the management of elderly patients with hepatocellular carcinoma (HCC). **Methods:** We retrospectively reviewed patients entered into the HCC registry of Samsung Medical Center between 2005 and 2017. The patients who were 75 years or older at the time of registration were defined as elderly. They were categorized into three groups based on the year of registration. Radiotherapy characteristics were compared between the groups to observe differences by age groups and period of registration. **Results:** In total, 9,132 patients were entered into the HCC registry during the study period. The elderly patients comprised 6.2% (566 patients) of the registry, and the proportion increased throughout the study period (from 3.1% to 11.4%). Radiotherapy was administered to 107 patients (18.9%) in the elderly group. Radiotherapy utilization in the early treatment process (within one year after registration) rapidly increased from 6.1% (patients registered during the early period) to 15.3% (patients registered during the late period). Radiotherapy techniques also changed dramatically. All treatments before 2008 were delivered with two- or three-dimensional conformal radiotherapy, while more than two-thirds of radiotherapy after 2017 were delivered with advanced radiotherapy techniques, such as intensity-modulated radiotherapy, stereotactic body radiotherapy, or proton beam therapy. The overall survival (OS) of elderly patients was significantly worse than that of younger patients throughout the study period. However, for patients who received radiotherapy during the initial management (radiotherapy within one month after registration), there was no statistically significant difference in OS between the age groups. **Conclusions:** The proportion of elderly patients with HCC is increasing. Radiotherapy utilization and the adoption of advanced radiotherapy techniques showed a consistently increasing trend for the group of patients, indicating that the role of radiotherapy in the management of HCC in the elderly is expanding. **Keywords:** Hepatocellular Carcinoma, Elderly, Radiotherapy, Trend

PE-79

Feasibility of Additional Radiotherapy for Advanced Hepatocellular Carcinoma Treated with Atezolizumab Plus Bevacizumab

Tae Hyun Kim[1,2], Bo Hyun Kim[1], Yu Ri Cho[1], Eun Sang Oh[2], Joo-Hyun Chung[2], Young-Hwan Koh[1], Joong-Won Park[1]

[1]Center for Liver and Pancreatobiliary Cancer, National Cancer Center, Goyang, Korea; [2]Center for Proton Therapy, National Cancer Center, Goyang, Korea

Aims: Radiotherapy (RT) is an effective local treatment for hepatocellular carcinoma (HCC). However, it is unclear whether additional RT is safe and effective in advanced HCC receiving atezolizumab plus bevacizumab. Thus, this retrospective cohort study aimed to evaluate the feasibility of additional RT in these patients. **Methods:** Between March and October 2021, we retrospectively analyzed seven patients with advanced HCC who received RT during treatment with atezolizumab plus bevacizumab. The median prescribed RT dose was 35 Gy (range, 33 – 66 Gy). Freedom from local progression (FFLP), progression-free survival (PFS), and overall survival (OS) after RT were assessed. **Results:** The median follow-up duration after RT was 14.2 months (range, 10.0 – 18.6 months). Of seven patients, disease progression was noted in six (85.7%), and the sites of disease progression were local in two (28.6%), intrahepatic in four (57.1%), and extrahepatic in four (57.1%) patients. The median time of FFLP was not reached and that of PFS and OS was 4.0 (95% confidence interval [CI], 3.6 – 4.5) and 14.8 months (95% CI, 12.5 – 17.2), respectively. The 1-year rates of FFLP, PFS, and OS

were 60 (95% CI, 43.8 – 76.2), 0, and 85.7% (95% CI, 75.9 – 95.5), respectively. Grade 3 or higher hematologic adverse events (AEs) were not observed, and grade 3 non-hematologic AEs unrelated to RT were observed in one patient. **Conclusions:** Addition of RT could be feasible in patients with advanced HCC treated with atezolizumab plus bevacizumab. Further studies are warranted to validate these findings. **Keywords:** Hepatocellular Carcinoma, Survival, Radiotherapy, Atezolizumab, Atezolizumab

PE-80

Poor Clinical Outcome of Deep-Seated Hepatocellular Carcinoma after Radiofrequency Ablation

Gwang Hyeon Choi[1], Jae Hwan Lee, Eun Sun Jang[1], Jin-Wook Kim[1], Sook-Hyang Jeong[1], Chang Jin Yoon[2]

[1]Department of Internal medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Republic of Korea; [2]Department of Radiology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Republic of Korea

Aims: To compare clinical outcomes of radiofrequency ablation (RFA) as first-line therapy in patients with hepatocellular carcinoma (HCC) less than 3cm according to anatomical tumor location. **Methods:** We performed a retrospective cohort study of patients with a new diagnosis of HCC <3 cm in up to 3 lesions that underwent RFA as first-line treatment between 2003-2019. Deep HCC was defined tumor center was located in distal 1/3 location of an imaginary line from IVC towards to liver surface via tumor center. Perivascular location was defined as a tumor abutting the 1- or 2-degree branches of a portal or hepatic vein. Recurrence free survivals (RFS) were compared among groups and potential risk factors were analyzed using multivariable Cox regression. **Results:** The 281 HCC patients showed a mean age of 61 years, male in 73.3%, HBsAg-positive in 66.2%, and Child-Pugh class A in 97.5%. The RFS was significantly shorter in the deep HCCs (HR [hazard ratio] 1.87, 95% CI [confidence interval] 1.20–2.93, *P*=0.005) than in the superficial to middle HCCs and significantly shorter in the perivascular HCCs than in the non-perivascular HCCs (HR 1.87, 95% CI 1.16–3.00, *P*=0.008). After grouping them into anatomical structures, Group A (no anatomical risk factor, n=217), Group B (deep or perivascular HCC, n=54), and C (deep and perivascular HCC, n=10) showed similar baseline characteristics except proportion of Child-Pugh A (99.1% vs 92.6% vs and 90%, *P*<0.001). Compared to Group A, RFS was significantly shorter in the Group B (HR 1.59, 95% CI 1.05–2.40, *P*=0.028) or Group C (HR 3.12, 95% CI 1.50–6.45, *P*=0.002). After multivariate analysis, deep or perivascular HCCs (HR 1.60, 95% CI 1.07–2.40, *P*=0.024) and deep & perivascular HCCs (HR 2.41, 95% CI 1.08–5.38, *P*=0.031)) were independently associated with RFS, along with maximal tumor size > 2cm (HR 1.62, 95% CI 1.12-2.34), creatinine (HR 1.14, 95% CI 1.01–1.29), and prothrombin time (HR 20.51, 95% CI 4.20-100.26). **Conclusions:** We identified deep-seated HCCs were associated with higher RFS. The anatomical location such as depth and perivascular location should be considered when choosing therapeutic modality for small HCCs. **Keywords:** Hepatocellular Carcinoma, Radiofrequency Ablation, Anatomical Location, Outcome

PE-81

Prognostic Performance of the China Liver Cancer Staging System in Hepatocellular Carcinoma Following Transarterial Chemoembolization

Bin-Yan Zhong[1], Jian-Qiang Jiang[2], Jun-Hui Sun[3], Jin-Tao Huang[1], Wei-Dong Wang[4], Qi Wang[5], Wen-Bin Ding[6], Xiao-Li Zhu[1], Cai-Fang Ni[1]

[1]Department of Interventional Radiology, The First Affiliated Hospital of Soochow University, Suzhou, China; [2]Department of Interventional Therapy, Nantong Tumor Hospital, Nantong, China; [3]Hepatobiliary and Pancreatic Interventional Treatment Center, Division of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [4]Department of Interventional Radiology, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi, China; [5]Department of Interventional Radiology, Third Affiliated Hospital of Soochow University, Changzhou First Hospital, Changzhou, China; [6]Department of Interventional Radiology, Nantong First People's Hospital, Nantong, China

Aims: To validate prognostic performance of the China liver cancer (CNLC) staging system as well as to compare these parameters with those of the Barcelona Clinic Liver Cancer (BCLC) staging system for Chinese hepatocellular carcinoma (HCC) treated with transarterial chemoembolization (TACE). **Methods:** This multicentric retrospective study included 1124 patients with HCC between January 2012 and December 2020 from six Chinese hospitals. Based on overall survival (OS), the prognostic performance outcomes for the CNLC and BCLC staging systems were compared according to model discrimination [C statistic and Akaike information criterion (AIC)], monotonicity of the gradient (linear trend chi-square test), homogeneity (likelihood ratio chi-square test), and calibration (calibration plots). **Results:** The median OS was 19.1 (18.2-20.0) months, with significant differences in OS between stages defined by the CNLC and BCLC observed (*P*<0.001). The CNLC performed better than the BCLC regarding model discrimination (C-index: 0.661 vs. 0.644; AIC: 10583.28 vs. 10583.72), model monotonicity of the gradient (linear trend chi-square test: 66.107 vs. 57.418; *P*<0.001), model homogeneity (159.2 vs. 158.7; *P*<0.001). Both staging systems demonstrated good model calibration. **Conclusions:** Combining model discrimination, gradient monotonicity, homogeneity, and calibration, the CNLC performs better than that of the BCLC for Chinese HCC receiving TACE. **Keywords:** Hepatocellular Carcinoma, CNLC, BCLC, TACE

PE-82

Radioembolization-Induced Liver Disease (REILD) in Hepatocellular Carcinoma (HCC) Patients after Treatment with Yttrium-90 (Y90) -A Retrospective Cohort Study

Kaina Chen[1,2], Aaron Kian Ti Tong[4], Fiona Ni Ni Moe[3], Timothy Ong Sheng Khai[5], Yeo Eng Xuan[5], Daniel Peh Yang Yao[5], David Chee Eng Ng[4], Kelvin Siu Hoong Loke[4], Apoorva Gogna[6], Sean Xuexian Yan[4], Sue Ping Thang[4], Hian Liang Huang[4], Chow Wei Too[6], Weng Yan Ng[3], Pierce Chow[2,3,7]

[1]Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore; [2]Duke-NUS Medical School, Singapore

[3]Department of Surgical Oncology, National Cancer Centre Singapore, Singapore; [4]Department of Nuclear Medicine, Singapore General Hospital, Singapore; [5]Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [6]Department of Vascular and Interventional Radiology, Singapore General Hospital, Singapore; [7]Department of Hepato-pancreatico-biliary Surgery, Singapore General Hospital, Singapore

Aims: REILD is a radiation-induced liver injury caused by Y90 microsphere deposition in nontumorous parenchyma. The incidence of symptomatic REILD varied between 0-8% in most reports, but risk factors remain poorly defined. Our aim is to determine risk factors for REILD in a cohort of patients treated with Y90 Selective Internal Radiation Therapy (SIRT-Y90) for HCC. **Methods:** 472 patients were treated with SIRT-Y90 for non-metastatic HCC from 2007 to 2019 at the National Cancer Centre Singapore and Singapore General Hospital. REILD was defined by the presence of ascites and jaundice between 4-12 weeks post Y90 in the absence of tumour progression or bile duct obstruction. Patient demographics, clinical history, pertinent laboratory values and radiological findings were collected pre- and 6 months post-treatment. Ethical approval was granted by the Institutional Review Board (IRB 2017/2541). **Results:** Twelve patients (2.54%) developed REILD. The mean and median T:N ratio were 3.8 and 3.46 respectively. A baseline ALBI score of 2 (*P*=0.037) and BCLC C HCC (*P*=0.002) were risk factors for REILD development. The proportion of patients with bilobar HCC (83.3%, *P*=0.012) was higher in REILD patients. Majority of patients developed low white blood cell (WBC) count post Y90 (8/12, 66.7%), all due to a decrease in lymphocytes, whereby lymphocyte count decreased by a mean of 53.4%. REILD patients were also more likely to have AFP >= 400 post Y90 (75.0%, *P*=0.002). REILD development did not correlate with age or administered Y90 dose. Eleven patients with REILD had progression of HCC after developing REILD. No patients demised from REILD. **Conclusions:** REILD is a well described complication of Y90 SIRT. Severity of cirrhosis estimated by the ALBI score is one of the most important risk factors for REILD development post Y90 SIRT. Lymphocytopenia is a common adverse outcome in REILD patients. **Keywords:** REILD, HCC, Y90, SIRT

Table 1: Summary of Clinical Findings of REILD Patients Post Y90 SIRT

Baseline Characteristics		N = 12	Proportions
Gender	Male	8	66.7%
	Female	4	33.3%
Ethnicity	Chinese	7	58.3%
	Malay	0	0.00%
	Indian	2	16.7%
	Others	3	25.0%
Alcohol	Y	1	11.1%
	N	8	88.9%
	NA	3	
Change in WBC	Increased	4	33.3%
	Decreased	8	66.7%
Percentage Decrease in WBC (N = 8)	Mean (SD)	27.4 (18.9)	
	Median (IQR)	25.1 (12.9-34.2)	
Change in Lymphocytes	Increased	0	0.00%
	Decreased	12	100%
Percentage Decrease in Lymphocytes (N = 12)	Mean (SD)	53.4 (21.7)	
	Median (IQR)	51.2 (34.5-76.1)	
T:N Ratio	Mean (SD)	3.8 (2.08	
	Median (IQR)	3.46 (2.79-5.37)	
Time Between REILD and Progression of Disease (PD) (Weeks)	Mean (SD)	7.92 (7.73)	
	Median (IQR)	5.86 (1.86-11.7)	
Time Between PD and Death (Weeks)	Mean (SD)	9.89 (6.94)	
	Median (IQR)	10.3 (5.57-13)	

Table 2: Comparison between REILD and Non-REILD Patients

Baseline Characteristics		REILD N = 12 (2.54%)	Non-REILD N = 460 (97.5%)	P
Age	Mean (SD)	65.3 (9.41)	64.0 (11.2)	0.664
	Median (IQR)	64 (60.5-69.0)	65 (58.0-71.0)	
Child Pugh	A	8 (66.7%)	391 (85.0%)	0.075
	B	4 (33.3%)	69 (15.0%)	
ALBI Grade	1	0 (0.00%)	130 (28.3%)	**0.037**
	2	21 (100%)	297 (64.6%)	
	3	0 (0.00%)	33 (7.17%)	
BCLC Stage	A	0 (0.00%)	77 (16.7%)	**0.002**
	B	0 (0.00%)	171 (37.2%)	
	C	12 (100%)	208 (45.2%)	
	D	0 (0.00%)	4 (0.870%)	
Aetiology of Hepatitis	Viral (Hep B/C)	8 (66.7%)	292 (63.5%)	0.450
	Non-Viral	4 (33.3%)	118 (25.7%)	
	Others	0 (0.00%)	50 (10.9%)	
Post Y90 AFP	<400	3 (25.0%)	265 (67.3%)	**0.002**
	>=400	9 (75.0%)	129 (32.7%)	
	NA	0	66	
Tumour Burden	Solitary	2 (16.7%)	142 (31.0%)	0.203
	2-5 tumours	1 (8.33%)	90 (19.7%)	
	>5 tumours	9 (75.0%)	226 (49.3%)	
	NA	0	2	
Tumour Location	Unilobar	2 (16.7%)	241 (52.7%)	**0.012**
	Bilobar	10 (83.3%)	216 (47.3%)	
	NA	0	3	
Administered Y90 Dose (Gbq)	Mean (SD)	1.74 (1.03)	1.67 (0.951)	0.842
	Median (IQR)	1.50 (1.33-1.90)	1.40 (0.945-2.20)	
Predicted Mean Radiation Dose to Tumour (Gy)	Mean (SD)	162 (62.1)	154 (83.9)	0.808
	Median (IQR)	138 (121-180)	132 (96.9-191)	

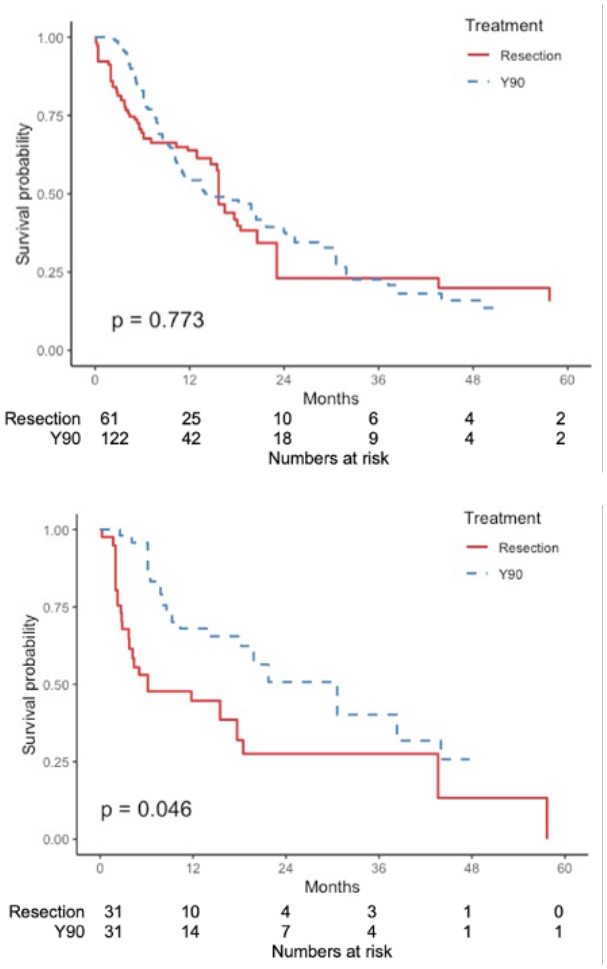
PE-83

A Propensity Score Analysis of Surgical Resection and Yttrium 90 Radioembolization in Hepatocellular Carcinoma Patients with Portal Vein Tumour Thrombosis

Zou Zhaozhen[1], Brian Kim Poh Goh[2], Peng Chung Cheow[2], Alexander Y.F. Chung[2], London Lucien P.J. Ooi[2], David C.E. Ng[2], Richard H.G. Lo[3], Nanda K.K. Venkatanarasimha[3], Apoorva Gogna[3], Chow Wei Too[3], Farah Irani[3], Sean X.X. Yan[4], Kelvin Loke[4], Sue Ping Thang[4], Aaron Tong[4], Hian Liang Huang[4], Chen Kaina[5], Fiona N.N. Moe[2], Jacelyn S.S. Chua[2], Ashley W.Y. Ng[2], Jade S.Q. Goh[2], Pierce K.H. Chow[1,2]

[1]Duke-National University Singapore Medical School, Singapore; [2]Department of Hepatopancreatobiliary and Transplantation Surgery, Singapore General Hospital and National Cancer Centre Singapore, Singapore; [3]Department of Vascular and Interventional Radiology, Singapore General Hospital and National Cancer Centre Singapore, Singapore; [4]Department of Nuclear Medicine and Molecular Imaging, Singapore General Hospital, Singapore; [5]Department of Gastroenterology, Singapore General Hospital, Singapore

Aims: Hepatocellular carcinoma (HCC) patients with portal vein tumour thrombosis (PVTT) usually have poorer prognosis due to the increased likelihood of tumour recurrence and metastasis. The best treatment methods for these patients remain undefined. In this study, we compared the overall survival (OS) and progression free survival (PFS) of HCC patients with type I or II PVTT undergoing surgical resection or Y90 radioembolization (Y90). **Methods:** The retrospective study involves non-metastatic HCC patients with MVI who underwent Y90 radiotherapy or surgical resection at National Cancer Centre Singapore and Singapore General Hospital between January 1 2000 and December 31 2019. The patients were stratified based on the degree of portal vein thrombosis and compared using inverse probability of treatment weighting (IPTW) -adjusted Kaplan-Meier analysis. **Results:** A total of 209 patients were analyzed, with 68 patients undergoing surgical resection and 141 undergoing Y90. After IPTW, the two groups were well balanced. Adjusted overall survival (OS) and progression-free survival (PFS) of resection patients were similar to Y90 patients (OS: 15.69 vs 13.94, *P*=0.343, PFS: 4.00 vs 3.35, *P*=0.132). Length of hospital stay for Y90 patients was significantly shorter than the resection group (3.94±1.27 vs 13.12±11.55 days, *P*=0.003). Serious adverse events occurred for 6.6% of patients in resection group, and 0.8% in Y90 group (*P*<0.001). IPTW-adjusted Kaplan Meier analysis however showed significantly better OS for the Y90 group than the resection group (Y90 vs resection: 30.61 months [8.58-not reached] vs 6.17 months [2.691-43.613], *P*=0.046) for type I PVTT patients. For type II PVTT, there was no significant difference between the two groups for either OS (*P*=0.243) or PFS (*P*=0.193). **Conclusions:** Compared with surgical resection, Y90 radiotherapy is associated with shorter hospital stay, lesser adverse events, and significantly prolonged overall survival especially in HCC patients with type I PVTT. **Keywords:** Hepatocellular Carcinoma, Portal Vein thrombosis, Surgical Resection, Yttrium 90



PE-84

Oncology

Yu Yin, Peng Huang, Pengcheng Tian, Caifang Ni

Department of Interventional Radiology, The First Affiliated Hospital of Soochow University, China

Aims: To investigate the safety and short-term efficacy of transarterial chemoembolization (TACE) combined with C-arm CT guided microwave ablation (MWA) in a single session for the treatment of hepatocellular carcinomas (HCCs) < 3 cm in critical conditions. **Methods:** This retrospective study included 21 patients (18 males and 3 females; mean age, 58.0 ± 8.4 years) with 22 HCCs (mean size, 17 ± 5.4 mm) received TACE combined with C-arm CT guided MWA in a single session between July 2018 and December 2019. The lesion was located in risk positions such as near diaphragm or big vessel, or cannot be visualized clearly by both US and plain CT. The Common Terminology Criteria for Adverse Events v5.0 was adopted to assess safety within 30 days after treatment. The modified Response Evaluation Criteria in Solid Tumors was used to evaluate the short-term efficacy based on magnetic resonance imaging during the 6-months follow-up. **Results:** Technical success was achieved in all patients. Major

complications occurred in 5 patients, including 3 with increased liver enzymes, 1 with hyperbilirubinemia, and 1 with arterio-portal fistula. All complications were successfully managed. No significant differences in all laboratory parameters were found before and 30 days after the procedure. The median follow-up was 8.5 months (95% CI: 7.6-8.9 months). The objective response rates at 1, 3 and 6 months were 95.5%, 100% and 100%, respectively. **Conclusions:** TACE combined with simultaneous C-arm CT-guided MWA in cases of HCCs < 3 cm seems to be a safe and effective treatment option in selected patients. This combination strategy can obtain ideal results and is quite suitable for small HCC, especially for those which cannot be ablated under CT guidance. **Keywords:** Hepatocellular Carcinoma, Therapeutic Chemoembolization, Microwave Ablation, C-arm CT, Combined Therapy

PE-85

Safety and Efficacy of Sequential Hepatic Arterial Infusion Chemotherapy and Transarterial Embolization for Unresectable Hepatocellular Carcinoma

Jun Yang, Yu Yin, Caifang Ni

Department of Interventional Radiology, the First Affiliated Hospital of Soochow University, China

Aims: To evaluate the safety and efficacy of sequential hepatic arterial infusion chemotherapy and transarterial embolization in the treatment of unresectable hepatocellular carcinoma. **Methods:** The clinical data of 25 patients who received sequential hepatic arterial infusion chemotherapy (HAIC) and transarterial embolization (TAE) during the period from April 2020 to April 2021 was collected. ALBI score was used to evaluate the changes of liver function and adverse reactions were recorded. The tumor objective remission rate (ORR) and disease control rate (DCR) were evaluated by the modified response evaluation criteria in solid tumor. All the patients were followed up, the time to progression and overall survival were recorded. **Results:** There was no significant change in ALBI score three months after therapy. The main adverse reactions included liver function damage, myelosuppression, abdominal pain, nausea, vomiting, fever, etc. There were 4 patients with grade III adverse reactions (3 cases of elevated alanine aminotransferase, 1 case of myelosuppression), and the rest were grade I-II adverse reactions. The postoperative 6- and 12-week ORR were 68% and 72% respectively; the postoperative 6- and 12-week DCR were 92% and 88% respectively. The median time to progression and overall survival were 271 days (95%CI：115.9-426.0) and 510 days (95%CI：491.5-528.5). **Conclusions:** Sequential hepatic arterial infusion chemotherapy and transarterial embolization for unresectable hepatocellular carcinoma is safe and effective. **Keywords:** Hepatic Arterial Infusion Chemotherapy, Transarterial Embolization, Hepatocellular Carcinoma, Adverse Reaction

PE-86

The Value of Preoperative Hepatic Vein Embolization Combined with Precise TACE in Stage II Resection of Primary Liver Cancer

Yao Liu[1], Linmao Sun[1], Changlong Hou[2], Lianxin Liu[1]

[1]Department of Hepatobiliary Surgery,Anhui Province Key Laboratory of Hepatopancreatobiliary Surgery, Anhui Provincial Clinical Research Center for Hepatobiliary Diseases,The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China; [2]Department of Intervention, The First Affiliated Hospital of USTC West District, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China

Aims: This retrospective study was to assess the effectiveness of inducing artificial atrophy of the liver by preoperative hepatic vein deprivation (LVD) combined with precise transcatheter arterial chemoembolization (TACE) in patients with large liver cancer, and to evaluate the impact of this treatment approach on compensatory proliferation of the contralateral liver, increasing hepatic functional reserve, and achieving surgical indications for stage II liver resection. **Methods:** Clinical data from 24 patients who underwent LVD combined with precise TACE therapy due to insufficient residual liver volume between October 2019 and December 2021 at the First Affiliated Hospital of University of Science and Technology of China were retrospectively analyzed. The study parameters included success rate of surgery, adverse reactions and complications, dynamic changes in liver function, blood routine and coagulation function, as well as the results of preoperative and postoperative liver CT examinations. **Results:** All 24 patients completed the simultaneous LVD and TACE treatment with a 100% success rate. The most common side effect after surgery was discomfort and pain in the liver area, and no serious complications were observed. Laboratory examination data revealed that alanine aminotransferase and aspartate aminotransferase increased significantly but recovered to preoperative levels after surgery. After LVD combined with TACE, the volume of the left liver gradually increased while the volume of the right liver gradually decreased. The preoperative future liver remnant (FLR) volume ratio was 45.2±7.4%, and the FLR volume ratios at weeks 1 and 3 after surgery were 49.8±17.9% and 55.2±21.3%, respectively. Three weeks after LVD combined with TACE, 17 cases (70.8%) met the surgical requirements for FLR. **Conclusions:** LVD combined with precise TACE is a minimally invasive and safe transformation therapy for primary liver cancer that promotes rapid proliferation of FLR and enables stage II surgical criteria to be met in a shorter waiting period. **Keywords:** Liver Venous Deprivation, TACE, Future Liver Remnant

PE-87

Dose the Tumor Marker Regression Predict the Survival after External Beam Radiotherapy in Hepatocellular Carcinoma?

Won Sup Yoon[1], Sunmin Park[1], Chai Hong Rim[1], Young Kul Jung[2], Hyung Joon Yim[2], Hwan Hoon Chung[3]

[1]Department of Radiation Oncology, Ansan Hospital, College of Medicine, Korea University, Ansan, Republic of Korea; [2]Department of Internal Medicine, Ansan Hospital, College of Medicine, Korea University, Ansan, Republic of Korea; [3]Department of Radiology, Ansan Hospital, College of Medicine, Korea University, Ansan, Republic of Korea

Aims: This study was conducted to find out whether the changes in tumor markers according to the treatment response after radiotherapy (RT) were correlated with the prognosis of hepatocellular carcinoma (HCC). **Methods:** It was a single-center retrospective study, and patients who underwent conventional fractionated RT for HCC from 2010 to 2021 were enrolled. The viable HCC was irradiated with >30 Gy over 10 fractions. Patients with regular follow-up for more than 3 months after completion of RT were included. HCC with distant metastases or lymph node metastases not included in the RT field was excluded, in addition to ECOG performance scale >2 and Child-Pugh-C. For initial tumor markers of AFP >20 ng/ml and PIVKA-II >50 mAU/ml, the degree of regression of AFP and PIVKA-II from pre-RT to post RT after 3months (window period +/-1 month) was examined. An ROC curve analysis was performed on 1-year and 2-year OS probability. **Results:** A total of 123 patients were enrolled. Median age was 58 years. BCLC stage A, B, and C were 30, 27, and 66, respectively. The median overall survival (OS) was 14.6 months, and the 1-year and 2-year OS rates were 54.5% and 35.8%, respectively. The area under curves (AUC) of AFP regression at 1-year and 2-year OS were 0.788 (95% CI 0.685–0.891) and 0.841 (95% CI 0.746–0.936), respectively. The cut-off value of 17.5% was presented as the sensitivity of 0.714 and the specificity of 0.905 at 2-year OS. The AUC of PIVKA-II regression at 1-year and 2-year OS were 0.752 (95% CI 0.646–0.859) and 0.713 (95% CI 0.594–0.833), respectively. In Cox regression analyses, OS was significantly related with portal vein tumor thrombus (P=0.028) and AFP regression (cutoff 20%, P<0.001). **Conclusions:** The regression degree of AFP at 3 months after completion of RT were associated with OS as major prognostic factor. **Keywords:** Hepatocellular Carcinoma, Radiotherapy, AFP, Survival

PE-88

Effects of Stereotactic Body Radiotherapy versus Conventional Fractionated Radiotherapy on Circulating Lymphocyte Levels in Patients with Hepatocellular Carcinoma

Yuan Zhuang, Ping Yang, Yi-xing Chen, Shi-suo Du, Zhao-chong Zeng

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

Aims: To compare effects of stereotactic body radiotherapy (SBRT) vs conventionally fractionated RT (CFRT) on peripheral lymphocyte counts in patients with hepatocellular carcinoma (HCC), and to explore the prognostic value of radiotherapy-induced lymphopenia (RIL). **Methods:** From July 2011 to January 2018, a total of 137 patients with HCC treated with RT were retrospectively analyzed. Variables were obtained within 1 week before RT, 1 day, and 2 months after RT. Effects of SBRT and CFRT on absolute lymphocyte counts (ALCs), subset levels including CD3+, CD4+, CD8+ T cells, CD19+ B cells, and CD16+56+ NK cells in HCC patients were compared. Univariate and multivariate Cox regression analyses were used to explore independent prognostic factors for patients' overall survival (OS). **Results:** The mean ALCs before RT, 1 day, and 2 months after RT were 1.3×10^9/L, 0.5×10^9/L, and 1.0×10^9/L, respectively. The levels of ALCs and lymphocyte subsets post-RT for patients receiving SBRT were higher than those treated with CFRT (P<0.05). Severe lymphopenia occurred in 23.0% of patients in SBRT group and 70.0% in CFRT. Among all the lymphocyte subsets, CD19+ B cells

Table 1: Summary of Demographics and Attributes of Patients Treated with Y90 SIRT that Developed Radiation Pneumonitis

Characteristic	All Patients N = 16	<65 years old N = 9	≥ 65 years old N = 7
Demographic Variables			
Male (%)	12 (75.0)	8 (88.9)	4 (57.1)
Age (years), median (IQR)	61.5 (54.8-69.8)		
Ethnicity (%)			
Chinese	10 (62.5)	3 (33.3)	7 (100)
Malay	1 (6.25)	1 (11.1)	0 (0)
Indian	0 (0)	0 (0)	0 (0)
Others	5 (31.3)	5 (55.5)	0 (0)
Social History			
Alcohol Consumption (%)	2 (12.5)	2 (22.2)	0 (0)
Medical Status (%)			
Child Pugh			
A	13 (81.3)	7 (77.8)	6 (85.7)
B	3 (18.8)	2 (22.2)	1 (14.3)
ALBI Grade			
1	3 (18.8)	2 (22.2)	1 (14.3)
2	12 (75.0)	6 (66.7)	6 (85.7)
3	1 (6.25)	1 (11.1)	0 (0)
BCLC Stage			
A	3 (18.8)	2 (22.2)	1 (14.3)
B	5 (31.3)	3 (33.3)	2 (28.6)
C	8 (50.0)	4 (44.4)	4 (57.1)
Etiology of Hepatitis			
Viral (Hep B/C)	8 (50.0)	7 (77.8)	1 (14.3)
Non-viral	8 (50.0)	2 (22.2)	6 (85.7)
Disease Factors			
Pre Treatment AFP*			
<400	4 (25.0)	2 (22.2)	2 (28.6)
≥400	12 (75.0)	7 (77.8)	5 (71.4)
Tumor Burden			
Solitary	6 (37.5)	3 (33.3)	3 (42.9)
2-5 tumours	3 (18.8)	1 (11.1)	2 (28.6)
>5 tumours	7 (43.8)	5 (55.6)	2 (28.6)
Tumor Location			
Unilobar	9 (56.3)	5 (55.6)	4 (57.1)
Bilobar	7 (43.8)	4 (44.4)	3 (42.9)
Treatment Factors (Mean (SD))			
Administered Y90 Dose (Gbq)	2.09 (0.734)	2.18 (0.657)	1.96 (0.861)
Lung Shunt Percentage (%)[1]	11.4 (4.98)	11.6 (6.59)	11.3 (2.65)
Predicted Mean Radiation Dose to Lungs (Gy)[2]	12.7 (6.96)	13.5 (7.14)	11.7 (7.42)
Predicted Mean Radiation Dose to Tumor (Gy)[3]	119 (76.7)	113 (78.1)	128 (85.2)

*: 2 out of 16 patients did not have their AFP recorded within 6 months of SIRT
1: 1 out of 16 patients did not have their lung shunt % recorded
2: 5 out of 16 patients did not have their predicted mean radiation dose to lungs recorded
3: 6 out of 16 patients did not have their predicted mean radiation dose to tumor recorded

were mostly depleted, while CD8+ T cells recovered faster. The median OS was 29.0 months and the one- and two-year OS rates were 80.0% and 55.0%, respectively. Multivariate analysis results revealed that variables including tumor size>4.5cm, CD4+ T cells< 231/uL, CD8+ T cells< 179/uL, portal vein tumor thrombus, and multiple lesions were independent factors for inferior OS. For the SBRT subgroup, patients with higher levels of CD4+ and CD8+ T cells had a longer OS (P<0.05). **Conclusions:** SBRT leads to less severe RIL than CFRT. Peripheral lymphopenia after RT might be an independent prognostic factor for shorter OS in HCC patients. **Keywords:** Hepatocellular Carcinoma, Radiotherapy, Lymphopenia, Overall Survival

PE-89

An Investigation into the Development of Radiation Pneumonitis Following Yttrium-90 Selective Internal Radiation Therapy in a Single Institution in Asia

Kaina Chen[1,2], Aaron Kian Ti Tong[4], Fiona Ni Ni Moe[3], Ong Sheng Khai Timothy[5], Yeo Eng Xuan[5], Daniel Peh Yang Yao[5], David Chee Eng Ng[4], Kelvin Siu Hoong Loke[4], Apoorva Gogna[6], Sean Xuexian Yan[4], Sue Ping Thang[4], Hian Liang Huang[4], Chow Wei Too[6], Weng Yan Ng[3], Pierce Chow[2,3,7]

[1]Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore; [2]Duke-NUS Medical School, Singapore; [3]Department of Surgical Oncology, National Cancer Centre Singapore, Singapore; [4]Department of Nuclear Medicine, Singapore General Hospital, Singapore; [5]Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [6]Department of Vascular and Interventional Radiology, Singapore General Hospital, Singapore; [7]Department of Hepato-pancreatico-biliary Surgery, Singapore General Hospital, Singapore

Aims: Radiation pneumonitis (RP) is a rare but serious complication of selective internal radiation therapy (SIRT) with Yttrium-90 (Y90). The incidence and risk factors of RP have not been well evaluated. We aim to investigate the incidence of RP in a cohort of Hepatocellular Carcinoma (HCC) patients after Y90-SIRT and assess the risk factors for its development. **Methods:** 593 patients treated with Y90-SIRT for non-metastatic HCC from July 2007 to December 2019 at the National Cancer Centre Singapore (NCCS) and Singapore General Hospital (SGH) were included. Important exclusion criteria were synchronous cancers or missing data. RP was diagnosed in patients with bilateral lung infiltrates on imaging, clinical dry cough and/or shortness of breath within 6 months of Y90-SIRT. Patients' baseline characteristics, laboratory tests, radiological findings, lung shunt percentage and predicted lung and tumour radiation doses were analysed. Ethical approval was granted by the Institutional Review Board (IRB:2017/2541). **Results:** Sixteen patients (16/472, 3.3%) met the definition of radiation pneumonitis. The baseline characteristics of HCC patients with RP post-SIRT are summarized in Table 1. The predicted mean radiation dose to the lungs was 14.7Gy (IQR 8.55-17.1). Patients who developed RP had a median lung shunt of 10.5% (IQR 8.35%-13.95%) compared to those who did not (median 4.50% IQR 2.80%-7.50%, P=0.001). The administered Y90 dose was significantly higher in patients with RP (median 2.00GBq versus 1.40GBq, P=0.037). Additionally, patients with baseline alpha-fetoprotein greater than 400ug/L were 5.41x more likely to develop radiation pneumonitis (95%CI=2.38-12.31). One of the 16 patients with RP was treated with dexamethasone immediately post-Y90 with clinical improvement afterwards. The development of RP was not a significant factor for progression-free survival or overall survival. **Conclusions:** Radiation pneumonitis is a rare complication of Y90 SIRT treatment. Higher lung shunt, higher Y90 doses, higher absorbed lung dose and baseline AFP>400 ug/L correlated with the development of RP. **Keywords:** Radiation Pneumonitis, HCC, Y90, SIRT, Complications

Table 2: Table Comparing Patients Treated with Y90 SIRT that Developed Radiation Pneumonitis against Patients that did not Develop Radiation Pneumonitis

Characteristic	RP Patients N = 16 (%)	Non-RP Patients N = 456	p-value
Demographic Variables			
Male (%)	12 (75.0)	381 (83.6)	0.322
Age (years), median (IQR)	61.5 (54.8-69.8)	65.0 (58.0-71.0)	0.094
Medical Status (%)			
ALBI Grade			
1	3 (18.8)	127 (27.9)	0.702
2	12 (75.0)	297 (65.1)	
3	1 (6.25)	32 (7.02)	
BCLC Stage			
A	3 (18.8)	74 (16.2)	0.949
B	5 (31.3)	166 (36.4)	
C	8 (50.0)	212 (46.5)	
D	0 (0)	4 (0.88)	
Etiology of Hepatitis			
Viral (Hep B/C)	8 (50.0)	292 (64.0)	0.294
Non-viral	8 (50.0)	164 (36.0)	
Disease Factors			
AFP*			
<400	4 (28.6)	265 (64.3)	**0.002**
≥400	12 (71.4)	147 (35.7)	
Tumor Burden			
Solitary	6 (37.5)	138 (30.4)	0.824
2-5 tumours	3 (18.8)	88 (19.4)	
>5 tumours	7 (43.8)	228 (50.2)	
Treatment Factors (Mean (SD))			
Administered Y90 Dose (Gbq)	2.09 (0.734)	1.66 (0.957)	**0.037**
Lung Shunt Percentage (%)[1]	11.4 (4.98)	5.68 (4.22)	**0.001**
Predicted Mean Radiation Dose to Lungs (Gy)[2]	12.7 (6.96)	-	
Predicted Mean Radiation Dose to Tumor (Gy)[3]	119 (76.7)	156.7 (83.5)	0.160

PE-90

Clinical Outcomes of Stereotactic Body Radiation Therapy Alone versus Stereotactic Body Radiation Therapy after Incomplete Transarterial Chemoembolization for a Single Small (≤ 5 cm) Recurrent Hepatocellular Carcinoma

Youngju Song[1], Jinhong Jung[1], Jin-hong Park[1], So Yeon Kim[2], Jonggi Choi[3], Danbi Lee[3], Ju Hyun Shim[3], Kang Mo Kim[3], Young-Suk Lim[3], Han Chu Lee[3], Sang Min Yoon[1]

[1]Departments of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Departments of Radiology, Asan Medical Center, University of

Ulsan College of Medicine, Seoul, Republic of Korea; [3]Departments of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: The objective of this study is to compare the clinical outcomes of stereotactic body radiation therapy (SBRT) alone versus SBRT following incomplete transarterial chemoembolization (TACE) for a single small (≤ 5 cm) recurrent hepatocellular carcinoma (HCC). **Methods:** We conducted a retrospective review of medical records of 1014 patients treated with SBRT for HCC without vascular invasion or extrahepatic metastases at Asan Medical Center between 2007 and 2017. Among these patients, 54 had received SBRT for a single recurrent HCC without prior treatment to the target lesion (SBRT alone group); whereas 423 patients received SBRT for a single viable HCC following incomplete TACE (TACE-SBRT group). The primary outcome was the local control (LC) rate, and secondary outcomes included overall survival (OS), out-of-field intrahepatic recurrence-free survival (IHRFS), recurrence-free survival (RFS), and treatment-related toxicities. Additionally, we compared the outcomes between the SBRT alone group and TACE-SBRT group using a 1:3 propensity score matching (PSM) method. **Results:** The study population had a median age of 63 years (range, 56–69 years) and the majority of the patients had Child-Pugh class A hepatic function (89.7%). Tumor size in the SBRT alone group (median 1.4 cm, interquartile range [IQR], 1.2–1.7 cm) was smaller than that in the TACE-SBRT group (median 1.9 cm, IQR 1.5–2.5 cm). Alpha-fetoprotein level in the SBRT alone group (median 5.9 ng/mL, IQR 2.7–16.0 ng/mL) was lower than that in the TACE-SBRT group (median 9.8 ng/mL, IQR 4.3–40.8 ng/mL). A median dose of 15 Gy (range, 10–20 Gy) per fraction was given over 3–4 consecutive days, and median total dose was 45 Gy (range, 30–60 Gy) in both groups. The median duration of follow-up was 37.2 months (IQR, 24.1–46.3 months). The LC rate at 3 years did not differ statistically between two groups (88.6% in SBRT alone group vs. 89.6% in TACE-SBRT group, *P*=0.92). Additionally, the OS (64.8% vs. 69.2%, *P*=0.48), IHRFS (41.3% vs. 31.8%, *P*=0.29), and RFS (34.9% vs. 28.6%, *P*=0.27) at 3 years were not significantly different between two groups. Even after PSM, the LC (91.0% in SBRT alone group vs. 93.9% in TACE-SBRT group, *P*=0.90), OS (67.9% vs. 73.2%, *P*=0.62), IHRFS (36.1% vs. 41.2%, *P*=0.50), and RFS (33.7% vs. 38.2%, *P*=0.58) rates at 3 years were not significantly different. The deterioration of Child-Pugh score ≥ 2 was observed in 0 patients (0.0%) in the SBRT alone group and 18 patients (4.3%) in the TACE-SBRT group. There were no gastrointestinal complications, such as bleeding or perforation, in both groups. **Conclusions:** Our study did not find any significant differences in local control and survival rates between the SBRT alone group and the TACE-SBRT group. Thus, SBRT alone, without prior treatment, may be considered as an alternative treatment option for a single recurrent HCC below 5 cm, especially when locoregional therapy is not feasible. **Keywords:** Hepatocellular Carcinoma, Stereotactic Body Radiation Therapy, Transarterial Chemoembolization, Local Control, Survival Rates

PE-91

Efficacy and Safety of Small-Size Drug-Eluting Beads Transcatheter Arterial Chemoembolization Combined with Lenvatinib for Unresectable Hepatocellular Carcinoma

*Jun Deng, Xiaonan Mao, Pengfei Zhao, Lanbo Wang, Feng Wen**

Department of Radiology, Shengjing Hospital of China Medical University, Shenyang, Liaoning Province, China

Aims: The aims of this study were to evaluate the efficacy and safety of small-size drug-eluting beads transcatheter arterial chemoembolization (DEB-TACE) combined with Lenvatinib in the treatment of patients with unresectable hepatocellular carcinoma. **Methods:** We evaluated the efficacy of 49 patients with unresectable hepatocellular carcinoma treated with DEB-TACE in combination with Lenvatinib between April 2019 and June 2022. All enrolled patients were embolized with small-size drug-eluting beads (Hepasphere 30-60μm). The survival curves of progression-free survival (PFS) and overall survival (OS) were plotted according to the Kaplan-Meier method. The modified Response Evaluation Criteria in Solid Tumors(mRECIST) were applied to evaluate the best tumor response. COX univariate and multivariate analyses were used to investigate the influencing factors related to PFS and OS. Adverse events during patient follow-up were recorded. Patients' modified Albumin-Bilirubin (mALBI) scores were recorded before DEB-TACE, 3 days after the operation, and at 1, 3, and 6 months after the DEB-TACE. **Results:** The median PFS were 8.8 months (95% CI:7.0-10.6 months) and the median OS was 18.2 months (95% CI:14.4-22.0 months). No independent prognostic factors were found to be associated with PFS. Univariate and multivariate analysis showed that maximum tumor diameter ≥ 7cm (HR=2.82; 95% CI, 1.09- 7.30; *P*=0.033) was an independent prognostic factor for OS. The objective response rate (ORR) was 65.3%. No grade 4 or above adverse events were found. Compared with mALBI before DEB-TACE and 3 days after the operation, there was a brief deterioration (*P*=0.000). Compared with 3 days after the operation, liver function was significantly improved at 1 month after the operation (*P*=0.004). **Conclusions:** Small-size DEB-TACE combined with Lenvatinib is an effective and safe treatment for patients with unresectable hepatocellular carcinoma. The maximum tumor diameter ≥7cm is an independent risk factor for OS. **Keywords:** Hepatocellular Carcinoma, Transcatheter Arterial Chemoembolization, Lenvatinib, Combined Therapy

PE-92

Liver Acute Cytolysis after Transarterial Chemoembolization in Hepatocellular Carcinoma

Tsakhim-Erdene Tsendjav[1], Erkhembayar Dima[2], Uchral Ochirbulgan[2], Temuujin Battogoo[2], Tugsjargal Purevsukh[3], Delgerdalai Khashbat[3],Tuvshinjargal Dashjamts[3], Munkhbaatar Dagvasumberel[3], Adilsaikhan Mendjargal[4], Gantulga Vanchinsuren[5], Erdenebulgan Batmunkh[5]

[1,2]Department of Radiology, Mongolia-Japan Hospital, Mongolian

National University of Medical Sciences, Mongolia; [3]Department of Radiology, School of Medicine, Mongolian National University of Medical Sciences, Mongolia; [4]Department of Oncology, School of Medicine, Mongolian National University of Medical Sciences, Mongolia; [5]National Diagnostic and Treatment Center, Second Central Hospital of Mongolia, Mongolia

Aims: Transarterial chemoembolization for hepatocellular carcinoma is a local treatment method included in international guidelines. In a following days after TACE, liver function is lost due to tumor necrosis and parenchymal damage, and cytolysis tend to develop. We evaluated a lost in liver function and acute cytolysis after TACE. **Methods:** We conducted a study, total of 41 cases of TACE from October 2022 to March 2023 in a retrospective model at the Mongolia-Japan Hospital, MNUMS. Liver function laboratory results were assessed and compared in the week before TACE and on the first, third, and fifth days after treatment. **Results:** In the first five days after TACE, the laboratory results AST increased by 54%, ALT by 48.1%, TBIL by 3.7%, and CRP by 27.3%, while albumin decreased by 0.9%, so liver function lost and acute cytolysis were detected. From the third day after treatment, result of recovery of liver function were observed in laboratory tests. **Conclusions:** After TACE, there is a risk of developing symptoms of acute cytolysis and liver dysfunction. Therefore, it is shown that proper patient selection and post-procedure care should be done attentively to prevent post-treatment complications. **Keywords:** Chemical Therapy, Liver Function, Medical Therapy

PE-93

Prediction of Early Treatment Response to Initial Conventional Transarterial Chemoembolization for Caudate Lobe Hepatocellular Carcinoma: A Retrospective Study

*Xinying Song[1], Bing Ma[2], Bohan Zhang[1], Xiaonan Mao[1], Feng Wen[*1]*

[1]Department of Radiology, Shengjing Hospital of China Medical University, Liaoning Province, China; [2]Department of Clinical Epidemiology and Evidence-based Medicine, The First Hospital of China Medical University, Liaoning Province, China

Aims: The aim is to evaluate the early tumor response in patients with caudate lobe hepatocellular carcinoma (CL-HCC) after initial transcatheter arterial chemoembolization (TACE), analyze its possible influencing factors, and provide evidence for predicting early treatment outcomes. **Methods:** A total of 64 CL-HCC patients who met the inclusion and exclusion criteria from January 2009 to December 2021 were analyzed retrospectively. According to the modified Response Evaluation Criteria in Solid Tumors, the patients after the first TACE was divided into OR group and non-OR group, and their demographic characteristics, laboratory indicators, and tumor-related indicators were collected. Univariate and multivariate analyses were performed respectively. The additive model analyzed the interaction between independent risk factors, and the variables with statistical significance were evaluated by simple effect analysis. **Results:** Univariate analysis showed that gender, AFP, AST, tumor-feeding arteries, and TACE level (super-selective or not) were statistically significant between the two groups (P <0.1). Multivariate analysis indicated that male (OR=0.11, 95% CI 0.02-0.73), multiple tumor-feeding arteries (OR=5.88, 95% CI 1.25-27.59), and non-superselective TACE (OR=15.54, 95% CI 3.31-73.00) were risk factors for early progression of CL-HCC after the first TACE. The Nomogram prediction model showed that non-selective embolization was the most significant risk of progression, followed by multiple tumor-feeding arteries and male. Simple effect analysis showed that multiple tumor-feeding arteries and non-superselective TACE were the most likely factors to progress after initial TACE (OR=95, 95%CI 8.95-1008.41). **Conclusions:** Male, multiple tumor-feeding arteries, and non-superselective TACE were the risk factors affecting the early tumor response in patients with CL-HCC after initial TACE. Attention should be paid to the risk of early treatment outcomes in these patients with multiple tumor-feeding arteries and non-superselective embolization. **Keywords:** Hepatocellular Carcinoma, Transarterial Chemoembolization, Treatment Response, Predictors

PE-94

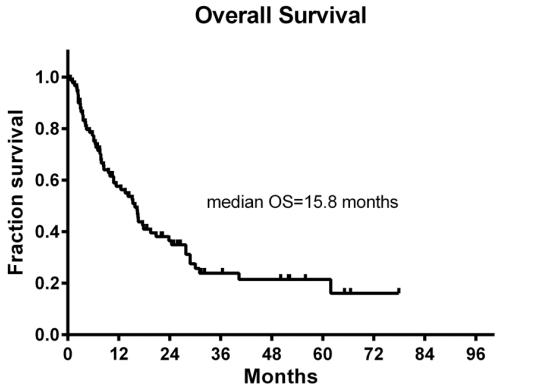
Comparison of Dosimetry Methods and Tumor Burden for Radioembolization in Patients with Unresectable Hepatocellular Carcinoma

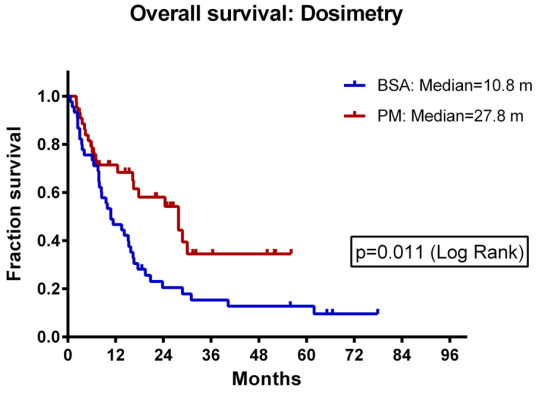
Hui-Chi Liu[1], Po-Chin Liang[1,2], Chih-Horng Wu[1,2,3]

[1]Department of Medical Imaging, National Taiwan University Hospital, Taipei, Taiwan; [2]Department of Radiology, College of Medicine, National Taiwan University, Taipei, Taiwan; [3]Hepatits Research Center, National Taiwan University Hospital, Taipei, Taiwan

Aims: Yttrium-90 (Y90) radioembolization is a loco-regional therapy for hepatocellular carcinoma (HCC) and has been included in the 2022 update of Barcelona Clinic Liver Cancer (BCLC) guideline for its safety and efficacy. This study aimed to compare the outcome of two dosimetry methods of Y-90 resin microspheres and evaluated the prognostic factors for optimal patient selections. **Methods:** A retrospective cohort study was conducted in a single tertiary medical center. Between May 2016 to September 2019, patients (n=89) with unresectable HCC (BCLC-B and BCLC-C) were treated with Y90 resin microspheres and followed up for at least six months. The dosimetric parameters, pre-treatment laboratory profiles and tumor response were collected. Kaplan-Meier analysis was performed for survival. In addition, Cox regression analysis was performed to identify the prognostic factors. **Results:** The median overall survival (OS) was 15.8 months. The progression-free survival was 7.2 months. The partition model (PM) had significantly improved OS as compared to the body surface area (BSA) model (PM, 27.8 months; BSA, 10.8 months, *P*=0.011). Disease control rate in the seventh month was 40.9% in PM and 31.1% in BSA. Tumor volume, TN ratio and the tumor dose of the BSA model patients were recruited retrospectively. There is no distribution difference in non-tumor dose and tumor dose between the two dosimetric groups. Subgroup analysis for each dosimetry model showed improved OS in patients who received tumor doses

over 125Gy (P=0.022 for PM; P=0.009 for BSA). Other significant prognostic factors upon multivariate cox regression were tumor burden and curative treatment post-Y90 radioembolization. For patients in the up-to-11 criteria, PM provided OS benefit (P=0.05); for those out of the criteria, two dosimetry methods did not differ from OS. **Conclusions:** This single-center study shows a strategy for improved survival outcomes with the partition model and tumor dose over 125Gy. **Keywords:** Radioembolization, Y90, Hepatocellular Carcinoma, Dosimetry





PE-95

Curative-Dose Radiotherapy and Multiagent Chemotherapy Improves Survival of Locally Advanced Intrahepatic Cholangiocarcinoma: A Multi-Institutional Cohort Study (KROG 20-02)

Jung Ho Im[1,5], Jeong Il Yu[2], Tae Hyun Kim[3], Tae Gyu Kim[4], Jun Won Kim[6], Jinsil Seong[1]

[1]Department of Radiation Oncology, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Center for Proton Therapy and Center for Liver and Pancreatobiliary Cancer, National Cancer Center, Goyang, Republic of Korea; [4]Department of Radiation Oncology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Republic of Korea; [5]Depratment of Radiation Oncology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea; [6]Department of Radiation Oncology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

Aims: Locally advanced unresectable intrahepatic cholangiocarcinoma shows detrimental oncologic outcome. In this study, we investigated the efficacy of chemoradiotherapy in patients with locally advanced intrahepatic cholangiocarcinoma (ICC). **Methods:** We retrospectively reviewed the records of 114 patients who received radiotherapy for ICC between 2001 and 2021 in multi-institutional cohort. The median equivalent radiotherapy dose (EQD2) was 52 (range, 30-124) Gy. Radiotherapy in combination with multiagent chemotherapy was administered in 59 patients. Local control (LC) and overall survival (OS) were analyzed using the Kaplan–Meier method; prognostic factors were analyzed using the Cox proportional hazards model. **Results:** Overall, 1-year LC and OS were 74% and 63.8%, respectively. Through multivariate analysis we identified the EQD2 ≥ 60 Gy and multiagent chemotherapy as significant positive factors for LC and OS. Based on the identified risk factors, patients were grouped; EQD2 ≥ 60 Gy with multiagent chemotherapy (Group A, n=23), EQD2 < 60 Gy with multiagent chemotherapy or radiotherapy with single agent chemotherapy (Group B, n=69), radiotherapy alone (Group C, n=22). The group A had significantly better OS than the group B and C (P<0.05). **Conclusions:** Curative-dose radiotherapy in combination with multiagent chemotherapy improved oncologic outcome of patients with locally advanced ICC. Further prospective study is warranted for validation. **Keywords:** Intrahepatic Cholangiocarcinoma, Radiotherapy, Chemotherapy

PE-96

Liver-Directed Combined Radiotherapy for Downstaging of over the Milan Advanced Hepatocellular Carcinoma Converting to Liver Transplantation

Yong Tae Kim[1], Dong Jin Joo[2], Jae Geun Lee[2], Do Young Kim[3], Jinsil Seong[1]

[1]Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Department of Surgery, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

Aims: The recent success of combined immunotherapy sheds a light to the future of advanced hepatocellular carcinoma patients but still remains as a palliative setting. The best oncologic outcome for HCC can be obtained by curative surgery either by resection or liver transplantation (LT). The efficacy of liver-directed combined radiotherapy (LD-CRT) for downstaging and subsequent surgical resection in locally advanced HCC had been reported earlier by our team. In this study, we investigated the role of LD-CRT as a downstaging strategy for converting

advanced hepatocellular carcinoma to LT. **Methods:** We reviewed 55 hepatocellular carcinoma patients who had undergone downstaging LD-CRT and subsequent liver transplantation from January 2009 to February 2022. Patients within Milan criteria at the time of receiving radiotherapy were excluded and clinical characteristics and histopathology of the explant liver were evaluated. The overall survival and disease-free survival were assessed using the Kaplan-Meier method. **Results:** The median follow-up period was 48.6 months (range 6.9 – 151.7 months). Of 55 patients, 24 (43.6%) were treatment naïve. At the time of RT, 36 patients presented large tumor (tumor diameter >5 cm) or multiple lesions(>3 lesions), 37 with major vessel involvement or portal vein tumor thrombosis, and 7 with extrahepatic lesion. LD-CRT was given as localized concurrent chemoradiation (CCRT) for 41 patients (74.5%) and transarterial chemoembolization (TACE) plus RT for 10 patients (18.2%). Substantial downstaging has been achieved in 38 (69%) patients with initially over the Milan to within Milan. Specifically, 29 of 37 patients initially with major vessel invasion or with tumor thrombosis were successfully converted to microscopic vessel invasion or tumor thrombus-free status in explant liver. 5-year overall survival was 68.1% and 2-year disease-free survival was 51%, respectively. Recurrence after transplantation was observed in 18 patients (4 intrahepatic recurrences and 14 extrahepatic metastasis) and the majority (14/18) occurred within 2 years. **Conclusions:** Liver-directed combined radiotherapy as a downstaging strategy for liver transplantation achieved favorable oncologic outcomes in advanced hepatocellular carcinoma patients. This study suggests that active adoption of radiotherapy needs full consideration for locally advanced HCC patients, opening a chance for curative LT. **Keywords:** Hepatocellular Carcinoma, Liver Transplantation, Downstaging, Radiotherapy

PE-97

Combined Radiotherapy, Anti-Angiogenesis and Immune Checkpoint Blockade Inhibition of Portal Vein Tumor Thrombus in Hepatocellular Carcinoma: A Real-World Study

Ying Xiao[1], Keren Li[3*], Ying Zhao[2], Shizhong Yang[3], Jun Yan[3], Canhong Xiang[3], Jianping Zeng[3], Qian Lu[3], Chen Zhang[4], Gong Li[2#], Guangxin Li[2#], Jiahong Dong[3,5#]*

[1]Department of Pathology, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China; [2]Department of Radiation Oncology, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China; [3]Hepatopancereatobiliary Center, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China; [4]Imaging department, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China; [5]Research Unit of Precision Hepatobiliary Surgery Paradigm, Chinese Academy of Medical Sciences, Beijing, China

Aims: Hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT) has an extremely poor prognosis. A previous study proved that low-dose radiotherapy (RT) could prolong the prognosis of HCC patients with PTVV. This study aims to explore whether PVTT is more sensitive than primary tumors to RT treatment. **Methods:** Patients were selected based on imaging diagnosis of HCC accompanied by PVTT and received combined treatment of radiotherapy, antiangiogenic drugs and immune checkpoint inhibitors, followed by hepatectomy or liver transplantation from January 2019 to August 2022. The efficacy was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines and pathological assessment. The sensitivity of tumor cells to the treatment was compared between the primary tumor and PVTT by analyzing their residual tumor and PCR incidence. **Results:** Data from 14 patients were collected in the study. After combined treatment, the size of PVTT decreased more significantly than that of the primary tumor in the imaging study (P<0.05). The residual cancer of the primary tumor was significantly higher than that of PVTT based on pathologic diagnosis (P=0.008). The PCR incidence of the primary tumor (21.42%) was significantly lower (P=0.008) than that of PVTT in the pathologic study (78.57%). Furthermore, imaging analysis showed that 42.86% of patients had SD and 57.14% PR for the primary tumor, whereas 50% of patients had SD and 50% PR for PVTT. **Conclusions:** PVTT is more sensitive to radiotherapy treatment than the primary tumor in patients with HCC. This combination therapy might be an effective option as a downstaging therapy for patients with HCC with PVTT. **Keywords:** Hepatocellular Carcinoma, Portal Vein Tumor Thrombosis, Radiotherapy, Combination Therapy

PE-98

Olaparib Contributes to Radiation Induced Primary and Abscopal Tumor Control by Activating STING-Dependent Innate Immune Response

Genwen Chen, Danxue Zheng, Shisuo Du, Zhaochong Zeng

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

Aims: Poly (ADP-ribose) polymerase (PARP) inhibitors have been clinically used in cancers with BRCA mutation and been under investigation for their ability to enhance responses to radiotherapy. However, the roles of PARP inhibitors in irradiated and abscopal tumors are poorly understood. Herein, we intend to investigate whether olaparib sensitizes hepatocellular carcinoma (HCC) cells to radiation and contributes to systemic antitumor response in abscopal tumors. **Methods:** HCC cells were treated with irradiation with or without olaparib and DNA damage and cell proliferation were analyzed. Immune deficient, immune competent, and cGAS knockout mice underwent X-ray irradiation of 24 Gy in three fractions were used to investigate the roles of olaparib, irradiation and anti-CTLA4 on tumor growth and tumor microenvironment. **Results:** We show that a low dose of olaparib sensitized HCC cells to radiation. Olaparib and irradiation coadministration resulted in severe DNA damage by producing double-strand breaks (DSBs) as revealed in vitro and in immune-deficient mice. Moreover, double-strand DNA activating cGAS-STING signaling, contributed to antitumor innate immunity in both irradiated and abscopal tumors. Olaparib further enhanced radiotherapy-stimulated CD8+ T

cell infiltration in xenografts. Mechanism study revealed that the activation of cGAS-STING and type I interferon production potentiates the T cell priming against tumor neoantigens induced by irradiation. Furthermore, olaparib attenuated immune exhaustion of radiation and contributes to abscopal tumor control of HCC to immune checkpoint inhibitors. **Conclusions:** Combination therapy with PARP inhibitors and radiotherapy contributes to local (primary) and systemic (abscopal) tumor control and enhance responsiveness of HCC to immunotherapy through inducing DNA damage and boosting innate immune response. **Keywords:** PARP Inhibitor, Radiotherapy, CGAS-STING, Abscopal Effect

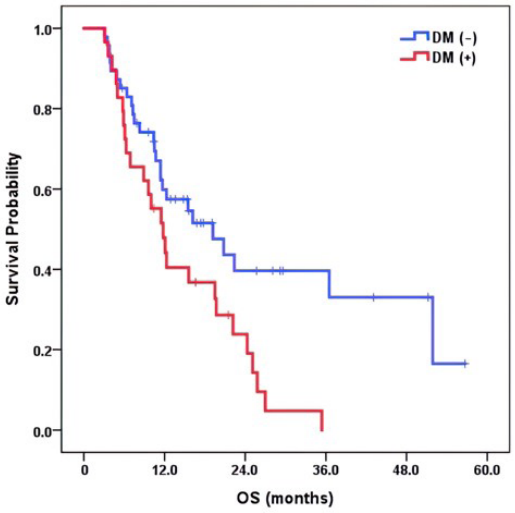
PE-99

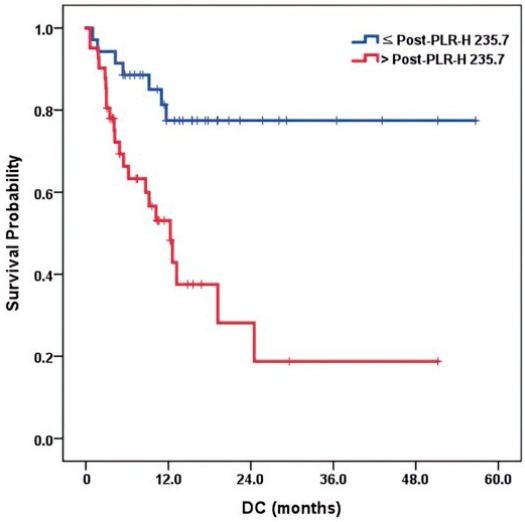
Prognostic Significance of Platelet-to-Lymphocyte Ratio in Patients with Hepatocellular Carcinoma Undergoing Curative Radiation Therapy

Dong Soo Lee[1], Chang Wook Kim[2], Hee Yeon Kim[2]

[1]Department of Radiation Oncology, College of Medicine, The Catholic University of Korea, Republic of Korea; [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Republic of Korea

Aims: Growing evidences support that elevated platelet-to-lymphocyte ratio (PLR) is associated with poor clinical outcomes in human cancer and distant metastasis (DM) is the major contributor to the devastating prognosis. We aimed to investigate whether serum inflammatory parameters can help to predict the clinical outcomes in patients with unresectable hepatocellular carcinoma (HCC) undergoing curative radiation therapy (RT). **Methods:** A total of 76 RT courses among 71 patients were analyzed. The following variables were included in the analysis: systemic inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio (PLR), prognostic nutritional index, absolute lymphocyte count, lymphocyte-to-monocyte ratio, albumin, albumin-to-alkaline phosphatase ratio, RT-related parameters, and levels of total protein, hemoglobin, α-fetoprotein, and PIVKA-II. The Kaplan–Meier method was used for survival analysis, and survival graphs were compared using the log-rank test. The multivariate Cox proportional hazards model was adapted to assess the prognostic significance. Overall survival (OS) and distant control (DC) rates were calculated and compared. **Results:** The mean age was 61.4 years, and most patients were men (n = 62, 81.6%). Most of the study population underwent pre-RT TACE/HAIC (n = 74, 97.4%). The median RT fraction number, fractional doses, and biologically equivalent doses by α/β=10 were 12 (range, 4–30), 5 (range, 2–12) Gy and 72.6 (range, 51.5–119) Gy, respectively. With a median follow-up of 12 (range, 3.1–56.7) months, the 1-year OS and DC rates were 55.2% and 64.4%, respectively. Development of DM significantly deteriorated OS rates (P=0.011), while local (P=0.690) and intrahepatic recurrences (P=0.102) did not. In the multivariate analysis for DC rates, significant independent prognostic indicator was the highest posttreatment PLR (≤ 235.7 vs. > 235.7, P=0.006). **Conclusions:** Posttreatment serum PLR might be used as a distinctive predictive biomarker of DC rates in unresectable HCC undergoing RT. Future research is necessary to confirm our findings. **Keywords:** Biomarker, Hepatocellular Carcinoma, Platelet-to-Lymphocyte Ratio, Radiation Therapy





PE-100

Radiation Therapy in Patients with Advanced Hepatocellular Carcinoma Presenting with Bile Duct Invasion

Sang Min Yoon[1], Jeong Yun Jang[1], Jinhong Jung[1], So Yeon Kim[2], Ju Hyun Shim[3], Jin-hong Park[1]

[1]Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Radiology and the Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [3]Department of Gastroenterology, Asan

Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: To investigate the efficacy and safety of radiotherapy in patients with unresectable hepatocellular carcinoma (HCC) accompanied by bile duct invasion. **Methods:** Between January 2010 and December 2020, we retrospectively reviewed 67 patients with unresectable HCC presenting with bile duct invasion who had undergone radiotherapy. The key inclusion criteria were as follows: (1) age ≥20 years; (2) the Eastern Cooperative Oncology Group performance score of 0–2; (3) bile duct invasion from HCC confirmed by dynamic contrast-enhanced images; (4) no previous history of radiotherapy to the upper abdomen. A total dose of 30–50 Gy was delivered using 2.0–5.0 Gy per fraction. The radiologic response was assessed according to the modified Response Evaluation Criteria in Solid Tumors. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE; version 5.0). Radiation-induced liver disease was graded according to CTCAE or an elevated Child-Pugh score of ≥2 in the absence of progressive disease within 3 months after radiotherapy. **Results:** The median age of patients was 56 years (range, 34–79), and 60 patients (89.6%) were men. Prior to radiotherapy, 21 (31.3%), 44 (65.7%), and 2 (3.0%) patients had Child-Pugh class A, B, and C hepatic function, respectively. Thirty-eight (56.7%) patients were diagnosed with combined portal vein tumor thrombus (PVTT). Most patients (88.1%) underwent bile drainage before radiotherapy. The median follow-up period was 13.2 months (range, 3.2–96.1). The objective response rate at 3 months after radiotherapy was 57.6%. The median freedom-from intraductal progression and progression-free survival (PFS) were 21.9 and 8.8 months, respectively. The 1-, 3-, and 5-year overall survival (OS) rates were 55.2%, 17.2%, and 12.0%, respectively, with a median survival time of 13.2 months. Univariate analysis revealed that infiltrative HCC, tumor size, and coexistence of PVTT were significantly associated with both PFS and OS rates, whereas Child-Pugh class, extrahepatic metastasis, and total bilirubin levels after bile drainage were related only to the OS rate. Grade ≥3 acute toxicities were observed in 14 (20.1%) patients, with 3 (4.5%) presenting an elevated Child-Pugh score (≥2). One patient (1.5%) experienced grade 3 duodenal bleeding after radiotherapy. **Conclusions:** HCC with bile duct invasion resulted in a poor prognosis. However, even in patients with unresectable HCC accompanied by hyperbilirubinemia, radiotherapy can be attempted to relieve intraductal progression. **Keywords:** Hepatocellular Carcinoma, Bile Duct Invasion, Radiotherapy, Prognosis

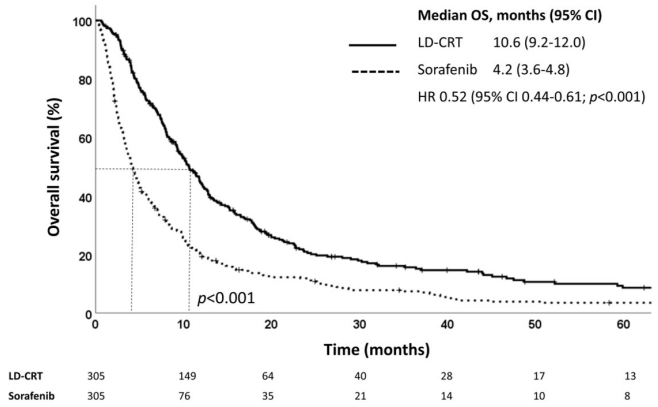
PE-101

Efficacy of Liver-Directed Combined Radiotherapy in Locally Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

Jina Kim[1], Jason Chia-Hsien Cheng[2], Taek-Keun Nam[3], Jinhee Kim[4], Byoung Kuk Jang[5], Wen-Yen Huang[6], Hiroshi Aikata[7], Myungsoo Kim[8], Jung Hyun Kwon[9], Jinbo Yue[10], Victor H.F. Lee[11], Zhao Chong Zeng[12], Jinsil Seong[1]

[1]Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Department of Radiation Oncology, National Taiwan University Hospital, Taipei, Taiwan; [3]Department of Radiation Oncology, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea; [4]Department of Radiation Oncology, Keimyung University School of Medicine, Daegu, Korea; [5]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Republic of Korea; [6]Department of Radiation Oncology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; [7]Department of Gastroenterology, Hiroshima Prefectural Hospital, Hiroshima, Japan; [8]Department of Radiation Oncology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [9]Division of Hepatology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [10]Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China; [11]Department of Clinical Oncology, The University of Hong Kong, Hong Kong, China; [12]Department of Radiation Oncology, Zhongshan Hospital Affiliated to Fudan University, Shanghai, China

Aims: Although systemic treatment is the mainstay for advanced hepatocellular carcinoma (HCC), numerous studies have highlighted the added value of local treatment. Therefore, this study aimed to investigate the clinical efficacy of liver-directed combined radiotherapy (LD-CRT) compared with that of sorafenib, a recommended treatment until recently for locally advanced HCC presenting portal vein tumor thrombosis (PVTT), using a multinational patient cohort. **Methods:** We identified patients with HCC presenting PVTT treated with either sorafenib or LD-CRT in 10 tertiary hospitals in Asia from 2005 to 2014. Propensity score matching (PSM) was performed to minimize the imbalance in patient and tumor characteristics between the two groups. The primary endpoint was overall survival (OS), and secondary endpoints were progression-free survival (PFS), and treatment-related toxicity. **Results:** A total of 1,035 patients (675 in the LD-CRT group and 360 in the sorafenib group) were included in this study. After PSM, 305 patients from each group were included in the analysis, and all features were well-balanced between the two groups. At a median follow-up of 22.5 months, the median OS was 10.6 and 4.2 months for the LD-CRT and sorafenib groups, respectively (P<0.001). Conversion rate to curative surgery was significantly higher (8.5% vs. 1.0%, P<0.001) while grade ≥ 3 toxicity was fewer (9.2% vs. 16.1%, P<0.001) in the LD-CRT group. **Conclusions:** Analysis of a multinational patient cohort revealed that LD-CRT improved survival outcomes with a higher conversion rate to curative surgery in patients with locally advanced HCC presenting PVTT. Therefore, although further prospective studies are warranted, active multimodal local treatment involving radiotherapy is suggested for locally advanced HCC presenting PVTT. **Keywords:** Hepatocellular Carcinoma, Portal Vein Tumor Thrombosis, Sorafenib, Radiotherapy



PE-102

New Score System Including Albumin-Bilirubin Grade Predicts Outcome of Transarterial Chemoembolization for Hepatocellular Carcinoma: A Nationwide Korean Cohort Study

Hae Lim Lee[1,2,3], Seok Hwan Kim[1,2,3], Myeong Jun Song[1,2,3]

[1]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Korean Liver Cancer Study Group, Republic of Korea; [3]Ministry of Health and Welfare, Korea Central Cancer Registry, Republic of Korea

Aims: Several scoring systems have been proposed to predict the outcome of transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC). However, the application of the albumin-bilirubin (ALBI) grades to TACE candidates is poorly validated. Evaluation of the applicability of prognostic factors for patients performing TACE is necessary. We aimed to develop new scoring system including ALBI grade. **Methods:** 2,632 patients with unresectable HCC, child class A/B and ECOG 0-1 performing TACE were included from national cohort of the Korean Central Cancer Registry between 2008 to 2017. Patients were randomly divided into training (n=1,304) and validation cohort (n=1,328). A prognostic model was developed and validated. We compared with previous scoring models. **Results:** In entire cohort, the patient's mean age was 63 years. The patients were hepatitis B virus (56.6%) and child class A (66.2%). The prognostic model of TACE was "largest tumor diameter+ tumor number, AFP, and ALBI grade", which consistently outperformed other currently available models in both training and validation datasets. Patients were assigned points according to sum of tumor burden (≤5, 5-10, ≥10), AFP or ALBI grade. Patients were divided into four risk groups based on their TACE-prognostic (TP) scores: A, B, C and D. The median survival for the groups A, B, C and D was 85.9, 67.3, 52.8 and 33.0 months, respectively. **Conclusions:** This new TP scoring system may prove a favorable tool to stratify ideal candidates of TACE and predict OS with favorable performance and discrimination. Further external validation is needed. **Keywords:** Transarterial Chemoembolization, Hepatocellular Carcinoma, Albumin-Bilirubin Grade, Overall Survival

Liver Cancer - Treatment: Systemic Therapy / Targeted Therapy / Immunotherapy

PE-103

Real-World Experience of Atezolizumab Plus Bevacizumab Combination Treatment in High-Risk Patients with Advanced Hepatocellular Carcinoma

Sang Youn Hwang[1], Hyun Young Woo[2], Jeong Heo[2], Hyung Jun Kim, Young Joo Park[2], Ki Youn Yi[2], Yu Rim Lee[3], Soo Young Park[3], Woo Jin Chung[4], Byoung Kuk Jang[4], Won Young Tak[3]*

[1]Department of Internal Medicine, Dongnam Institute of Radiologic & Medical Sciences, Busan, Republic of Korea; [2]Department of Internal Medicine, College of Medicine, Pusan National University, Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea; [3]Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, Republic of Korea; [4]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Republic of Korea

Aims: A recent phase 3 trial led to the approval of atezolizumab plus bevacizumab (ATE+BEV) as a first-line treatment for advanced hepatocellular carcinoma (HCC). However, real-world data regarding the response to this regimen is lacking for high-risk patients with advanced HCC. **Methods:** In this multicenter retrospective cohort study, a total of 215 patients who had advanced HCC and received ATE+BEV treatment at four different tertiary hospitals were examined. High-risk patients were those with grade Vp4 portal vein thrombus, bile duct invasion, or more than 50% liver infiltration. **Results:** Among all 215 patients, 98 (45.6%) were in the high-risk population, 186 (86.5%) had Child-Pugh class A, 29 (13.5%) had Child-Pugh class B, and 128 (59.5%) previously received neoadjuvant or concomitant radiation treatment. In the high-risk population, the median PFS was 6.50 months (95% CI, 3.93–9.08), and the median OS was 10 months (95% CI, 8.19–11.82). The OS and PFS were significantly shorter in the high-risk population than those of non-high-risk population. In the high-risk population, multivariate analysis indicated that receipt of neoadjuvant or concomitant radiation therapy was associated with better PFS and OS. Ninety-two patients (42.8%) experienced adverse events (AEs) of any grade, and the most common AE was proteinuria (14.8%). **Conclusions:** ATE+BEV treatment had consistent efficacy and tolerability in the total population and in the high-risk population. Previous radiation therapy increased the PFS and OS times in the high-risk group. **Keywords:** Hepatocellular Carcinoma, Immunotherapy, Radiotherapy

PE-104

Risk of Gastrointestinal Bleeding in Patients Receiving Atezolizumab–Bevacizumab Treatment for Hepatocellular Carcinoma

Kanghee Park[1], Hyeyeon Hong[1], Jiwon Yang[1], Won-Mook Choi[1], Danbi Lee[1], Ju Hyun Shim[1], Kang Mo Kim[1], Young-Suk Lim[1], Han Chu Lee[1], Changhoon Yoo[2], Sook Ryun Park[2], Min-Hee Ryu[2], Baek-Yeol Ryoo[2], Jonggi Choi[1]

[1]Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: IMbrave 150 excluded patients with a history of variceal bleeding or high-risk varices. We assessed the real-world gastrointestinal (GI) bleeding risk in patients with hepatocellular carcinoma (HCC) receiving atezolizumab–bevacizumab treatment and identified the risk factors for GI bleeding. **Methods:** A total of 345 patients with HCC who underwent endoscopy before atezolizumab–bevacizumab treatment were retrospectively analyzed. The primary outcome was grade ≥3 GI bleeding as per CTCAE 5.0. Using a multivariable model, GI bleeding-associated factors were identified, and a prediction model was developed. **Results:** The mean age was 60.6 years, and 81.7% were male. At baseline, 257 (74.5%) patients were classified as Child-Pugh class A. GI bleeding occurred in 21 patients, with a median onset of 3.1 months. No patient died from bleeding. Variceal bleeding (n=18) was the most common cause of GI bleeding. Platelet count <100,000/mm^3, prothrombin time (PT) with international normalized ratio (INR) ≥1.3, portal vein invasion (PVI), and esophageal varices (EV) grade ≥ 2 on pretreatment endoscopy were significantly associated with increased GI bleeding risk. Scores were assigned to platelet <100,000/mm^3 (1), PT INR ≥1.3 (1), PVI (1), and EV grade ≥2 (2). Patients categorized into the low (0), intermediate (1–2), and high-risk (≥3) groups showed GI bleeding risk of 0%, 8.9%, and 49.7% at 6 months, respectively. Our prediction model had a time-dependent AUROC of 0.868 and 0.874 for the risk of GI bleeding at 3 and 6 months, respectively. **Conclusions:** A low platelet count, INR≥1.3, PVI, and EV grade ≥2 increased risk of GI bleeding after atezolizumab–bevacizumab treatment for HCC. We proposed a simple model to predict GI bleeding with a high predictive performance. **Keywords:** Hepatocellular Carcinoma, Atezolizumab and Bevacizumab, Gastrointestinal Bleeding, Systemic Therapy

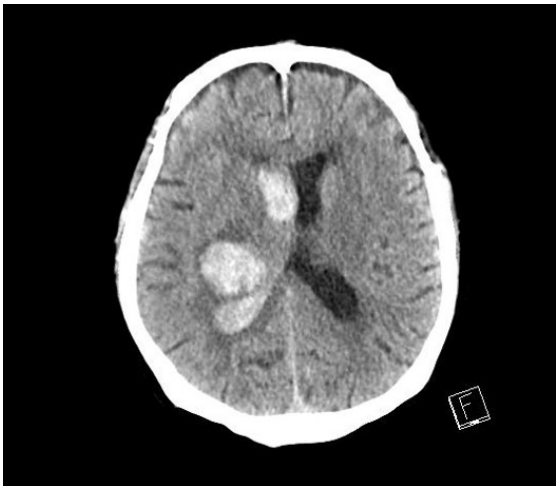
PE-105

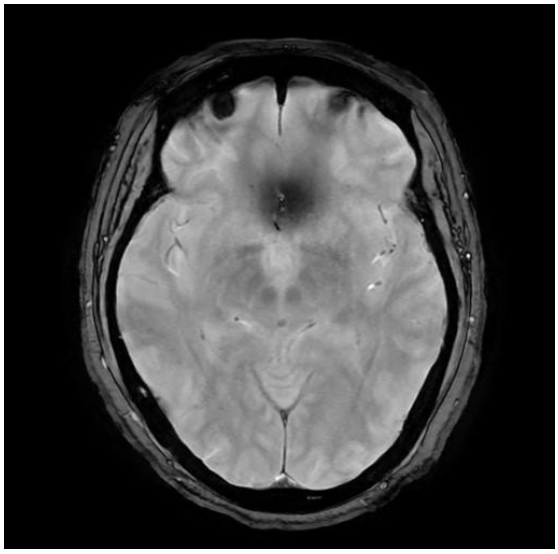
Case Reports: Advanced Hepatocellular Carcinoma Patients Treated with Atezolizumab and Bevacizumab Develop Brain Hemorrhages

Bang Ju Kim, Hyun Joon Park[1], Kwang Il Seo[1], Jung Wook Lee[1], Byung Cheol Yun[1], Sang Uk Lee[1]

Department of Internal Medicine, Kosin University, Gospel Hospital, Republic of Korea

Aims: Atezolizumab plus bevacizumab (AB) regimen is widely used for advanced Hepatocellular carcinoma (HCC). It is well-known that AB regimen increases the variceal bleeding risk. However, the relevance between AB regimen and brain hemorrhage is yet unknown. **Methods:** The authors reported two patients who developed brain hemorrhage after AB regimen. The first patient had been diagnosed with HCC in 2017 without any past histories including hypertension and received transcatheter arterial chemoembolization 6 times. After 5 years, HCC recurred and the patient received two cycles AB regimen over the period between November 2022 and December 2022. Two days after the last immunotherapy, the patient came to emergency room with mental change and then he was diagnosed with intracranial hemorrhage and intraventricular hemorrhage on brain CT (figure 1). He expired the following day. The second patient was also diagnosed with HCC in 2021 and received liver segmentectomy. The patient had taken a calcium-channel blocker and blood pressure was well-controlled. But HCC was recurred and hepatoduodenal lymph node metastasis was also observed. The patient received transcatheter arterial chemoembolization and radiotherapy. However, HCC recurred 3 months after radiotherapy with multiple distant lymph node metastasis. Then the patient went through two cycles of AB regimen. For surveillance, a brain angiography was performed and an aneurysm in A-comm was found. One day before the scheduled third immunotherapy, the patient came to emergency room with headache. The initial CT scan showed no significant hemorrhage, but the following MRI showed subtle subarachnoid hemorrhage and successful coil embolization was done (figure 2). **Results:** Both of patients had forms of brain hemorrhage after a couple of cycles of AB regimen. The first patient who had intracranial hemorrhage and intraventricular hemorrhage, expired. And the other patient who was found with aneurysm had subarachnoid hemorrhage is being monitored with follow up exams. Follow up exams showed no further bleeding so far. **Conclusions:** These two cases suggest that there are possibilities of not only the high risk of variceal bleeding but also a risk of brain hemorrhage in patients treated with AB regimen in advanced HCC. Moreover, further real-world study about AB regimen with brain hemorrhage would be needed. **Keywords:** Hepatocellular Carcinoma, Bevacizumab, Brain Hemorrhage





PE-106

Lung-Specific Response to Atezolizumab Plus Bevacizumab Is Associated with Overall Survival in Patients with Lung Metastasis from Hepatocellular Carcinoma

Jiwon Yang, Jonggi Choi, Won-Mook Choi, Kang Mo Kim, Han Chu Lee, Ju Hyun Shim

Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: Atezolizumab plus bevacizumab (Atezo/Bev) has been established as a standard first-line systemic treatment for advanced hepatocellular carcinoma (HCC). We aimed to investigate overall and organ-specific responses and their impact on survival in a specific group of patients with HCC and pulmonary metastases receiving Atezo/Bev. **Methods:** This study included 59 consecutive HCC patients with lung metastasis and preserved liver function who received at least three 3-weekly cycles of Atezo/Bev at the Asan Medical Center, South Korea. Responses assessment was based on RECIST v1.1: all metastatic lung lesions in 9 cases were not considered measurable. We defined "responders" as patients who achieved complete remission (CR) or partial remission (PR); and "progressors" as those with progressive disease (PD) at an initial evaluation after 3 cycles of treatment. The Kaplan-Meier method and Cox proportional model were used for overall survival (OS) analyses. **Results:** Of the 59 patients, 36 (61.0%) had a single lung metastasis with/without intrahepatic lesions, and 50 (84.7%) and 26 (44.1%) were accompanied by intrahepatic HCC and vascular invasion of the tumors, respectively. The OS rate was 77.2% at 10 months and 59.2% at 15 months after treatment in the entire cohort with a median follow-up of 8.2 months. Among 50 patients with measurable lesions in all affected organs, 7 (11.9%) achieved overall response (1 CR and 6 PR), with 9 (18%) lung-specific responders (2 CR and 7 PR). Overall and lung-specific progressors were 15 (25.4%) and 16 (32%), respectively. Overall and pulmonary progressors had significantly lower survival rates than the counterparts (33.8% vs. 100% and 58% vs. 100% at 8 months; Ps<0.05), as was neither overall nor pulmonary responders. The lung-specific progressor was an independent factor affecting survival, irrespective of intra- and extra-hepatic status of the tumors. **Conclusions:** Based on our data, pulmonary response to Atezo/Bev could help clinicians decide whether to continue the drug or switch to second-lines at an early phase of the initial therapy for HCCs with metastasis to the lung. **Keywords:** Hepatocellular Carcinoma, Atezolizumab Plus Bevacizumab, Lung Metastasis, Organ Specific Response

PE-107

Effectiveness and Safety of Sorafenib 400mg Initial Dose Compared with Sorafenib 800mg Initial Dose on Survival in Patients with Advanced and Intermediate Stage Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

Roland Helmizar

Faculty of Medicine, Baiturrahmah University, Padang, West Sumatera, Indonesia

Aims: Sorafenib is a multi-tyrosine kinase inhibitor that has been shown to improve survival in patients with advanced and intermediate-stage hepatocellular carcinoma (HCC). Based on the search to date, there is quite a number of studies evaluating the effectiveness and safety of sorafenib 400 mg compared to sorafenib 800 mg on the survival of patients with advanced and intermediate HCC; however, the previous studies have shown varying results. This study aims to determine the effectiveness of sorafenib 400 mg initial dose compared with sorafenib 800 mg initial dose on survival in patients with advanced and intermediate HCC and its side effects in both groups. **Methods:** We performed a systematic search of Randomized Controlled Trials and Non-Randomized Studies of Interventions from PUBMED, EMBASE, EBSCO, PROQUEST, snowballing, global index medicus, GARUDA, SINTA, and several digital libraries of universities in Indonesia until April 30, 2021. Of the 603 articles, there were 5 NRSI studies that met the eligibility criteria. Data were analyzed using Review Manager 5.4.1. **Results:** Sorafenib 400 mg initial dose was significantly more effective on overall survival compared to sorafenib 800 mg initial dose in patients with advanced and intermediate HCC (HR 0.84; 95% CI 0.71–0.98; *P*=0.03). There was no difference in the overall incidence of adverse events to various degrees between the two groups (pooled OR 0.93; 95% CI 0.67–1.30; *P*=0.68). **Conclusions:** Sorafenib 400 mg initial dose has a better effectiveness on overall survival with no significant difference in the incidence of adverse events compared to sorafenib 800 mg initial dose in patients with advanced and intermediate HCC. **Keywords:** Hepatocellular Carcinoma, Sorafenib, Overall Survival, Side Effects

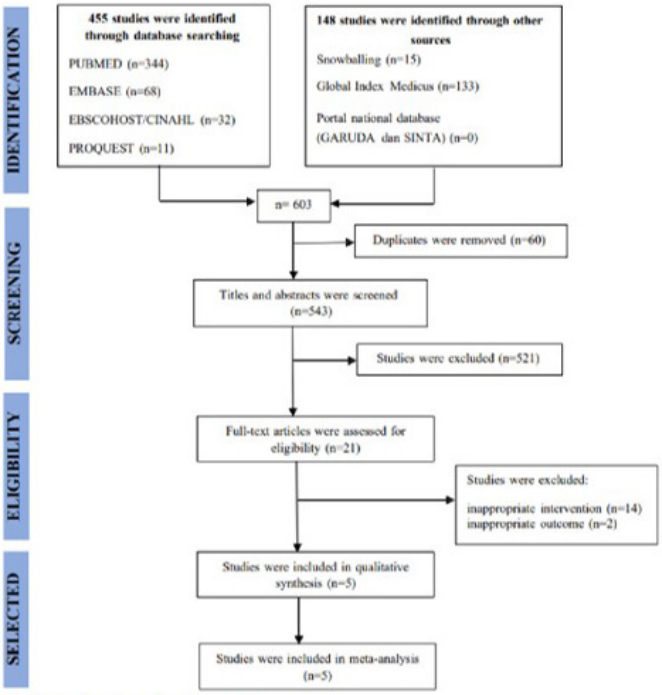


Figure 1. Flowchart of study selection process

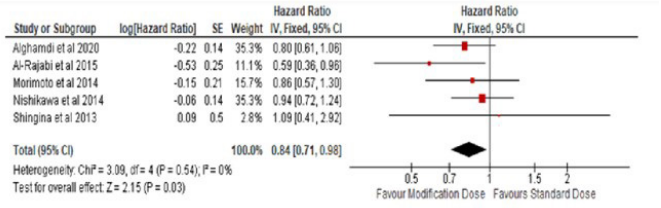


Figure 3. Effectiveness of sorafenib 400 mg initial dose on overall survival

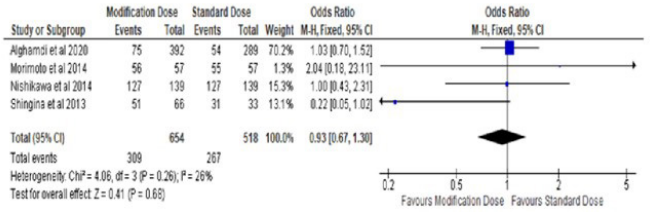


Figure 4. Odds ratio for overall side effects between two groups

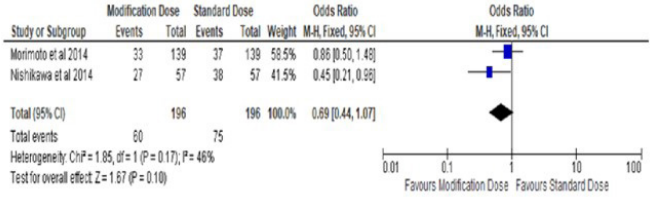


Figure 5. Odds ratio for severe (grade 3 or higher) side effects between two groups

PE-108

Efficacy and Safety of 5-Fluorouracil-Oxaliplatin with Ramucirumab in Patients with Advanced Hepatocellular Carcinoma: A Case Series

Joycelyn Jie Xin Lee, Suat Ying Lee, David Tai

Division of Medical Oncology, National Cancer Centre Singapore, Singapore

Aims: In 2020, combination atezolizumab-bevacizumab (AB) established itself as the standard first-line systemic therapy options for eligible patients with advanced HCC (aHCC)[1]. Many second line options however were approved before the advent of AB[2]. Hence, post-progression on AB, the optimal sequence and use of subsequent treatment lines is less well-studied. The use of single-agent ramucirumab (Ram) post-AB is of unclear benefit[345]. Ram is often safely combined with 5-fluorouracil-oxaliplatin (5FU-Ox) chemotherapy for treatment of other gastrointestinal cancers; and 5FU-Ox also has evidence of activity in HCC. This combination of 5FU-Ox-Ram has been used in nth line aHCC patients in our centre. **Methods:** We performed a retrospective review to describe the preliminary efficacy and safety of 5FU-Ox-Ram in aHCC patients treated at our centre between June 2020 and Feb 2023. **Results:** We identified 5 patients with aHCC who received at least one dose of combination 5FU-Ox-Ram. Of these 5 patients, 3 received 5FU-Ox-Ram after prior AB. Median number of prior lines of treatment was 5 (2 – 6). 3 patients had HBV related disease while 2 patients had non-viral disease. All patients had BCLC C disease, had AFP>400 ng/mL and were Child-Pugh A on treatment initiation. Both patients who were AB naïve had best response of PD while the three patients who had prior AB had best response of disease control 1 PR, 2 SD). 1 patient was still on treatment at time of data cutoff. For the other four patients, median TTP was 85 days (44 – 146). 2 patients had >=G2 cytopenias (G2 thrombocytopenia, G3 neutropenia) lasting more than 7 days, but no episodes of febrile neutropenia or bleeding events occurred. **Conclusions:** 5FU-Ox-Ramucirumab can have efficacy in aHCC patients even after prior AB. Usage however may be associated with risk of cytopenias but is otherwise well tolerated. This regimen deserves further assessment but may require further optimization of dosing. **Keywords:** Hepatocellular Carcinoma, Chemotherapy, Ramucirumab

PE-109

Real-World Efficacy and Safety of Cabozantinib in Korean Patients with Advanced Hepatocellular Carcinoma: A Multicenter Retrospective Analysis

Yeong Hak Bang[1], Choong-kun Lee[2]*, Changhoon Yoo[1]†, Hong Jae Chon[3], Moonki Hong[2], Beodeul Kang[3], Hyung-Don Kim[1], Sook Ryun Park[1], Won-Mook Choi[4], Jonggi Choi[4], Danbi Lee[4], Ju Hyun Shim[4], Kang Mo Kim[4], Young-Suk Lim[4], Han Chu Lee[4], Min-Hee Ryu[1], Baek-Yeol Ryoo[1]†*

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Division of Medical

Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Medical Oncology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea; [4]Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: Cabozantinib, a multiple kinase inhibitor, was recently approved for patients with previously treated unresectable hepatocellular carcinoma (uHCC). We aimed to investigate the safety and efficacy profiles of cabozantinib. **Methods:** This multicenter retrospective study included 110 patients with uHCC who received cabozantinib after progression on other systemic treatments between October 2019 and May 2021. Several prognostic factors were investigated using the multivariable Cox proportional hazard model. **Results:** The median age was 58 years (range, 20-77), and 98 (89.1%) were male. Prior to cabozantinib, all patients were treated with other systemic therapies: sorafenib (n=104, 94.5%) and regorafenib (n=91, 82.7%) were the most commonly used agents. Immune checkpoint inhibitors were previously used in 93 patients (84.5%). Cabozantinib was used beyond the 3rd line of therapy in most patients (n=90, 81.8%). With a median follow-up duration of 11.9 months (95% confidence interval [CI], 10.8-17.2), the median progression-free survival (PFS) was 3.7 months (95% CI, 3.1 and 4.9), and the median overall survival (OS) was 7.5 months (95% CI, 5.5 and 9.5). The disease control rate and overall response rate were 66.3% and 3.6%, respectively. All grade adverse events (AEs) were noted in 83 (75.5%) pts, while grade 3-4 AEs were present in 18 (16.4%) pts: Hand-foot skin reaction was the most common all-grade AEs, and grade 3-4 AEs. The 18 pts (16.4%) underwent dose reduction because of toxicity. In multivariable analysis, the duration of prior systemic treatment < 12 months, previous systemic treatment lines (≥3) were independent factors for poor PFS, while Child-Pugh class B and AFP ≥ 400 were associated with poor OS. The history of immunotherapy did not show a significant association with PFS and OS. **Conclusions:** Cabozantinib showed consistent efficacy outcomes with prior phase III trial, although this was used as later-line therapy for patients who were refractory to multiple systemic treatments, including immune checkpoint inhibitors. **Keywords:** Cabozantinib, Liver Cancer

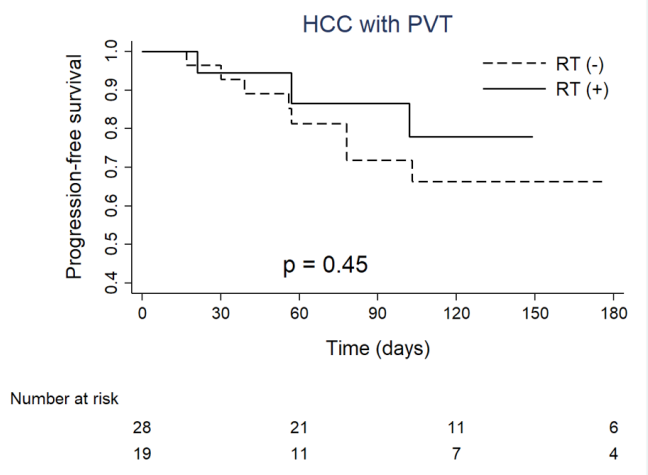
PE-110

Radiotherapy Combined with Atezolizumab Plus Bevacizumab for Hepatocellular Carcinoma with Portal Vein Tumor Thrombus: Progression-Free Survival Analysis

Yunjeong Lee, Jihye Kim, Gwang Hyeon Choi, Eun Sun Jang, Sook-Hyang Jeong, Jin-Wook Kim

Department of Medicine, Seoul National University Bundang Hospital and Seoul National University College of Medicine, Republic of Korea

Aims: Based on the IMbrave150 trial, the combination of atezolizumab and bevacizumab has been the first-line standard of care for advanced hepatocellular carcinoma. However, the efficacy of the combination regimen has been unsatisfactory in HCC patients with portal vein tumor thrombosis (PVTT) indicating a need for novel therapeutic options. The use of concomitant external beam radiation therapy may increase local tumor control rate, but this hypothesis has not been rigorously tested. Here, we test the efficacy of the concurrent radiotherapy with the combination of atezolizumab/bevacizumab comparing to the combination regimen alone. **Methods:** This retrospective study included 133 patients with the combination of atezolizumab and bevacizumab with or without concurrent radiotherapy from June 2003 to February 2023. The presence of portal vein thrombosis was defined as the intraluminal filling defect in portal venous system on computed tomography. The modified response evaluation criteria in solid tumors (RECIST) on CT/MRI images was used to assess treatment responses of each therapy. The progression-free survival (PFS) was assessed by Kaplan Meier analysis and Cox regression. **Results:** A total of 56 patients received of atezolizumab and bevacizumab for HCC with portal vein invasion. The 6-month PFS was 70.6% and combined radiation therapy did not significantly increase the survival (HR = 0.40, 95% CI = 0.10 – 1.65; *P*=0.45; FIg). **Conclusions:** Addition of external beam radiation did not significantly increase local tumor response rate in HCC patients with portal vein invasion. **Keywords:** Hepatocellular Carcinoma, Portal Vein Tumor Thrombus, Radiotherapy, Atezolizumab Plus Bevacizumab



PE-111

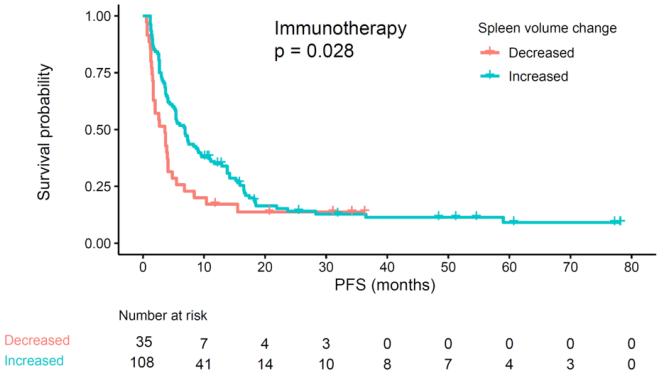
Changes in Splenic Volume as a Predictor of Response and Survival in Advanced Hepatocellular Carcinoma Patients Receiving Immunotherapy or Sorafenib

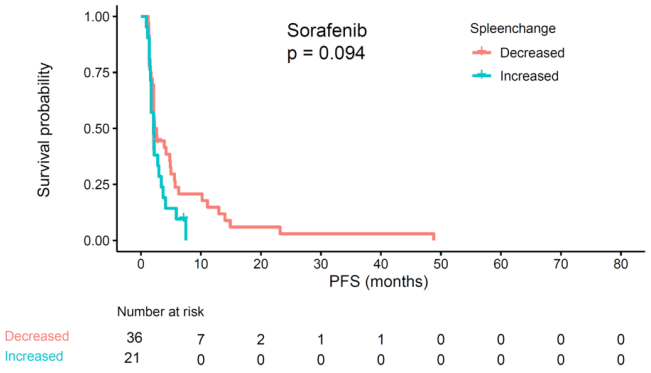
Bang-Bin Chen[1], Yu-Yun Shao[2]

[1]Department of Medical Imaging, National Taiwan University Hospital, Taipei City, Taiwan; [2]Department of Oncology, National Taiwan University Hospital, Taipei City, Taiwan

Aims: An association between immunotherapy and an increase in splenic volume (SV) has been described. The purpose of this

study was to investigate whether changes in splenic volume are associated with response to treatment and progression-free survival (PFS) among patients with advanced hepatocellular carcinoma (HCC) after immunotherapy or sorafenib treatment. **Methods:** We retrospectively analyzed patients with advanced HCCs receiving immunotherapy (n = 143) or first-line sorafenib (n= 57) who were prospectively enrolled at our tertiary care center. SV was assessed before treatment and the first follow-up CT (1~3 months) by outlining the splenic contour on every relevant image and the total volume was summated. The demographic, clinical, and imaging characteristics of the enrolled patients were collected. Tumor assessment was performed according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Disease control rate (DCR), objective response rate (ORR), and durable clinical benefit (DCB, stable disease lasting more than 6 months) were assessed by the best radiological response. The PFS was calculated from the date of treatment to the date of progression or the last follow-up. The Kaplan–Meier method was used to estimate survival outcomes, and the log-rank test was used to evaluate the association of potential predictors of PFS in univariate analysis. Cox proportional hazards regression models assessing hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were used to determine the effect of the risk stratification. A two-sided P-value of< 0.05 was considered statistically significant. **Results:** An increase in SV between the initiation of treatment and the first follow-up was observed in 108/143 (75.5%) patients in the immunotherapy group, and 21/57 (36.8%) in the sorafenib group. The response rate was 29.4% in the immunotherapy group and 7% in the sorafenib group. In the immunotherapy group, patients with increased SV had higher DCR (*P*=0.041) and DCB (*P*=0.01) than those with decreased SV. In addition, increased spleen volume was associated with longer PFS in the immunotherapy group in the univariate (*P*=0.029, HR = 0.63, 95% CI = 0.42-0.95) and multivariate analysis (*P*=0.031, HR = 0.59, 95% CI = 0.36-0.95). However, In the sorafenib group, an increase in spleen volume was not associated with treatment response and may be associated with shorter PFS (*P*=0.094). **Conclusions:** A large proportion of patients showed an increase in SV after the initiation of immunotherapy. An increase in SV is a favorable prognostic factor in the immunotherapy group but may be a poor prognostic factor in the sorafenib group. CT splenic volume change may be used as a potentially simple biomarker of response to immunotherapy. **Keywords:** Hepatocellular Carcinoma, Immunotherapy, Sorafenib, Survival





PE-112

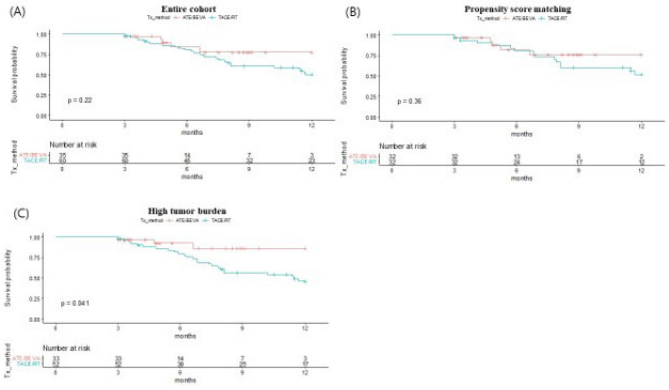
A Real-World Comparative Analysis of Atezolizumab Plus Bevacizumab and Transarterial Chemoembolization Plus Radiotherapy in Hepatocellular Carcinoma Patients with Portal Vein Tumor Thrombosis

Soon kyu Lee[1,2], Jung Hyun Kwon[1,2], Sung Won Lee[2,3], Hae Lim Lee[2,3], Hee Yeon Kim[2,3], Chang Wook Kim[2,4], Do Seon Song[2,5], U Im Chang[2,5], Jin Mo Yang[2,5], Soon Woo Nam[1,2], Seok-Hwan Kim[2,6], Myeong Jun Song[2,6], Ji Hoon Kim[2,4], Ahlim Lee[2,5], Hyun Yang[2,7], Si Hyun Bae[2,7], Ji Won Han[2,8], Heechul Nam[2,4], Pil Soo Sung[2,8], Jeong Won Jang[2,8], Jong Young Choi[2,8], Seung Kew Yoon[2,8]*

[1]Division of Hepatology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [3]Division of Hepatology, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [4]Division of Hepatology, Department of Internal Medicine, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [5]Division of Hepatology, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [6]Division of Hepatology, Department of Internal Medicine, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [7]Division of Hepatology, Department of Internal Medicine, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [8]Division of Hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Immune checkpoint inhibitors (ICI), such as atezolizumab plus bevacizumab (Ate/Bev), have revolutionized treatment strategy for advanced hepatocellular carcinoma (HCC). Transarterial chemoembolization plus radiotherapy (TACE/RT) has also shown notable outcomes in HCC patients with portal vein tumor thrombosis (PVTT). In this study, we compared the treatment outcomes of Ate/Bev and TACE/RT in HCC patients with PVTT. **Methods:** Between June 2009 and October 2022, we consecutively

enrolled 855 HCC patients with PVTT who were treated at the Catholic University of Korea. Among them, 760 patients were excluded due to concurrent metastasis, treatment with tyrosine kinase inhibitors, ICI combined with RT, and follow-up loss within 3 months. Finally, 95 patients (35 in the Ate/Beva group and 60 in the TACE/RT group) were analyzed in our study. The primary outcome was one-year survival. Secondary outcomes were one-year progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR). Treatment outcomes were assessed using propensity-score matching (PSM) and multiple subgroup analyses. **Results:** The median age was 59.2 years, and 86 patients were male. The majority of patients (n=81, 85.3%) had Child-Turcotte-Pugh class A liver function. The TACE/RT group had higher total bilirubin and alanine transaminase levels than the Ate/Bev group. The size and number of intrahepatic HCC and the level of tumor markers were similar between the TACE/RT and Ate/Bev groups. The TACE/RT and the Ate/Bev group had similar ORR (40.0% vs. 37.1%, *P*=0.954, respectively) and DCR (78.3% vs. 71.4, *P*=0.610, respectively). The TACE/RT and Ate/Bev group had similar one-year survival rates in the entire population (*P*=0.22, Figure A) and after PSM (*P*=0.36, Figure B). Moreover, both groups showed similar one-year PFS. In patients with high tumor burden (intrahepatic HCC size ≥7 cm or multiple intrahepatic HCC or main PVTT), the Ate/Bev group had better one-year survival than the TACE/RT group (*P*=0.041, Figure C). **Conclusions:** Both Ate/Bev and TACE/RT treatments are effective in HCC patients with PVTT. Furthermore, in patients with high tumor burden, Ate/Bev treatment provides better survival than TACE/RT therapy. **Keywords:** Hepatocellular Carcinoma, Portal Vein Thrombosis, Response, Survival, Progression Free Survival, Immune Checkpoint Inhibitors, Transarterial Chemoembolization, Radiotherapy



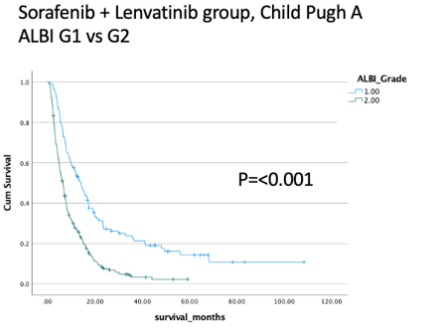
PE-113

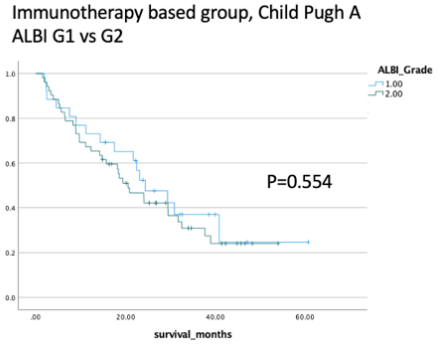
Is Modified Albumin-Bilirubin (mALBI) Grade Prognostic for All Hepatocellular Carcinoma Patients Who Receive Systemic Treatment?

Kevin Mok[1], Landon Chan[2], Frankie Mo[2], Leung Li[1], Kwan Hung Wong[1], Nicole Yim[2], Stephen L. Chan[2]

[1]Department of Clinical Oncology, Prince of Wales Hospital, Hong Kong; [2]Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong

Aims: Child Pugh A (CP-A) patients with HCC who receive systemic therapy represent a heterogenous population. mALBI can potentially provide further prognostic stratification in these patients. Real world data on the predictive value of mALBI in newer HCC systemic therapies such as immunotherapy is limited. **Methods:** All (463) patients with HCC with baseline CP-A and mALBI G1-2, who received systemic treatment between Jan 2008 to Dec 2021 from a tertiary center were included. Those who received unapproved first-line treatment except when used in combination with immunotherapy (IO) were excluded. Kaplan-Meier and log-rank test were used for survival analysis. Cox regression was used for hazard ratio calculation. **Results:** Of the 385 patients who received first-line multikinase inhibitors (MKI) sorafenib or lenvatinib, 111 (28.8%) were baseline mALBI G1 and 274 (71.2%) were G2, of which 96 were G2a and 178 were G2b. Of the 77 who received first line IO-based treatment (monotherapy or in combination with MKI/anti-VEGF/IO), 26 (33.3%) were G1 and 52 (66.7%) were G2, of which 24 were G2a and 28 were G2b. For the MKI group, patients with G1 had better median overall survival (OS) than G2, 14.1 mo (10.7-17.5) versus 6.4 mo (5.5-7.3), *P*=<0.001, HR 0.46 (0.36-0.59). G2a patients had numerically superior mOS of 6.9 mo (5.1-8.7) vs G2b of 5.8 mo (4.6-7.1), *P*=0.085. For the IO based group, patients with G1 had similar median OS to G2, 24.4 mo (14.8-34.0) vs 20.6 mo (13.3-27.8), *P*=0.554. There was no difference in OS between G2a 20.9 mo (5.0-36.9) vs G2b patients 19.4 mo (12.3-26.5), *P*=0.956, and between G1 and 2b, *P*=0.611. **Conclusions:** mALBI was not a significant prognostic factor for CP-A HCC patients who receive first-line IO-based treatment. However, mALBI G1 vs 2 was significantly prognostic for patients who receive first-line MKI and may be prognostic for G2a vs G2b. **Keywords:** ALBI, Hepatocellular Carcinoma, Treatment, Modified ALBI, HCC, Immunotherapy





PE-114

Real-World Outcomes of Patients with Unresectable Intrahepatic Cholangiocarcinoma Treated with Radiotherapy, Lenvatinib, Anti-PD-1 Antibody, and GEMOX Chemotherapy

Qianqian Zhao, Zhaochong Zeng

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

Aims: This study aimed to evaluate the real-world outcomes of patients with recurrent, metastatic, or unresectable ICC who received quadruple therapy involving radiotherapy (RT), Lenvatinib, anti-PD-1 antibody, and GEMOX (oxaliplatin and gemcitabine) chemotherapy. **Methods:** Forty-one patients with recurrent, metastatic, or unresectable ICC who received quadruple therapy at Zhongshan Hospital, Fudan University, between September 2018 and May 2022 were enrolled. The primary outcomes were progression-free survival (PFS), overall survival (OS), and treatment-related adverse events (AEs). **Results:** All 41 patients had completed the prescribed chemotherapy, with a median of 6 cycles (IQR 6-8) of chemotherapy received. The median exposure times to Lenvatinib and anti-PD-1 antibody were 10.00 months (IQR, 6.50-18.00) and 11.50 months (IQR, 7.25-17.50), respectively. The median time interval between radiotherapy and systemic therapy was 7 months (IQR, 4-10). After a median follow-up period of 15 months, disease progression was diagnosed in 36 patients (87.8%), and 18 patients (43.9%) died, while three patients were lost to follow-up. The causes of death included liver failure induced by intrahepatic tumor progression (n=6, 33.3%), distant metastases (to the lungs or brain) (n=6, 33.3%), abdominal lymph node metastases (n=3, 16.7%), cancer cachexia (n=2, 11.1%), and unknown cause (n=1, 5.6%). Detailed information on the quadruple therapy used in our study population and disease progression was shown in Figure 1. The median PFS was 11 months (95% CI, 9.2 to 12.8), and the median OS was 35 months (95% CI, 17.0 to 52.0) (Figure 2). The 12-month PFS rate was 81.3% (95% CI, 68.8%-93.8%), and the 12-month OS rate was 65.9% (95% CI, 51.4%-80.4%). Thirteen patients (31.7%) experienced Grade 3 or higher AEs. No radiation-induced liver disease or treatment-related deaths were observed. **Conclusions:** Our results demonstrate that the combination of RT, Lenvatinib, anti-PD-1 antibody, and GEMOX was well-tolerated and showed sustained clinical efficacy in patients with unresectable ICC. **Keywords:** Intrahepatic Cholangiocarcinoma, Radiotherapy, Anti-PD-1 Antibody, Lenvatinib, GEMOX Chemotherapy

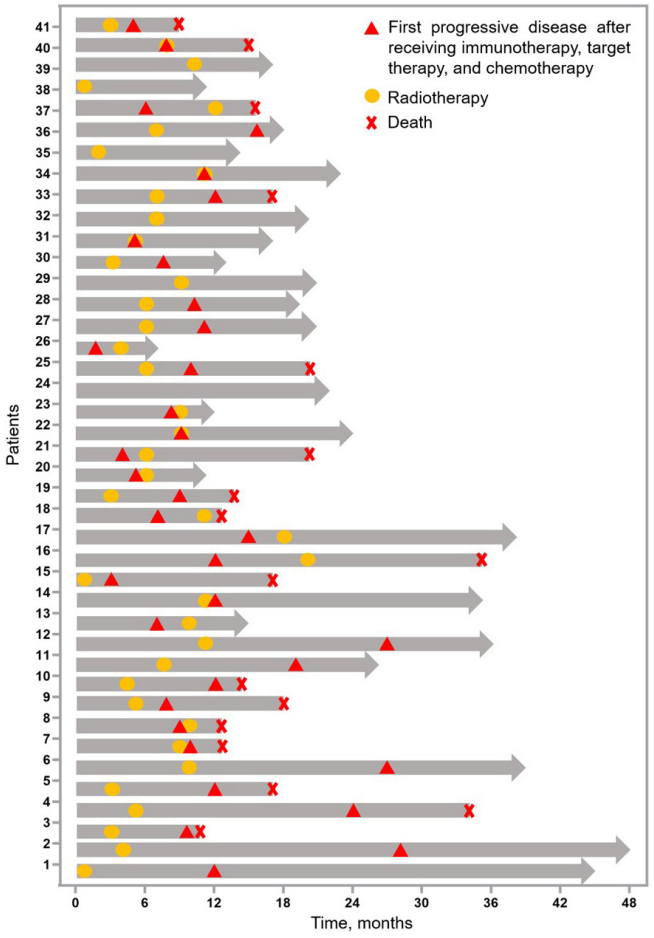


Figure 1. Swimming plot visualizing the treatment and response details for all patients.

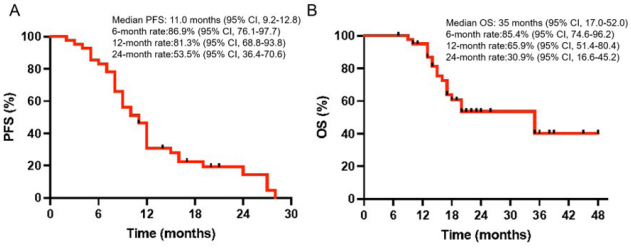


Figure 2. Survival outcomes. (A) Progression-free survival (PFS) (n=41). (B) Overall survival (OS) (n=41).

PE-115

Hepatic Arterial Infusion Chemotherapy Combined with Anti-PD-1 /PD-L1 Immunotherapy and Molecularly Targeted Agents for Advanced Hepatocellular Carcinoma: A Real World Study in China

Kai Zhang, Weihao Zhang,, Changfu Liu, Wei Gao, Tongguo Si, Qiang Zou, Zhi Guo, Xueling Yang, Mei Li, Dongming Liu, Han Mu, Huikai Li, Wenge XING, Haipeng Yu

Tianjin Medical University Cancer Institute and Hospital, China

Aims: Molecular targeted therapy combined with immunotherapy significantly improves the prognosis of patients with advanced liver cancer. Additionally, hepatic arterial infusion chemotherapy (HAIC) can improve the prognosis of patients with advanced liver cancer. This real-world study aimed to evaluate the clinical efficacy and safety of HAIC combined with molecular targeted therapy and immunotherapy in the treatment of primary unresectable hepatocellular carcinoma (uHCC). **Methods:** A total of 135 patients with uHCC were enrolled in this study. Progression-free survival (PFS) was the primary endpoint. The efficacy of the combination therapy was assessed based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines. Overall survival (OS), adverse events (AEs) and surgical conversion rate were the secondary endpoints. Univariate and multivariate Cox regression analyses were performed to examine independent prognostic factors. For sensitivity analysis, inverse probability weighting (IPW) was used to balance the influence of the tested confounding factors between groups to verify the robustness of conversion surgery for survival benefits. **Results:** The median number of therapies was three. Approximately 60% of the patients had portal vein tumour thrombosis (PVTT). The most common targeted drugs were lenvatinib and bevacizumab, whereas the most common immunotherapy drug was sintilimab. The overall objective response rate (ORR) was 54.1%, and the disease control rate (DCR) was 94.6%. A total of 97 (72%) patients experienced AEs of grades 3–4. Fatigue, pain and fever were the most common symptoms of grade 3-4 AEs. The median PFS was 28 months and 7 months in the successful and unsuccessful conversion groups, respectively. The median OS was 30 months and 15 months in the successful and unsuccessful conversion groups, respectively. Successful conversion surgery, number of interventions, PVTT and total bilirubin levels were independent prognostic factors for OS. After IPTW, no standardised differences exceeding 0.1 were found. IPW-adjusted Kaplan–Meier curves showed that successful conversion surgery was an independent prognostic factor for both PFS and OS. **Conclusions:** Patients with primary uHCC undergoing HAIC combined with immunotherapy and molecular targeted therapy have a higher tumour regression rate and the side effects are manageable. Patients undergoing surgery after combination therapy have survival benefits. **Keywords:** Hepatic Arterial Infusion Chemotherapy, Anti-PD-1 /PD-L1 Immunotherapy, Molecularly Targeted Agents, Advanced Hepatocellular

PE-116

Final Results of RENOBATE: Multicenter Phase 2 Trial of First-Line Regorafenib Plus Nivolumab for Unresectable Hepatocellular Carcinoma (uHCC)

Changhoon Yoo[1], Baek-Yeol Ryoo[1], Hyung-Don Kim[1], Min-Hee Ryu[1], Beodeul Kang[2], Hong Jae Chon[2], Jung Yong Hong[3], Ho Yeong Lim[3]

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Medical Oncology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea; [3]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Aims: The immunomodulatory effect of regorafenib may enhance the anti-tumor activity of nivolumab in patients with uHCC. We report results from a phase 2 study of regorafenib plus nivolumab as first-line therapy in patients with uHCC. **Methods:** In this open-label, multi-center, single-arm study, patients with >19 years, ECOG PS 0 or 1, BCLC stage B or C, and no prior systemic therapy were eligible. Patients received intravenous nivolumab 480 mg, every 4 weeks, and oral regorafenib 80 mg daily, 3 weeks on/1 week off, every 4 weeks. Tumor response was evaluated per RECIST v1.1, every 8 weeks (fixed schedule). Primary endpoint was overall response rates (ORR) per RECIST v1.1. Secondary endpoints were progression-free survival (PFS), overall survival (OS), ORR per mRECIST, and safety profile per NCI-CTCAE v5. **Results:** A total of 42 patients were enrolled between JUL-2020 and JAN-2021. Median age was 61 years (range, 40-79), and 31 patients (73.8%) were male. Most patients had BCLC C stage (n=38, 90.5%) and hepatitis B virus infection as an etiology of HCC (n=30, 71.4%). Baseline serum AFP levels were >400 ng/mL in 17 patients (40.5%). ORR per RECIST v1.1 was 31.0% (CR 1 [2.4%] and PR 12 [28.6%]), and ORR per mRECIST was 33.3% (CR 2 [4.8%] and PR 12 [28.6%]). With median follow-up duration of 11.1 months (95% CI, 6.11-14.0 months), median PFS was 7.4 months (95% CI, 4.2-13.0 months) and median OS was not reached. The 1-year OS rate was 80.5% (95% CI, 63.0-90.3%). In patients who achieved CR/PR per RECIST v1.1, duration of response was median 10.3 months (95% CI, 8.2-13.9 months). Most common adverse events were hand-foot skin reaction (n=14, 33.3%), skin rash (n=12, 28.5%), and alopecia (n=11, 26.2%). **Conclusions:** Regorafenib plus nivolumab shows promising efficacy outcomes in uHCC. There were no unexpected safety signals and most of toxicities were manageable. Biomarker analysis is ongoing. **Keywords:** Hepatocellular Carcinoma, Regorafenib-Nivolumab, First-Line Treatment

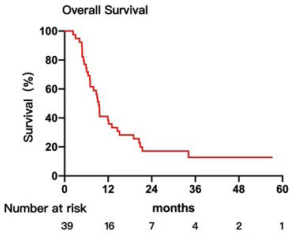
PE-117

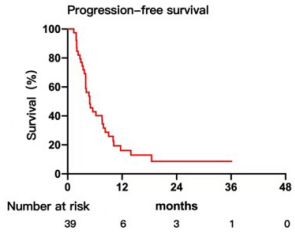
Effectiveness and Safety of Lenvatinib, a PD-1 Inhibitor Plus Radiotherapy, in Patients with Hepatocellular Carcinoma with Main Portal Vein Tumour Thrombus: Real-World Experience from a Tertiary Center

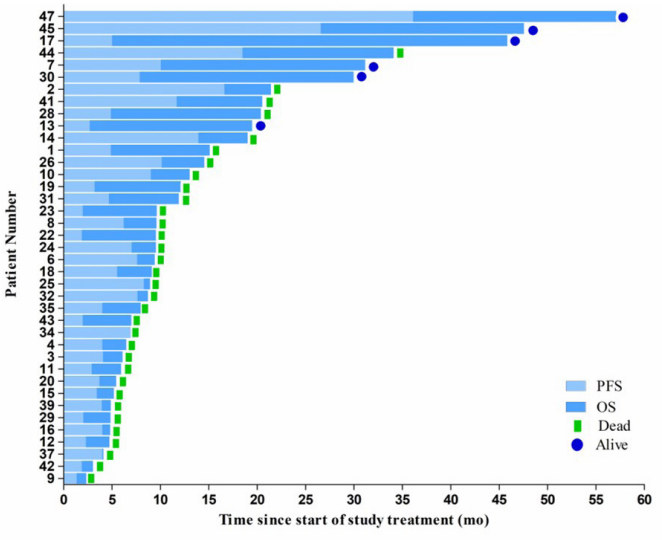
Guang Xin Li[1], Ying Zhao[1], Ke Ren Li[2], Gong Li[1]

[1]Department of Radiation Oncology, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China; [2]Hepatopancereatobiliary Center, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China

Aims: Patients with hepatocellular carcinoma (HCC) with portal vein tumour thrombus (PVTT), especially type Vp-4, usually have a poor prognosis. However, the vast majority of phase III clinical trials exclude this population based on the inclusion criteria. Lenvatinib plus a PD-1 inhibitor has shown promising antitumour activity and tolerable safety in patients with unresectable HCC in Asian populations. Radiotherapy has also demonstrated high response rates and favorable survival for HCC patients with PVTT. This study aimed to explore the preliminary clinical efficacy and safety of lenvatinib plus a PD-1 inhibitor combined with radiotherapy for HCC patients with main portal vein tumour thrombus. **Methods:** Between 1 March 2018 and 31 October 2020, HCC patients with main PVTT who received lenvatinib plus a PD-1 inhibitor (pembrolizumab, nivolumab or sintilimab) combined with radiotherapy from Beijing Tsinghua Changgung Hospital in China were reviewed for eligibility. The efficacy was evaluated by the survival and PVTT response rate, and the safety was evaluated by the frequency of key adverse events (AEs). **Results:** In total, 39 eligible HCC patients with type Vp-4 PVTT who received triple therapy were included in this study. The 2-year OS rate was 15.4%, which was the primary end-point of our study. The median overall survival (OS) and progression-free survival (PFS) were 9.4 months (range 2.3 to 57.1) and 4.9 months (range 1.4 to 36.1), respectively. The objective response rate (ORR) of PVTT based on mRECIST was 61.5%. AFP dropped to normal 3 months after radiotherapy and was an independent risk factor associated with OS. All AEs were controlled, and no treatment-related deaths occurred. **Conclusions:** Lenvatinib plus PD-1 inhibitor combined with radiotherapy had a significant therapeutic effect and manageable AEs in HCC patients with type Vp-4 PVTT and may be a potential treatment option for advanced HCC. **Keywords:** Hepatocellular Carcinoma, Portal Vein Tumour Thrombus, Lenvatinib, PD-1 Inhibitor, Radiotherapy







PE-118

Arterial Chemotherapy in Advanced Hepatocellular Carcinoma: An Evolutionary Trajectory, Pooled Outcomes and Cost-Effectiveness Analysis

Ming Zhao[1,2,3], Qi-Feng Chen[1,2,3], Ning Lyu[1,2,3]

[1]Department of Minimally Invasive Interventional Therapy, Liver Cancer Study and Service Group, Sun Yat-sen University Cancer Center, Guangzhou, China; [2]State Key Laboratory of Oncology in South China, Guangzhou, Guangdong, China; [3]Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China

Aims: To conduct a bibliometric analysis to explore the historical development of hepatic artery infusion chemotherapy (HAIC), a pooled analysis to evaluate the outcomes of HAIC in advanced hepatocellular carcinoma (HCC), and a Markov model to evaluate the cost-effectiveness of HAIC. **Methods:** Relevant documents were collected from the Web of Science Core Collection until October 2022 and analyzed using R bibliometrix. Two international clinical trial registered platforms, ClinicalTrials.gov and ChiCTR.org, were searched for oxaliplatin-based HAIC utilization in HCC. A total of 845 patients treated with HAIC or its combination therapy from 17 pre-registered studies were analyzed. A Markov model was applied in the cost-effectiveness analysis. **Results:** We identified 539 studies and derived the evolutionary trajectory of HAIC from the perspective of scientometry. Contributions of publications were presented. Conversion therapy, Folfox, oxaliplatin and immunotherapy became new research foci. A total of 88 registered trials were identified and a comprehensive landscape of these trials was provided. This individual patient data meta-analysis suggested that, following HAIC and its combinational therapy, the overall survival and progression free survival were 13.7 and 7.0 months, respectively. Objective response rate and disease control rate reached 0.34 and 0.80, respectively. Adverse events were manageable. HAIC resulted in an incremental cost-effectiveness

ratio (ICER) of $12,242.56 per quality-adjusted life year compared to sorafenib. This ICER was lower than the willingness-to-pay threshold, and the results remained robust across a wide range of parameters, indicating that HAIC was a cost-effective treatment strategy. **Conclusions:** This study illustrates the evolutionary trajectory of HAIC from the perspective of scientometry. The efficacy outcomes of HAIC in the treatment of advanced HCC were verified with manageable safety profiles. HAIC is a cost-effective treatment strategy when compared to sorafenib. Further trials regarding HAIC implementation are emerging, and more effort is required to improve the quality of trials. **Keywords:** Hepatic Arterial Infusion Chemotherapy, Hepatocellular Carcinoma, Bibliometric, Clinical Trial, Efficacy, Safety, Cost-Effectiveness

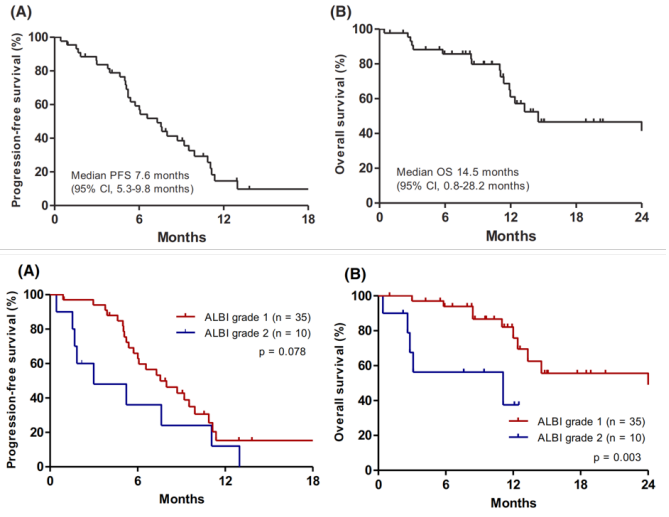
PE-119

Efficacy and Safety of Lenvatinib in Patients with Recurrent Hepatocellular Carcinoma after Liver Transplantation

Kyunghye Bang[1], Andrea Casadei-Gardini[2], Changhoon Yoo[1], Young-In Yoon[3], Deok-Bog Moon[3], Ki-Hun Kim[3], Gi-Won Song[3], Stephen L. Chan[4], Baek-Yeol Ryoo[1], Sung-Gyu Lee[3]

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Medical Oncology, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute, Milan, Italy; [3]Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [4]State Key Laboratory of Translational Oncology, Department of Clinical Oncology, Sir YK Pao Centre for Cancer, The Chinese University of Hong Kong, Hong Kong

Aims: Lenvatinib is approved for the treatment of patients with metastatic or recurrent hepatocellular carcinoma (HCC); however, clinical outcomes of lenvatinib therapy in patients with post-liver transplantation (LT) HCC recurrence remain unclear. We investigated the efficacy and safety of lenvatinib in patients with post-LT HCC recurrence. **Methods:** This multinational, multicenter, retrospective study included 45 patients with recurrent HCC after LT who received lenvatinib at six institutions in three countries (Korea, Italy, and Hong Kong) from June 2017 to October 2021. **Results:** At the time of lenvatinib initiation, 95.6% (n = 43) of patients had Child–Pugh A status, and 35 (77.8%) and 10 (22.2%) participants were classified as having albumin–bilirubin (ALBI) grades 1 and 2, respectively. The objective response rate was 20.0%. With a median follow-up duration of 12.9 months (95% confidence interval [CI]: 11.2–14.7), the median progression-free survival and overall survival (OS) were 7.6 (95% CI: 5.3–9.8) months (Figure 1A), and 14.5 (95% CI: 0.8–28.2) months (FIgure 1B), respectively. Patients with ALBI grade 1 showed significantly better OS (52.3 months, [95% CI: not assessable]) than patients with ALBI grade 2 (11.1 months [95% CI: 0.0–30.4 months], *P*=0.003) (Figure 2B). The most common adverse events were hypertension (n = 25, 55.6%), fatigue (n = 17, 37.8%), and anorexia (n = 14, 31.1%). **Conclusions:** Lenvatinib showed consistent efficacy and toxicity profiles in patients with post-LT HCC recurrence that were comparable to those reported from previous studies among non-LT HCC patients. The baseline ALBI grade correlated with better OS in post-LT lenvatinib-treated patients. **Keywords:** Hepatocellular Carcinoma, Lenvatinib, Liver Transplantation, Chemotherapy, Albumin-Bilirubin Grade



PE-120

Clinical Outcomes of Immune Checkpoint Inhibitors in Unresectable or Metastatic Combined Hepatocellular-Cholangiocarcinoma

Yoon Jung Jang[1,2], Eo Jin Kim[3], Hyung-Don Kim[1], Kyu-Pyo Kim[1], Min-Hee Ryu[1], Sook Ryun Park[1], Won-Mook Choi[4], Danbi Lee[4], Jonggi Choi[4], Ju Hyun Shim[4], Kang Mo Kim[4], Young-Suk Lim[4], Han Chu Lee[4], Baek-Yeol Ryoo[1], Changhoon Yoo[1]

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Hematology/Oncology, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, Seoul, Republic of Korea; [3]Department of Hematology/Oncology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [4]Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: Immune checkpoint inhibitors (ICIs) have been demonstrated to be effective for unresectable or metastatic hepatocellular carcinoma (HCC) or cholangiocarcinoma (CCA) in prior prospective trials. However, the clinical outcomes of ICIs in patients with combined HCC-CCA (cHCC-CCA) have not been investigated. Accordingly, we retrospectively evaluated the effectiveness and safety of ICIs in patients with unresectable or metastatic cHCC-CCA. **Methods:** Among 101 patients with histologically documented cHCC-CCA who received systemic therapy, 25 received ICIs between January 2015 and September 2021 and were included in the current analysis. Overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, progression-free survival (PFS), overall

survival (OS), and adverse events (AEs) were retrospectively evaluated. **Results:** The median age was 64 years (range 38–83) and 84% (n=21) of patients were males. Most patients had Child-Pugh A liver function (n=22, 88%) and hepatitis B virus infection (17, 68%). Nivolumab (n=17, 68%) was the most frequently used ICI, followed by pembrolizumab (n=5, 20%), atezolizumab plus bevacizumab (n=2, 8%), and ipilimumab plus nivolumab (n=1, 4%). All patients, except one, had previously received systemic therapy; median two lines (1–5 lines) of systemic therapy were administered prior to ICIs. With a median follow-up duration of 20.1 months (95% CI, 4.9–35.2 months), the median PFS was 3.5 months (95% CI, 2.4–4.8 months), and the median OS was 8.3 months (95% CI, 6.8–9.8 months). The ORR was 20.0% (n=5, nivolumab for 2 patients, pembrolizumab for 1, atezolizumab plus bevacizumab for 1, and ipilimumab plus nivolumab for 1) and the duration of response was 11.6 months (95% CI, 11.2– 12.0 months) **Conclusions:** ICIs displayed clinical anti-cancer effectiveness, aligning with the results of prior prospective studies for HCC or CCA. Further international studies are required to define the optimal strategies for managing unresectable or metastatic cHCC-CCA. **Keywords:** Combined HCC-CCA, Immune Checkpoint Inhibitor

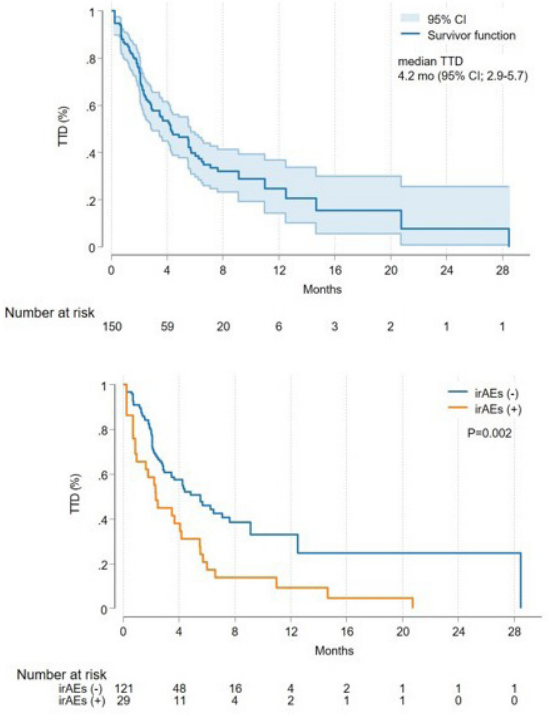
PE-121

Analysis of Immune-Related Adverse Events and Time-to-Treatment Discontinuation of Atezolizumab and Bevacizumab in Patients with Hepatocellular Carcinoma: A Multicenter Cohort Study

Heechul Nam[1,2], Ji won Han[1,2], Soon Kyu Lee[1,2], Hyun Yang[1,2], Hae Lim Lee[1,2], Pil Soo Sung[1,2], Hee Yeon Kim[1,2], Myeong Jun Song[1,2], Jung Hyun Kwon[1,2], U Im Chang[1,2], Chang Wook Kim[1,2], Si Hyun Bae[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2], Jin Mo Yang[1,2], and Jeong Won Jang[1,2]*

[1]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]The Catholic Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Pragmatic endpoints, such as time-to-treatment discontinuation (TTD), defined as the duration from starting a medication to the date of treatment discontinuation or death, have been proposed as a potential efficacy endpoint for real-world practice. This study aims to analyze the frequency and severity of immune-related adverse events (irAEs) and TTD in patients with hepatocellular carcinoma (HCC) receiving Atezolizumab and Bevacizumab (A+B) treatment. **Methods:** This is a retrospective, multi-center study that includes consecutive HCC patients received A+B treatment from September 2020 to December 2022. The neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) were used as surrogate markers of inflammation and immune cell reservoir. The prognostic nutritional index (PNI) was calculated using serum albumin levels, neutrophil count, and lymphocyte count was used for nutritional status evaluation. The associations of factors on TTD were analyzed using Cox proportional hazards regression and multivariable logistic regression models. **Results:** The study included 150 patients, with a median age of 64 years, of whom 85.3% were male and 69.3% were classified as having HCC due to viral hepatitis etiology. Overall, 34.0% patients experienced grade 3 or higher treatment-related adverse events, with 19.3% reported irAEs. The incidence rates of irAEs were hepatitis (10.7%), fatigue (2.0%), colitis (2.0%), pneumonitis (2.0%), cholangitis (1.3%), myositis (0.7%), nephritis (0.7%), skin rash (0.7%), and anaphylactic shock (0.7%). Median TTD was 4.2 months (95% CI, 2.9-5.7). Occurrence of irAEs, low PNI, and ALBI grade ≥2 were identified as significant indicators of TTD in the univariate analysis. The occurrence of irAEs (HR, 1.839; 95% CI, 1.162-2.909, *P*=0.009) was identified as the only independent predictor of TTD. TTD showed a strong correlation with the OS (r=0.737, *P*<0.001) and PFS (r=0.876, *P*<0.001), respectively. **Conclusions:** The current multicenter retrospective cohort study reported the characteristics of irAEs in real-world clinical practice. IrAEs occurrence is an independent prognostic factor for TTD, which is strongly correlated with both OS and PFS. **Keywords:** HCC, Systemic Chemotherapy, TTD, Immune-Related Adverse Events



PE-122

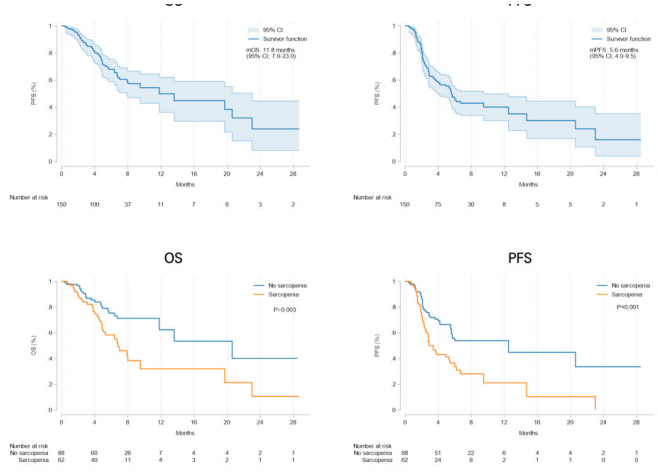
Sarcopenia Predicts Outcomes in Patients with Hepatocellular Carcinoma Treated with Atezolizumab and Bevacizumab: A Multicenter Cohort Study

Heechul Nam[1,2], Ji won Han[1,2], Soon Kyu Lee[1,2], Hyun Yang[1,2], Hae Lim Lee[1,2], Pil Soo Sung[1,2], Myeong Jun Song[1,2], Jung Hyun Kwon[1,2], Jeong Won Jang[1,2], U Im Chang[1,2], Chang Wook Kim[1,2], Si Hyun Bae[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2], Jin Mo Yang[1,2], Hee Yeon Kim[1,2]*

[1]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]The Catholic Liver Research Center, College of Medicine, The Catholic University

of Korea, Seoul, Republic of Korea

Aims: The combination of atezolizumab and bevacizumab (A+B) is now the standard of care for the first-line systemic treatment of unresectable hepatocellular carcinoma (HCC). This study aims to determine the potential prognostic value of sarcopenia and inflammatory biomarker in predicting the outcome of A+B treatment. **Methods:** This is a retrospective, multi-center study that includes consecutive HCC patients received A+B treatment from September 2020 to December 2022. Pre-treatment computed tomography imaging was used to measure the cross-sectional area of skeletal muscle at the third lumbar vertebra, and the skeletal muscle index (SMI) was calculated by normalizing by patient`s height. The neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) were used as surrogate markers of inflammation and immune cell reservoir. The associations of factors on overall survival (OS) and progression free survival (PFS) were analyzed using Cox proportional hazards regression and multivariable logistic regression models. **Results:** The study included 150 patients, with a median age of 64 years, of whom 85.3% were male and 69.3% were classified as having HCC due to viral hepatitis etiology. Sarcopenia was found in 41.3% of the patients, while 50% had portal vein tumor thrombosis (PVTT), and 60.7% had extrahepatic spread (EHS). Median OS and PFS were 11.8 (95% CI, 7.9-23.0) and 5.6 months (95% CI, 4.0-9.5), respectively. In the response-evaluable patients (n = 131), objective response rate was 35.1%. Sarcopenia (HR, 2.027; 95% CI, 1.172-3.506, *P*=0.012), NLR ≥3 (HR, 1.879; 95% CI, 1.074-3.289, *P*=0.027), ALBI grade (≥2) (HR, 2.943; 95% CI, 1.031-8.398, *P*=0.044) and PVTT (HR, 1.884; 95% CI, 1.040-3.411, *P*=0.037) were independently associated with OS. Sarcopenia (HR, 1.774; 95% CI, 1.0.5-3.038, *P*=0.037) and EHS (HR, 2.532; 95% CI, 1.352.5-4.741, *P*=0.004) were independent predictors of PFS. **Conclusions:** In this multi-center, retrospective cohort study provides evidence that sarcopenia and inflammatory biomarker are important predictors of prognosis in patients with HCC receiving A+B treatment. Taking these factors into consideration can aid in making treatment decisions and predicting outcomes. Further research is needed to better identify high-risk HCC patients with sarcopenia or systemic inflammation. **Keywords:** HCC, Systemic Chemotherapy, Sarcopenia



Liver Cancer - Treatment: Novel Target or Experimental Therapy

PE-123

Multimodal Integrative Genomics and Pathology Analyses in Neoadjuvant Nivolumab Treatment for Borderline Resectable HCC

Tan-To Cheung[1], Daniel Wai-Hung Ho, Shirley Xueying Lyu, Qingyang Zhang, Yu-Man Tsui, Joyce Man-Fong Lee, Vince Wing-hang Lau, Yin-Lun Edward Chu, Simon Hing-Yin Tsang, Wong-Hoi She, Roland Ching-Yu Leung, Thomas Chung-Cheung Yau, Irene Oi-Lin Ng[2]

The University of Hong Kong, Hong Kong

Aims: Neoadjuvant immunotherapy has resulted in pathological responses in cancers including hepatocellular carcinoma (HCC) but is often given on a 'one-size-fits-all' basis. We aimed to evaluate the efficacy of neoadjuvant nivolumab (anti-PD1) in patients with borderline resectable HCC and identify biomarkers for predicting treatment response in this phase 2, single-arm trial. **Methods:** Treatment-naïve HCC patients with intermediate and locally advanced tumours received neoadjuvant nivolumab at 3 mg/kg for 3 cycles prior to surgical resection. The primary endpoint was tumour necrosis on pathological examination (defined as ≥30% necrosis of the resected tumour). Secondary endpoint were the immediate surgical outcome and patient survival. Pre-nivolumab liver biopsies and post-nivolumab resected tumour specimens were obtained from all patients. **Results:** Between July 2020 and November 2021, 20 patients completed the treatment protocol; 70% of them were hepatitis B positive. All patients received neoadjuvant nivolumab and 19 patients underwent surgical resection on-trial. The overall response rate was impressive at 52.6% (n=10), with a positive pathological tumour response when the resected tumours had ≥30% necrosis. Of these 10 nivolumab-responsive patients, 3 (15.8%) had almost complete (>90%) tumour necrosis, 4 (21.1%) had 60-80% tumour necrosis, and 3 (15.8%) had 30-40% tumour necrosis. RNA-sequencing was performed on 13 of the 19 paired pre-nivolumab liver biopsies and post-nivolumab resected tumour samples and showed, in the nivolumab-responsive cases, the proportion of CD8 T cells increased after treatment, whereas the proportions of CD4 memory resting T cells and resting mast cells decreased after treatment. Moreover, we derived copy number variation (CNV) using target-panel sequencing on plasma cell-free DNA (cfDNA) of all patients and identified key CNV regions that correlated with the extent of tumour necrosis. Our derived non-invasive, CNV-based anti-PD1 score could predict the response of anti-PD1 immune checkpoint blockade and our findings were validated in an independent cohort with anti-PD1 treatment. **Conclusions:** Neoadjuvant nivolumab demonstrated promising clinical activity in borderline resectable HCC patients. Notably, none of the patients developed adverse reaction contradicting from receiving hepatectomy and over half of the patients displayed a positive pathological tumour response. We also identified useful non-invasive biomarkers predicting responsiveness. **Keywords:**

HCC, Neoadjuvant, Multiomics, Anti-PD1

PE-124

Comparison of Anti-Thrombotic Activity of Known Medicinal Herbs on P2P12 Receptor: An In-Silico Approach

Dhananjay Yadav

Department of Life Science, Yeungnam University, Republic of Korea

Aims: The objective of this study was to compare the anti-thrombotic activity of curcumin, naringin and quercetin on P2P12 receptor using molecular docking approach. **Methods:** The three-dimensional structure of P2Y12 receptor used for the present docking study was taken from Protein Data Bank (PDB ID: 4pxz). The ligands used in the study were (curcumin, naringin and quercetin) and 3D structure of were retrieved from PubChem Compound Database. Consequently, the ligands were docked to P2Y12 protein using "Autodock 4.2." We have set the AutoDock parameter and the distance-dependent dielectric functions useful for the calculation of the van der Waals and the electrostatic terms, respectively. The final figures were generated with the help of Discovery Studio Visualizer. **Results:** Our result shows that the antithrombotic activity of curcumin to be most effective based on the in-silico molecular docking simulation study against thrombosis. Further, we have measured minimum inhibition constant, Ki and highest negative free energy of binding with the maximum interacting surface area. We reported that the binding energy was highest in curcumin (-5.14 kcal/mol). The free binding energies were (-5.07 kcal/mol), (-1.72 kcal/mol) for quercetin, naringin respectively. **Conclusions:** This study may offer the evidence that curcumin could deliver the best therapeutic potential, in comparison to other medicinal herbs in the treatment of thrombosis, cancer and cardiovascular diseases. **Keywords:** Medicinal Herbs, Thrombosis, Liver Cancer, P2Y12 Receptor

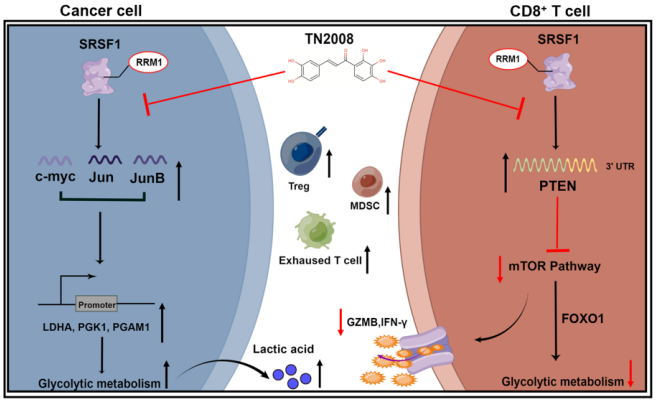
PE-125

Immunotherapy Resistance

Gui-Qi Zhu[1,2], Wei-Ren Liu[1,2], Zhi Dai[1], Jia Fan[1,2], Ying-Hong Shi[1,2]

[1]Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University,Key Laboratory of Carcinogenesis and Cancer Invasion of Ministry of Education, Shanghai, China; [2]Research Unit of Liver cancer Recurrence and Metastasis, Chinese Academy of Medical Sciences, Beijing, China

Aims: Although immune checkpoint blockade (ICB) has revolutionized cancer therapy, only a small proportion of cancer patients exhibit a durable clinical response. A number of cancer drugs activate host immune pathways in tumor cells but unfortunately also compromise anti-tumor immune function. Hence, it is important to develop tumor cell targeted drugs which enhance rather than compromise immune function. **Methods:** We obtained 7 human HBV-related HCC tumors and 7 murine HCC samples and single-cell RNA-seq (scRNA-seq) were performed. Cell growth and the ability of anchorage-dependent growth (cell survival) was assessed by colony formation assays. The extracellular acidification rate (ECAR) was measured by the XF96 extracellular flux analyzer with glucose stress fuel flex test kits in tumor or T cells. In vivo proliferation assays were performed using 5-week-old female BALB/c-nude mice or C57BL/6 mice. SRSF1 inhibitors were determined by virtual screening and SPR binding assay was performed by using a BiacoreTM T200 system. **Results:** We discovered that knockout of SRSF1, an RNA-binding protein, elicited beneficial anti-tumor activity in $CD8^+$ T cells and tumor cells. In $CD8^+$ T cells, SRSF1 depletion reshapes metabolic programs, enhances antitumor immune function and adoptive T cell therapy in mice. In tumor cells, SRSF1 inactivation decreased transcription factors c-myc, c-Jun and JunB, which allows the rewiring of glycolytic metabolism, thereby restoring $CD8^+$ T cells function and inhibiting tumor growth. These dual antitumor effects by depleting SRSF1 in both tumor and $CD8^+$ T cells prompt us to develop a potent small molecule inhibitor of SRSF1, TN2008, elicited effective antitumor immunity and sensitized resistant tumors to checkpoint blockade. **Conclusions:** Our findings unveiled a dual tumorigenesis role of SRSF1 in tumor and T cells during immune evasion, and targeting its aberrant activity with new potent inhibitor TN2008 enhanced the T cell functionality and synthesized with immunotherapy of anti-PD-1 in cancer patients. **Keywords:** Resistant Tumors, Splicing Factors, Metabolic Reprogramming, Immunotherapy



PE-126

Liquid Crystalline Nanoparticles (LCNPS) Based Delivery of an Anticancer Bioactive, Methotrexate

Mani Bhargava, Saurabh Bhargava

[1]Signa College of Pharmacy, India; [2]United Institute of Pharmacy, India

Aims: Liver cancer is a disease of uncontrolled cell growth, which may invade adjacent tissue and cause infiltration beyond the liver. Most of the potent and effective anticancer drugs used in liver cancer therapy shows poor bioavailability at desired site

as well as toxic in nature. The aim of the study was to investigate mannose modified Liquid Crystalline Nanoparticle (LCNPs) carrier for efficient and site specific delivery of potent anticancer drug (Methotrexate) used in hepatic carcinoma therapy. **Methods:** MTX loaded LCNPs were prepared by lipid cast film method and sonication method. The nanoparticles were characterized in-vitro for their shape, size, percent drug entrapment and stability by Optical Microscopy, Cross Polarized Light Cross Polarized Light Microscopy (CPLM), Transmission Electron Microscopy (TEM), X-ray diffraction (XRD) and Atomic Force Microscopy (AFM). **Results:** In-vitro stability studies reveal that LCNPs formulations are stable for 120 days at room temperature. Ex-vivo cell cytotoxicity was performed on Human hepatoma cell line. In-vivo studies included fluorescence microscopy and organ distribution studies which show the Mannose modified LCNPs exhibit better accumulation in liver as compared to unmodified system. The results of the present study indicate, this system is more stable as compared to other system. **Conclusions:** Eventually it may be concluded that incorporation of MTX in mannose modified LCNPs increases the residing time of drug in the body by altering of pharmacokinetics and biodistribution pattern, and the drug primarily concentrates in the liver. This system showed excellent cytotoxicity towards cancer cells. From the present investigation it is evident that this system may be used for liver cancer and other liver disease. **Keywords:** Nanoparticles, Methotrexate, Liver Cancer

PE-127

Galactose Conjugated PPI Dendrimers for Liver Targeting

Saurabh Bhargava

United Institute of Pharmacy, India

Aims: Cancer therapy needs site-specific drug delivery to affected cells and should avoid affecting healthy cells. Liver is prominent organ of body and has Asialoglycoprotein receptor expression. The research aimed to develop and characterize dendrimer based drug delivery providing enhanced therapeutic potential of anti-cancer agent (doxorubicin) by effective targeting to liver cells. **Methods:** 5.0G Dendrimers were synthesized by divergent method. Ethylene diamine was core material and Acrylonitrile branching unit. Synthesis was performed on the basis of two steps ie Double Michael addition and Catalytic hydrogenation of nitriles to primary amines. Dendrimers were confirmed by FTIR, NMR and Mass spectroscopy and then conjugated with galactose. The shape and size were characterized by Transmission Electron Microscopy (TEM), drug loading efficiency, In-vitro drug release and stability studies. Ex-vivo studies constituted Hemolytic toxicity study. In-vivo studies were performed on albino rats and Pharmacokinetic parameters were studied, also Biodistribution Studies were done to access doxorubicin level attained in different organs. **Results:** Thus Galactosylated PPI dendrimers showed high doxorubicin loading, sustained release and excellent biocompatibility as evident by low hemolytic toxicity. Presence of ligand on dendrimer molecule, elevated receptor mediated binding thereby targeting higher concentration of doxorubicin to lung. The higher concentration of GPPI-DOX was found to be significant compared to PPI-DOX and DOX. Possibly galactose having more affinity towards asialoglycoprotein receptors of liver parenchymal cells, more amount of drug had accumulated in liver. **Conclusions:** Finally, it can be concluded that galactose-coated PPI dendrimers found to be most suitable for delivery of Doxorubicin HCl. Galactose conjugation can be utilized to not only target asialoglycoprotein receptors of liver, but also to reduce hemolytic toxicity associated with amine terminated PPI dendrimers. Furthermore, this delivery system could reduce drug associated toxic effects by selectively targeting hepatoma cells. Carbohydrate coated dendrimers have proved well their applicability in drug delivery to the liver, especially. **Keywords:** Dendrimer, Doxorubicin

Liver Cancer - Cell Biology and Translational Research

PE-128

Molecular Docking as a Therapeutic Approach for Targeting Hepatocellular Carcinoma Cells

Prof Preeti Puranik

Shri Jain Diwakar Mahavidyalaya, Indore, India

Aims: Hepatocellular carcinoma, often known as liver cancer, is becoming more common due to a lack of coordinated cancer screening programs, a lack of diagnostic tools, and conflicting priorities for women's health in the patriarchal society of India. It is described as the abnormal spread and unchecked development of cells in the human body. Environmental factors, aging, food, infectious diseases, hormone imbalance, and chronic inflammation are major cancer-causing variables. Although there are many synthetic medications on the market, plant derivatives are known to cure various cancers with greater effectiveness and fewer side effects. The anticancer activity of the phytochemicals has been assessed using a number of molecular docking experiments, which are helpful in illuminating molecular identification. When looking for possible hits during the drug discovery process, molecular docking research is a crucial tool. This lesson focuses on the results of a molecular docking study conducted on numerous phytochemicals and cancer-causing proteins, as well as the possibility for new drugs to be developed using these findings. **Methods:** Docking studies, The phytochemicals that are known to have therapeutic activities are used as ligands in the current study. Any structural method, such as LCMS, GCMS, NMR, etc., was used to first determine the structures of the ligands. The chemical composition of the selected phytochemicals was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and represented in Advanced Chemistry Development's ChemSketch

before being converted into a three-dimensional (3D) structure with the help of the Open Babel or Lig prep 2.2 applications. These ligands are currently used in additional molecular docking analyses. A computer simulation approach called molecular docking is used to forecast how a receptor-ligand combination would interact, with the receptor typically being a protein or a nucleic acid molecule and the ligand being either a tiny molecule or another protein. **Results:** Through autocrine or paracrine secretion, the EGF pathway can be inappropriately activated in HCC, promoting cell migration and proliferation. EGF binds to the EGF receptors, and then through a series of subsequent signal transduction events, activates the PI3K/Akt, MAPK/ERK, P38/MAPK, or NF-kB proteins. As a result, the use of targeted anti-EGF therapy for the treatment of HCC may be beneficial. While EGFR is a protein found on the cell surface, it promotes tyrosine kinase phosphorylation, which is a critical step in the process that leads to cell proliferation. Therefore, we can directly stop malignant cell proliferation by blocking EGFR. Chemotherapy is combined with the EGFR inhibitor to treat HCC. With EGFR and VEGFR 2, several phytochemicals were docked. These three flavonoids were found to have the lowest binding scores in this study (-12.2 kcal/mol–9.8 kcal/mol). **Conclusions:** Computed drug-likeness of phytochemicals, in addition to docking studies, also showed that the majority of compounds were in the range of promising candidates for high bioavailability according to Lipinski's rule of five. We were able to comprehend the mechanism underlying cancer-causing enzymes and their potential inhibitors thanks to the compilation of docking analysis data from a variety of phytochemicals. It is possible to further examine the anti-cancer behavior of the phytochemical components of medicinal plants using in vitro and in vivo models. **Keywords:** Molecular Docking, Anticancer Properties, Phytochemicals, HCC

PE-129

Non-Coding and Coding RNA Regulatory Network for Early Diagnosis of Liver Cancer

DR Nidhi Puranik

Yeungnam University, South Korea, Republic of Korea

Aims: Liver cancer (commonly, hepatocellular carcinoma) incidence is on the constant rise due to inadequate availability or organized cancer screening program, paucity of diagnostic aids, and competing priorities towards women's health in the Indian patriarchal society. The applicability of recommencing-based diagnosis is often questioned due to limitations such as overdiagnosis, excessive cost, radiation exposure, risks, and less efficiency in women. This creates an urgent need to identify minimal-invasive biomarkers for the early detection of lung cancer. Currently, cell-free nucleic acids are extensively researched as potential biomarkers due to their critical role in tumor proliferation, invasion, and metastasis. Differential expression of miRNA-lncRNA-mRNA regulatory network may provide clinically valuable predictive tools for early diagnosis of hepatocellular carcinoma in defined cohorts with established dose-response and exposure-response relationships. **Methods:** Samples from females (n>200) exposed to biomass fumes residing in rural pockets of Madhya Pradesh and an equal number of unexposed controls were collected. Demographics were recorded after performing a primary exposure assessment of the household settings. Detailed information on age, body mass index, education, occupation, smoking status, alcohol consumption, use of contraceptives, and exposure length/duration/type were appropriately recorded for both groups. A cross-sectional sampling strategy was adopted and collection and processing have been completed for 5 identified pockets of Madhya Pradesh. **Results:** From the pilot investigations conducted so far, we have noted changes in the gene expression level of miRNAs, lncRNAs, and mRNA with respect to unexposed samples. Evaluating the crosstalk between cells free circulating miRNA-lncRNA-mRNA regulating the onset and progression of liver cancer involves intricate regulatory patterns. **Conclusions:** Our wet-lab results shall be integrated with data structures and algorithms to establish a triple regulatory pathway that might help early prediction of liver cancer in public health screening programs. **Keywords:** Liver Cancer, Translational Biology, LncRNA, MRNA

PE-130

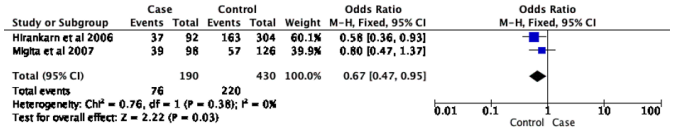
Interleukin-1b -511C>T Gene Polymorphisms and Its Association with HBV Infection-Associated Hepatocellular Cell Carcinoma Susceptibility: A Systematic Review and Meta-Analysis

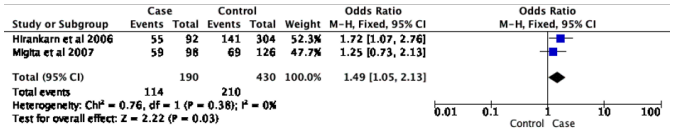
Indah Sagitaisna Putri[1], Bastomy Eka Rezkita[1]

Faculty of Medicine, Sebelas Maret University, Surakarta, Indonesia

Aims: Interleukin-1b (Il-1b) is one of pro-inflammatory cytokines that participate in the elimination of hepatitis b virus (HBV) infection. Chronic HBV infection plays as independent risk factor in hepatocellular cell carcinoma (HCC). Several studies have shown that genetic polymorphisms within the IL-1β gene are associated with gastric cancer and HCC in HCV infection. The association between the IL-1β gene and HBV infection-associated HCC is still inconclusive. This study aimed to investigate the association between the Il-1b -511C>T gene polymorphisms and HBV infection-associated HCC susceptibility. **Methods:** This study followed the PRISMA 2020 guidelines for meta-analysis and systematic reviews. The literature search was performed using databases such as PubMed and EMBASE until September 2022. Studies included in this meta-analysis were accessed using The Newcastle Ottawa Score (NOS). The association between Il-1b gene and the risk of HCC were evaluated using pooled odds ratios (ORs) and 95% confidence intervals (CIs). **Results:** Five studies (895 cases/1057 controls) were included in this study. Overall, no significant association between the polymorphism of Il-1b -511C>T gene and chronic HBV infection susceptibility. In subgroup analysis, the results indicated that C allele of Il-1b -511C>T gene polymorphisms was associated with the increased risk of HBV infection-associated HCC, while the T allele was shown to be a protective factor (OR95%CI = 1.49 [1.05 – 2.13], *P*=0.03 and OR95%CI = 0.67 [0.47 – 0.95], *P*=0.03, respectively). **Conclusions:** Our findings demonstrated that C allele of Il-1b

-511C>T gene polymorphisms was associated with risk of HBV infection-associated HCC, while T allele had a protective effect. No significant association between Il-1b -511C>T gene polymorphisms and chronic HBV infection susceptibility. **Keywords:** Hepatitis B Virus, Hepatocellular Carcinoma, Il-1b Gene, Polymorphism





PE-131

Identification of Macrophage Associated Gene Landscape to Evaluate Immune Infiltration and Therapeutic Response in Hepatocellular Carcinoma

Tong Li[1], Xin Xu[1], Kiyoko Nakayama[2], Zhenggang Ren[1], Lan Zhang[1]

[1]Liver Cancer Institute & Key Laboratory of Carcinogenesis and Cancer Invasion, Zhongshan Hospital, Fudan University, Shanghai, China; [2]Department of Gastroenterology and Hepatology, Zhongshan Hospital, Fudan University, Shanghai, China

Aims: Only a minority of hepatocellular carcinoma (HCC) patients can benefit from systemic regimens due to drug resistance. Macrophage, which abundantly infiltrate in HCC, could mediate tumour microenvironment remodeling and immune escape, proving to be powerful weapons in combating HCC. Thus, a deeper understanding of macrophages is necessary for improving existing antitumour treatments. **Methods:** With a series of bioinformatic and machine learning approaches, we comprehensively delineated the transcriptomic landscape of human HCC and explored the role of macrophage-related genes in HCC with multiple Single-cell and bulk RNA sequencing datasets. Unsupervised clustering was performed using "ConsensusClusterPlus" to cluster the macrophage marker genes (MMGs). Subsequently, gene set variation analysis and functional enrichment analysis were used to elucidate the functional differences in the MMG-associated clusters. Furthermore, principal component analysis was employed to construct the Macrosig scoring system. The relationships of the Macrosig score with prognosis, biological characteristics, mutation profiles, immune cell infiltration and drug response were analysed. **Results:** Our studies first identified 13 MMGs based on 574 HCC samples, based on which three MMG-associated clusters were defined. Patients in cluster B were significantly associated with favorable overall survival, clinicopathological features and a lower immune infiltration score. Importantly, patients with low Macrosig score, characterized by higher immune infiltration, increased mutation frequency, and higher immune checkpoint including CTLA-4, LAG3, PDCD1 and TIGIT, exhibiting enhanced efficacy of immunotherapy as expected. Moreover, as for targeted therapy analysis, low Macrosig score indicates increased sensitivity to AZD.2281, A.443654, ABT.263, ABT.888, AG.014699 and ATRA, while high Macrosig score were more likely to be sensitive to AZD6482, AKT inhibitor VIII, AS601245, AZ628, AZD.0530 and AZD6244. **Conclusions:** A novel scoring system based on macrophage subclusters was constructed, thereby guiding more effective prognostic evaluation and tailored potential drug agents strategies of HCC patients. **Keywords:** Hepatocellular Carcinoma, Single-Cell RNA Sequencing, Macrophages, Scoring System, Immunotherapy, Targeted Therapy

PE-132

METTL3-Mediated STING Upregulation and Activation in Kupffer Cells Contribute to Radiation Induced Liver Disease via Pyroptosis

Biao Wang,Shisuo Du,Zhaochong Zeng

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

Aims: Radiation therapy is a vital adjuvant treatment for liver cancer, although the challenge of radiation-induced liver diseases (RILDs) limits its implementation. Kupffer cells (KCs) are a crucial cell population of the hepatic immune system and their biological function can be modulated by multiple epigenetic RNA modifications, including N6-methyladenosine (m6A) methylation. However, the mechanism for m6A methylation in KC-induced inflammatory response in RILD remains unclear. The present study investigated the function of m6A modification in KCs contributing to RILD. **Methods:** Methylated RNA-immunoprecipitation sequencing (MeRIP-seq) and RNA transcriptome sequencing were used to explore the m6A methylation profile of primary KCs isolated from mice after irradiation with 3x8 Gy. Western blotting and quantitative real-time polymerase chain reaction were used to evaluate gene expression. RNA pull-down assay was performed to identify target gene binding. **Results:** MeRIP-seq revealed a significantly increased m6A modification level in human KCs after irradiation, suggesting the potential role of upregulated m6A in RILD. In addition, the study results corroborated that methyltransferase-like 3 (METTL3) acts as a main modulator to promote the methylation and gene expression of TEAD1, leading to STING-NLRP3 signaling activation. Importantly, it was shown that IGF2BP2 functions as an m6A "reader" to recognize methylated TEAD1 mRNA and promote its stability. METTL3/TEAD1 knockdown abolished the activation of STING-NLRP3 signaling and protected against RILD in addition to suppressing inflammatory cytokines and hepatocyte apoptosis. Moreover, clinically collected human normal liver tissue samples post-irradiation showed increased expression of STING and IL-1β in KCs compared to the non-irradiation group. Notably, STING pharmacological inhibition alleviated irradiation-induced liver injury in mice, indicating its potential therapeutic role in RILD. **Conclusions:** The results of our study reveal that TEAD1-STING-NLRP3 signaling activation contributes to RILD via METTL3-dependent m6A modification. **Keywords:** Radiation Related Liver

Disease, RILD, M6A Methylation, STING, NLRP3

PE-133

Antitumourigenic Effect of Silver Nanoparticle in Experimental Liver Cancer Rat Model

Ankush Kumar and Prachi Mishra

Department of basic sciences, DAV, A State University, India

Aims: Hepatocellular carcinoma (HCC) is the subtype of liver cancer with the highest incidence, which is a heterogeneous malignancy with increasing incidence rate and high mortality. In recent years, green synthesized silver nanoparticles (SNP) have been increasingly investigated for their anti-cancer potential. Aim of present study was to investigate antitumourigenic effect of SNP against N-methyl-N-nitrosourea [NMU] and benzo(a)pyrene (BaP) in female rats. **Methods:** Sixty four female Wistar rats were equally assigned into four groups and treated with normal saline (control), [NMU + BaP], [NMU + BaP+SNP], and [NMU + BaP + erlotinib]. Animals were pretreated with NMU and BaP three times (age 7, 10, and 13 weeks). Thereafter, erlotinib (10mg/kg) and SNP (100 mg/kg) were administered twice and three times per week, respectively, for 13 weeks. **Results:** Results showed that the administration of NMU and BaP increased serum nitric oxide [NO] and myeloperoxidase [MPO] with activities of aspartate and alanine aminotransferases in experimental rats. Furthermore, mammary inflammatory [NO and MPO] and oxidative stress (LPO) markers were significantly increased (P<00.5). There was significantly decreased in antioxidant enzymes activities in [NMU + BaP]-administered rats. Immunohistochemistry showed downregulation of Bax, p53, and caspase-3, while histology revealed the presence of malignant epithelial cells with pyknotic nuclei and high nucleocytoplasm in [NMU + BaP]-administered rats. Treatment with SNP attenuated oxidative stress, apoptosis, and inflammation and restored the antioxidant enzymes and cytoarchitecture of the tissue. **Conclusions:** It can be conclude that SNP treatment show an antitumourigenic effect in experimental liver cancer by modulating different cellular targets. **Keywords:** Experimental Liver Cancer Rat Model, Silver Nanoparticle, Antitumourigenic

PE-134

Role of Micro-RNA Gene Polymorphisms in Egyptian Patients Who Developed Hepatocellular Carcinoma

Maha M. Allam[1], Karema A. Diab[1], Fatma O. Khalil[2], Fatma A. Khalaf[3], Mohamed Abdel-Samiee[4], Nashwa Sheble[4], Mohamed A. Eljaky[4], Essam Zayed[4], A. Badran[4], Warda Othman[4], Mervat Abd-Elkreem[4], Eman Abdelsameea[4]*

[1]Clinical Pathology department, National Liver Institute-Menoufia University, Egypt; [2]Microbiology and Immunology department, National Liver Institute-Menoufia University, Egypt; [3]Biochemistry department, National Liver Institute-Menoufia University, Egypt; [4]Hepatology and Gastroenterology department, National Liver Institute-Menoufia University, Egypt

Aims: Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer worldwide. It is also the fifth cause of death due to cancer in the world. This is mainly due to the fact that HCC is usually being diagnosed at an advanced stage due to a difficult early diagnosis. To safe life, new diagnostic and prognostic biomarkers for HCC are of paramount significance. Multiple risk factors correlate with HCC, including hepatitis B or C viruses infection, alcohol abuse, aflatoxin exposure, metabolic diseases and nonalcoholic steatohepatitis. Hepatitis B (HBV) infection is an important reason of HCC, but only a fraction of infected patients develops HCC during their lifetime. This suggests that some genetic factors may play a role in tumor development. The development and progression of hepatocellular carcinoma (HCC) is a multistage process involving the deregulation of genes that are crucial to cellular processes. Multiple risk factors are correlated with HCC. MicroRNA is differentially expressed in development of different types of malignancies, including hepatic malignancy. Single nucleotide polymorphisms (SNPs) are the most common sequence variation in human genome. SNPs in miRNAs may affect transcription, processing or target recognition and result in malignant diseases. Aim is to determine the association between micro-RNA gene polymorphisms and development of HCC in Egyptian Patients. **Methods:** The current study is a case-control study included 200 participates, they were recruited from the Outpatient Clinics and Inpatient Department, National Liver Institute-Menoufia University, Egypt, 90 of them were proved as HCC by clinical examination, laboratory and triphasic CT findings. As well as 110 of participates randomly selected from healthy subjects with matched age, sex, risk factors that may affect HCC development as (Diabetes Mellitus, Hypertension and/or smoking) were enrolled in the study as a control group. Cases with chronic hepatitis without HCC, autoimmune hepatitis and chronic inflammatory diseases are excluded by clinical and laboratory investigations. Tumor staging was done using BCLC staging system. Quantification and genotyping of Micro-RNA were performed. **Results:** Among the 200 patients, 2 groups were described: group I included 90 HCC patients with a male majority (72.2%) and 110 controls in group II. Three microRNA SNPs were assayed in both patients and controls. There was a significant association between rs10061133 miR-499b and the risk of HCC. The genotypes GG or G allele were associated significantly to an increased risk of HCC (GG: OR (95% CI) = 2.91 (1.23-4.22), P=0.013; G allele: OR (95% CI) = 1.79 (1.12-2.15), P=0.026) compared with the genotype of AA or AG or A allele. **Conclusions:** In conclusion, this study shows an association between the miRNA499SNPs and the susceptibility to HCC, aiming to explore some roles and mechanisms of SNPs within miRNAs in the occurrence and development of primary liver cancer. To the best of our knowledge, no previous studies elicited such finding. We hope that our efforts and findings will facilitate the use of miRNA SNPs in early detection of HCC and may be targeting for HCC therapy. Further prospective investigations with a large number of cases would allow us to evaluate miRNA-499 polymorphism in a variety of clinical settings to help us better understand its role in HCC. **Keywords:** MicroRNA, Hepatocellular Carcinoma, Gene Polymorphisms, Viral Hepatitis

Table 1. The miRNA SNPs among the studied groups

Polymorphism	HCC cases (90) n (%)	Control subjects (110) n (%)	OR (95% CI)	P-value
miR-196a2				
rs11614913 C> T:				
Genotype:				
CC	34 (37.8)	43 (39.1)	1.00 (Ref.)	----
CT	44 (48.9)	56 (50.9)	1.02 (0.87–1.92)	0.45
TT	12 (13.3)	11 (10.0)	1.61 (0.97–2.08)	0.27
Allele:				
C	112 (62.2)	142 (64.5)	0.77 (0.59-1.22)	
T	68 (37.8)	78(35.5)	0.98 (0.65–1.73)	0.33
miR-499a				
rs3746444 T >C				
Genotype:				
TT	34 (37.8)	43 (39.1)	1.00 (Ref.)	-----
TC	41 (45.6)	51 (46.4)	0.89 (0.55–1.39)	0.472
CC	15 (16.7)	16 (14.5)	1.12 (0.89–1.61)	0.390
Allele:				
T	109 (60.5)	137 (62.3)		
C	71 (39.4)	83 (37.7)	1.06 (0.78–1.53)	0.261
miR-499b				
rs10061133 A>G:				
Genotype:				
AA	41 (45.6)	69 (53.6)	1.00 (Ref.)	----
AG	35 (38.9)	34 (40.9)	1.12 (0.96– 1.72)	0.167
GG	14 (15.5)	7 (6.4)	2.91 (1.23– 4.22)	0.013
Allele:				
A	117 (65.0)	172 (78.2)		
G	63 (35.0)	48 (21.8)	1.79 (1.12–2.15)	0.026

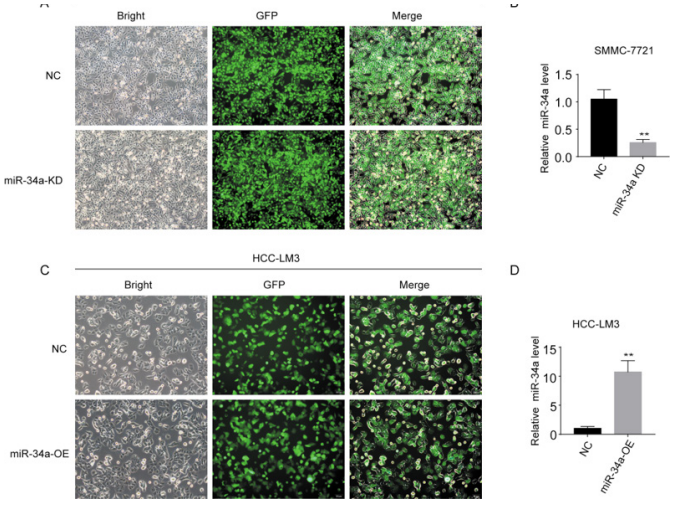
PE-135

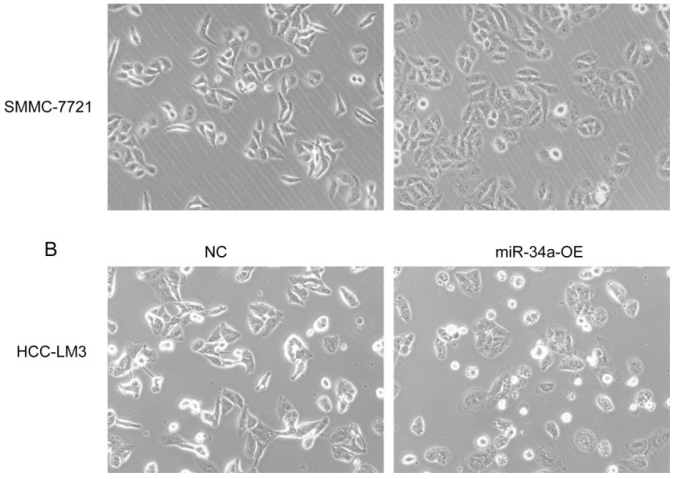
MiR-34a Inhibits Epithelial-Mesenchymal Transition in Hepatocellular Carcinoma by Targeting CDH13

Zhang Li, Niu Hao, Zeng Zhaochong

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

Aims: Previously we found miR-34a suppress invasion and metastasis in hepatocellular carcinoma (HCC). Epithelial-to-mesenchymal transition (EMT) is a crucial step for epithelial carcinoma cells to acquire invasive capacity. However, the relationship between miR-34a and HCC EMT has not been reported before. The study was conducted to identify the molecular mechanism of miR-34a in EMT of hepatoma cells. **Methods:** Bioinformatic databases prediction and further analysis indicated that CDH13 was the potential downstream target of miR-34a. The expressions of miR-34a and CDH13 were detected respectively by in situ hybridization and immunohistochemical techniques. Relationship between miR-34a and CDH13 expression in HCC tissue was analysed using the relative quantification method. The expression of CDH13 was detected after the overexpression or down-regulation of miR-34a in HCC-LM3 and SMMC7721 cells. Dual luciferase reporter assay was performed.to verify the binding site of miR-34a and CDH13. **Results:** MiR-34a inhibited the EMT of hepatoma cells. And our results showed a statistically positive correlation between miR-34a and CDH13 expression. Moreover, up-regulation of miR-34a enhanced CDH13 expression in HCC-LM3 cell, whereas decreased miR-34a expression significantly diminished CHD13 expression in SMMC-7721 cell. The target binding sites between miR-34a and CDH13 were further validated by dual luciferase reporter system. And our data suggest that miR-34a inhibits the progression of EMT by targeting CDH13-mediated Wnt/β-Catenin signaling pathway in HCC. **Conclusions:** MiR-34a inhibits EMT of hepatoma cells through positively regulating CDH13 expression, thereby suppressing HCC development and metastasis. Through this project, we will reveal the molecular mechanisms of miR-34a in HCC EMT process, and provide valuable targets for improving the therapeutic effect of HCC.
Keywords: Hepatocellular Carcinoma, Epithelial-Mesenchymal Transition, miR-34a, CDH13





PE-136

Efficacy of X-Ray Irradiation in Combination with CCR5 Antagonist for Hepatocellular Carcinoma in C57BL/6J Mice

Yi-xing Chen, Yuan Zhuang, Bao-ying Yuan, Shi-suo Du, Zhao-chong Zeng

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

Aims: The combination of radiotherapy (RT) and immunotherapy can enhance anti-tumor efficacy in various malignancies. The aim of this paper is to observe the effects of X-ray irradiation and C-C chemokine receptor 5 (CCR5) antagonist (maraviroc) on hepatocellular carcinoma (HCC) in an orthotopic mouse model. **Methods:** First, 56 HCC patients who received partial hepatectomy with or without preoperative RT were enrolled. The expression of CCR5 in irradiated tumors were evaluated by immunohistochemistry and compared with patients' overall survival (OS). An orthotopic model of liver tumor in C57BL/6J mice was constructed. Mice were treated with a single dose of 16 Gy X-ray irradiation and/or CCR5 inhibitor. Tumor size was measured weekly with high-frequency ultrasound. Flow cytometry (FCM), immunofluorescence (IF), quantitative real-time polymerase chain reaction (qRT-PCR), western blot and Luminex techniques were conducted to examine the levels of tumor associated macrophages (TAMs), lymphocytes and TAM-related markers in tumors or serum. **Results:** Higher CCR5 intensity in irradiated tumors portended poor OS for patients with HCC. For HCC orthotopic mouse model, results showed that both X-ray irradiation and maraviroc suppressed liver tumor growth. The combined modality treatment was much more effective than either radiation or maraviroc alone. Irradiation induced an increasing influx of CCR5+ TAMs into tumor sites which was partially blocked by maraviroc. Results from FCM and IF analyses showed that maraviroc significantly reduced the accumulation of irradiation-induced M2-like TAMs. Results of qRT-PCR and western blots indicated that maraviroc decreased the levels of TAM-related markers including arginase-1, transforming growth factor-β1, interleukin (IL) -10, vascular endothelial grown factor (VEGF) and VEGF-C enhanced by irradiation. **Conclusions:** X-ray irradiation combined with CCR5 inhibitor synergistically impeded the progression of liver tumors in C57BL/6J mice. **Keywords:** Irradiation, CCR5 Antagonist, Hepatocellular Carcinoma

PE-137

Biological Importance of Calycopterin against Human Hepatoblastoma Cancer through Different Molecular Mechanism: Therapeutic Importance in the Medicine

Dinesh Kumar Patel

Faculty of Health Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, India

Aims: Plants have been used as an alternative medicine for the treatment of human health complications. Several herbs and spices are used as food and medicine due to the rich source of natural antioxidants. Epidemiological studies have proven the health benefits of phenolics and flavonoids class phytochemical in the medicine. Consumption of foods rich in phenolic has been proven health benefits due to their free radical scavenging properties. Phytochemicals are pure active constituents which have been used for the treatment of numerous human health complications due to its Nutraceuticals and medicinal properties from the very ancient time to till modern age. Calycopterin is a flavonoid commonly called 5,4-dihydroxy-3,6,7,8-tetramethoxyflavone were isolated from Dracocephalum kotschyi. Calycopterin have the biological effectiveness against destructive effect of oxidative stress. **Methods:** Biological potential and pharmacological activities of calycopterin in the medicine against hepatoblastoma cancer has been investigated in the present work through scientific data analysis of various scientific research works in order to know their effectiveness against various types of human disorders including hepatoblastoma cancer. Scientific data of calycopterin were collected from different databases and analyzed in the present work to know the biological importance of calycopterin in the medicine. **Results:** Scientific data analysis revealed the biological effectiveness of calycopterin in the medicine for the treatment of human hepatoblastoma cancer through their apoptotic effect. Scientific data analysis revealed its biological potential against human hepatoblastoma cancer through different molecular mechanism including increased level of intracellular reactive oxygen species level. **Conclusions:** Scientific data analysis revealed the therapeutic effectiveness of calycopterin in the medicine for the treatment of human hepatoblastoma cancer. **Keywords:** Calycopterin, Hepatoblastoma Cancer, Molecular Mechanism

PE-138

Sorafenib Combined with Dickkopf-1 Inhibitor Synergistically Inhibited PI3K/Akt and Wnt/β-Catenin Signaling Pathways in Hepatocellular Carcinoma

Sang Hyun Seo[1], Kyung Joo Cho[1], Hye Jung Park[1], Jae Seung Lee[1,2], Hye Won Lee[1,2], Beom Kyung Kim[1,2], Jun Yong Park[1,2], Do Young Kim[1,2], Sang Hoon Ahn[1,2], Seung Up Kim[1,2]

[1]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea; [2]Department of International Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea

Aims: Sorafenib increases survival time in patients with advanced hepatocellular carcinoma (HCC). Dickkopf-1 (DKK1) is significantly overexpressed in HCC. Aim of this study is to identify the mechanism role of sorafenib combined with DKK1 inhibitor in HCC. **Methods:** HCC cells were treated with IC_{50} values of sorafenib and/or DKK1 inhibitor for 24 h. Transposon encoding $Hras^{G12V}$, micro RNA down-regulating p53 (miRp53), $PI3K^{E545K}$ were delivered to the mouse liver through hydrodynamic tail vein injection. Mice were orally administered with sorafenib (32 mg/kg) and/or DKK1 inhibitor (16 mg/kg) for 10 days. Western blot analysis, quantitative real time-polymerase

chain reaction and immunohistochemistry staining were used to explore the mechanism role of sorafenib + DKK1 inhibitor in HCC. **Results:** Sorafenib + DKK1 inhibitor more synergistically decreased the expression of p110α, p-Akt, active-β-catenin and p-GSK3β (Ser9), whereas more synergistically increased p-GSK3β (Tyr216) expression, compared to sorafenib treatment alone in vitro and in vivo. Simultaneous expression of $Hras^{G12V}$, miRp53 and $PI3K^{E454K}$ more increased p110α, p-Akt, active-β-catenin and cyclin D1 expression compared simultaneous expression $Hras^{G12V}$ and miRp53. Sorafenib + DKK1 inhibitor more synergistically decreased the expression of p110α, p-Akt and GSK3β (Ser9), whereas more synergistically increased GSK3β (Tyr 216) expression, compared to sorafenib treatment alone in transgenic mouse induced by $Hras^{G12V}$, miRp53 and $PI3K^{E545K}$. **Conclusions:** Sorafenib combined with DKK1 inhibitor more synergistically inhibited PI3K/Akt and Wnt/β-catenin signaling pathways through activation of GSK3β in HCC. These findings indicated that inhibition of DKK1 might be a novel therapeutic strategy in HCC. **Keywords:** Sorafenib, Dickkopf-1, Hepatocellular Carcinoma

PE-139

Beneficial Potential of Photodynamic Therapy and Chemotherapy in Murine Liver Cancer Cells

Pardeep Kumar, Sagar Lavania

Department of Medicine, F H Medical College & Hospital, India

Aims: Nanoengineering of hydrophobic photosensitizers is a promising approach for improved tumor delivery and enhanced photodynamic therapy efficiency. A variety of delivery carriers have been developed for tumor delivery of photodynamic therapy through the enhanced permeation and retention effect. The purpose of this study was to investigate the action of different nanoemulsions designed to encapsulate photosensitizer chlorin e6 (Ce6), a polyvalent and hydrophobic photosensitizer used in photodynamic therapy, and vincristine, a well-known chemotherapeutic agent used to treat aggressive liver cancer cells. The mean nanostructured system size ranged from 152 to 178 nm, and the nanoemulsions presented spherical morphology. **Methods:** Murine liver cancer cells (Hep G2) were incubated with nanoemulsions for two hours at various concentrations and were subjected to cell viability tests to find the concentration dependence profile. Thereafter, the in vitro phototoxic effect was evaluated in the presence of the visible laser light irradiation. Less than 10% of Hep G2 viable cells were observed when photodynamic therapy and chemotherapy were combined at a 1.0 J · cm-2 laser light dose with 1.0 μM Ce6 and 0.5 μM vincristine. **Results:** The cell death assay and cell cycle arrest analysis confirmed the therapy efficiency demonstrating an increase in the apoptosis rate and in the cell cycle arrest on G2. Additionally, 20 genes related to apoptosis and 28 target genes of anti-cancer drugs were overexpressed. Four genes related to apoptosis and four target genes of anti-cancer drugs were downregulated in Hep G2 cells after treatment with nanoemulsion with Ce6 and vincristine associated with photodynamic therapy. **Conclusions:** It can be concluded that nanoemulsions loaded with Ce6 and vincristine presented appropriate physical stability, improved photophysical properties, and remarkable activity in vitro to be considered as promising formulations for photodynamic therapy and chemotherapeutic use in liver cancer treatment. **Keywords:** Murine Liver Cancer Cells, Photodynamic Therapy, Nanoengineering

PE-140

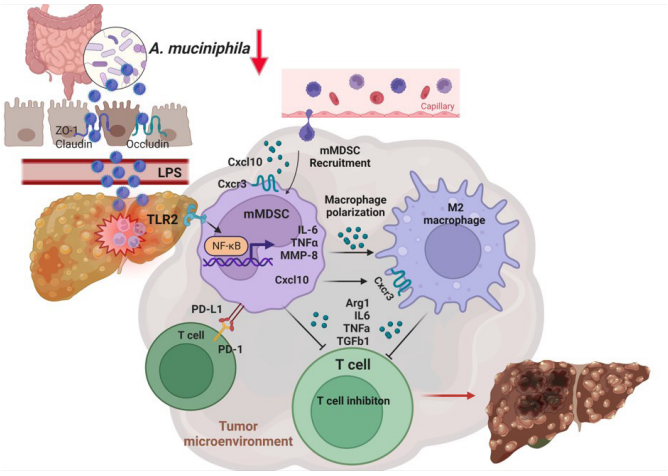
Akkermansia Muciniphila Regulates Development and Immune Resistance of Non-Alcoholic Fatty Liver Disease (NAFLD)-Induced Hepatocellular Carcinoma

Fan Ying[1], Katherine Po Sin Chung[1], Xue Qian Wu[1], Terence Kin Wah Lee[1,2]

[1]Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong; [2]State Key Laboratory of Chemical Biology and Drug Discovery, The Hong Kong Polytechnic University, Hong Kong

Aims: Nonalcoholic fatty liver disease (NAFLD)-induced hepatocellular carcinoma (HCC) is an emerging malignancy in the developed world; however, the mechanisms contributing to its formation are largely unknown, and immune checkpoint therapy is ineffective. Although several studies have reported that the intestinal microbiota plays an important role in the pathogenesis of NAFLD, the exact role of gut microbiota in NAFLD-induced HCC remains exclusive. In this study, we aim to dissect the role of gut microbiota in development of NAFLD-induced HCC. **Methods:** 16S rRNA sequencing was employed to identify the changes of gut microbiota composition during the course of DEN/HFD-induced mouse HCC model. MCD-diet induced HCC mouse model was employed for functional characterization of Akkermansia muciniphila (AKK). The role of AKK in membrane integrity was evaluated by immunofluorescence staining, qPCR, mass spectrometry analysis, and ELISA assay. The effect of AKK in immune microenvironment was evaluated by single cell RNA sequencing (scRNA-seq), coupled with immune profiling analysis. The therapeutic value of AKK alone in combination with PD1 treatment was investigated in vivo. **Results:** AKK was decreased by ~40-folds from healthy to HCC tissues during the course of HCC tumor development; and daily administration of AKK could effectively attenuate the development of NAFLD-induced HCC. Given the physiological function of AKK in the maintenance of intestinal integrity, AKK was shown to repair the intestinal lining as evidenced by increase in tight-junction proteins, with concurrent decrease in the serum concentration of LPS and bile acid metabolites. Since LPS/ bile acid metabolites is regarded as an important regulator of innate immune cells, we examined the effect of AKK on the regulation of innate immunity in the tumor microenvironment by scRNA-seq and immunoprofiling analyses. We found that AKK decreased the populations of immunosuppressive cells, including monocytic myeloid-derived suppressor cells (mMDSCs) and M2 macrophages. By Trajectory analysis, AKK suppressed differentiation of M2 macrophages/

mMDSCs from monocytes, which may lead to T cell proliferation and activation. AKK administration in combination with PD1 treatment exerts the maximal growth suppressive effect, which is accompanied with increased infiltration of T cells. **Conclusions:** AKK in critically involved in development and immune resistance of NAFLD-induced HCC. Interestingly, AKK may serve as a biomarker for prediction of PD1 response in these HCC patients.
Keywords: Gut Microbiota, HCC, Immune Resistance, NAFLD



PE-141

DGKH as a Novel Metabolic Driver of Cancer Stemness and Therapy Resistance in Hepatocellular Carcinoma

Jia Jian Loh[1], Kai Yu Ng[1], Mingdan Deng[1], Ki Fong Man[1], Ianto Bosheng Huang[1], Yanyan Wang[1], Tin Lok Wong[1,2], Stephanie Ma[1,2,3]

[1]School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong; [2]The University of Hong Kong-Shenzhen Hospital, China; [3]State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong

Aims: A hallmark of hepatocellular carcinoma (HCC) involves aberrations in metabolic pathways. The acquisition of a reprogrammed metabolic network permits cancer cells to satisfy the energy demand, thus escalating malignant progression. Conceivably, there is a need to identify novel metabolic players governing therapy resistance and self-renewal in HCC, with the latter properties well-recognized as likely roots of tumor recurrence. **Methods:** Pathway enrichment analysis was performed on publicly available data to identify gene sets involved in metabolism which are upregulated in HCC. Immunohistochemistry was performed on tissue microarray to examine the clinical significance. In vitro functional assays including limiting dilution spheroid formation assay, migration and invasion chamber assay and apoptosis assay were performed to characterize the functional impact of the gene of interest. In vivo models measuring self-renewal, metastasis and therapy resistance were conducted to substantiate the in vitro discoveries. **Results:** Pathway enrichment analysis of genes commonly upregulated in TCGA-LIHC and ICGC-LIRI identified a dysregulated glycerophospholipid metabolism. Among these glycerophospholipid metabolism genes, we focus on diacylglycerol kinase eta (DGKH) as it is ranked as the top hit in predicting patients' response to sorafenib. Clinically, DGKH were elevated in tumor tissues compared to non-tumor tissues. Furthermore, patients with higher DGKH expression corresponded with a worse prognosis and more undifferentiated tumors. In vitro functional assays using DGKH-manipulated HCC cell lines demonstrated that DGKH augments aggressive features encompassing cancer stemness, therapy resistance, and invasion and migration. Consistently, in vivo xenograft models recapitulated the in vitro findings. Upstream of DGKH, we discovered E1A-associated protein p300 (EP300) binds to the promoter region of DGKH, thereby driving the transcriptomic expression of DGKH. Mechanistically, DGKH facilitates mTOR signaling via producing phosphatidic acid (PA). Using an immunocompetent mouse model, combination treatment with sorafenib and adeno-associated virus 8 (AAV8)-mediated depletion of Dgkh significantly suppressed tumor burden and cancer stemness. **Conclusions:** Collectively, our research illustrates DGKH functions as a novel metabolic regulator of cancer stemness and therapy resistance. As such, inhibition of DGKH may facilitate a more effective treatment for liver cancer.
Keywords: Metabolism, Hepatocellular Carcinoma, Cancer Stemness, Therapy Resistance

PE-142

Cancer Stem Cell

Huajian Yu[1], Lei Zhou[1,2,8#], Jane HC Loong[1], Ka-Hei Lam[1], Tin-Lok Wong[1,3], Kai-Yu Ng[1], Man Tong[1,3], Victor WS Ma[1], Yanyan Wang[1], Xiang Zhang[4], Terence K Lee[5,6], Jing-Ping Yun[7], Jun Yu[4], Stephanie Ma[1]

[1]School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong; [2]Department of Clinical Oncology, Shenzhen Key Laboratory for Cancer Metastasis and Personalized Therapy, The University of Hong Kong-Shenzhen Hospital, China; [3]State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong; [4]Institute of Digestive Disease and The Department of Medicine and Therapeutics, State Key Laboratory of Digestive Disease, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong; [5]Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong; [6]State Key Laboratory of Chemical Biology and Drug Discovery, The Hong Kong Polytechnic University, Hong Kong; [7]Department of Pathology, Sun Yat-Sen University Cancer Centre, China; [8]Precision Medicine Institute, The First Affiliated Hospital, Sun Yat-Sen University, China

Aims: Hepatocellular carcinoma (HCC) is an aggressive disease with a poor clinical outcome. Understanding the mechanisms that drive cancer stemness, which we now know is the root cause of therapy failure and tumor recurrence, is fundamental for designing improved therapeutic strategies. This study aims to identify molecular players specific to CD133+ liver cancer stem cells (CSCs) to better design drugs that can precisely interfere

with CSCs but not normal stem cell function. **Methods:** Mouse models representing liver regeneration and proto-oncogene driven or inflammation-associated HCC were established. CD133+/- cells were isolated from the mouse models and subjected to transcriptome sequencing profiling. Human HCC cell lines, HCC patient-derived organoids, sporadic HCC mouse models, and tissues of patients with HCC were used to assess the role of SERPINA12 in driving HCC stemness, metastasis and resistance to standard therapy. AAV8-mediated liver-directed therapy targeted at SERPINA12 knockdown, alone or in combination with sorafenib, was introduced into NRAS+AKT-driven HCC mice as a proof-of-concept therapeutic approach. **Results:** Transcriptome profiling of epithelial-specific 'normal' CD133+ cells isolated from fetal and regenerating liver against 'HCC' CD133+ cells isolated from proto-oncogene driven and inflammation-associated HCC revealed preferential overexpression of SERPINA12 in HCC but not fetal and regenerating liver CD133+ cells. SERPINA12 upregulation in HCC is tightly associated with aggressive clinical and stemness features, including survival, tumor stage, cirrhosis, and stemness signatures. Enrichment of SERPINA12 in HCC is mediated by promoter binding of the well-recognized β-catenin effector TCF7L2 to drive SERPINA12 transcriptional activity. Functional characterization identified a unique and novel role of endogenous SERPINA12 in promoting self-renewal, therapy resistance, and metastatic abilities. Mechanistically, SERPINA12 functioned through binding to GRP78, resulting in a hyperactivated AKT/GSK3β/β-catenin signaling cascade, forming a positive feed-forward loop. Intravenous administration of rAVV8-shSERPINA12 sensitized HCC cells to sorafenib and impeded the CSC subset in an immunocompetent HCC mouse model. **Conclusions:** Our findings revealed that SERPINA12 is preferentially overexpressed in epithelial HCC CD133+ cells and is a key contributor to HCC initiation and progression by driving an AKT/β-catenin feed-forward loop. **Keywords:** SERPINA12, Cancer Stemness and Therapy Resistance, CD133, β-Catenin

PE-143

SPINK1-Induced Tumor Plasticity Provides a Therapeutic Window for Chemotherapy in Hepatocellular Carcinoma

Ki-Fong Man[1], Lei Zhou[1,2,10]*, Huajian Yu[1], Ka-Hei Lam[1], Jun Yu[4], Terence K. Lee[5], Jing-Ping Yun[6], Xin-Yuan Guan[2,7], Ming Liu[8,9], Stephanie Ma[1,2,3#]*

[1]*School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong;* [2]*Department of Clinical Oncology, Shenzhen Key Laboratory for Cancer Metastasis and Personalized Therapy, The University of Hong Kong-Shenzhen Hospital, China;* [3]State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong; [4]Institute of Digestive Disease and The Department of Medicine and Therapeutics, State Key Laboratory of Digestive Disease, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong; [5]Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong; [6]Department of Pathology, Sun Yat-Sen University Cancer Centre, China; [7]Department of Clinical Oncology, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong; [8]Affiliated Cancer Hospital and Institute of Guangzhou Medical University, China; [9]Guangzhou Municipal and Guangdong Provincial Key Laboratory of Protein Modification and Degradation, School of Basic Medical Science, Guangzhou Medical University, China; [10]Precision Medicine Institute, The First Affiliated Hospital, Sun Yat-Sen University, China
*Co-first authors
Corresponding author

Aims: Intratumor molecular heterogeneity of hepatocellular carcinoma (HCC) is partly attributed to the presence of cancer stem/progenitor cells (CSCs), which represents a root of tumor recurrence and chemoresistance. Tumor lineage plasticity is an emerging hallmark of cancer where tumor cells hijack developmental signaling pathways to gain cellular plasticity and evade therapeutic targeting. However, the underlying molecular events remain largely elusive. **Methods:** We have previously demonstrated CD133, an important marker of liver CSCs, to enrich following chemotherapy treatment. Our recent work found a population of CD133/Prom1-derived proliferative tumor-propagating HCC cells that follows a dedifferentiation trajectory towards a more embryonic state (Zhou et al. Gut 2022). RNA-seq was performed to compare sorted CD133+/- cells isolated from mouse models representing liver regeneration or inflammation-associated or protooncogene-driven HCC. Targeted depletion of Prom1/CD133 in HCC using $Prom1^{C\text{-}L/+}$;$Rosa26^{DTA/+}$ mice were also used. The significance of SPINK1 in driving stemness, dedifferentiation and chemoresistance was assessed in HCC cell lines and HCC immunocompetent mice. EGFR-facilitated ERK-CDK4/6-E2F2 signaling axis was also explored as a SPINK1-mediated HCC mechanism. **Results:** SPINK1 was found closely associated with CD133+ HCC, liver development and tumor dedifferentiation in HCC. Enhanced transcriptional activity of SPINK1 was mediated by promoter binding of ELF3, which like CD133, was found increased following chemotherapy treatment. Functionally, SPINK1 inhibition mitigated tumor initiation, self-renewal and chemoresistance. Mechanistically, EGFR facilitated SPINK1 to drive a deregulated ERK-CDK4/6-E2F2 regulatory axis to induce dedifferentiation of HCC cells into their ancestral lineages. **Conclusions:** Oncofetal protein SPINK1 drives CD133+ HCC towards a dedifferentiated progenitor lineage. Targeting SPINK1 may represent a novel therapeutic option for the treatment of HCC, targeting at the CD133+ CSC tumor roots and overcoming chemoresistance. **Keywords:** SPINK1, Oncogenic Dedifferentiation, Cancer Stemness, Chemoresistance, CD133

PE-144

Isolation of Tumor Endothelial Cells from Human Hepatocellular Carcinoma and Functional Analysis of Intercellular Interaction

Mitsuru Yanagaki, Koichiro Haruki, Tomohiko Taniai, Munetoshi Akaoka, Kenei Furukawa, Shunta Ishizaki, Masashi Tsunematsu, Norimitsu Okui, Michinori Matsumoto, Taro Sakamoto, Takeshi

Gocho, Toru Ikegami

Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, The Jikei University School of Medicine, Tokyo, Japan

Aims: Hepatocellular carcinoma (HCC) is a common and often terminal type of cancer. The prognosis of HCC is poor and is related to tumor progression. The malignant potential of HCC is regulated by the tumor microenvironment (TME). Tumor endothelial cells (TECs), which is an important component of the TME, promote tumor angiogenesis and regulate cytotoxic T cells. However, the role of TECs in the intercellular interaction of HCC is still unknown. The aim of this study was to determine whether the interaction of HCC cells and TECs is involved in the progression of HCC. **Methods:** Five sets of matched HCC and adjacent tissues from patients with primary HCC who underwent liver resections in our institution were examined. The TECs and normal endothelial cells (NECs) were isolated with magnetic selection of CD31+ cells. To confirm the presence of endothelial cells, CD31 protein, which is a specific marker, was evaluated with Western blotting and immunofluorescent staining. The percentage of CD31-positive cells was assessed with flow cytometry. Tube-formation assays were performed to evaluate endothelial cell function. Condition medium (CM) derived from NECs, TECs, and the human HCC cell lines Huh7 and Hep3B were co-cultured, and assays of proliferative, migratory, and invasive ability were performed to evaluate tumor cell phenotype. **Results:** Both TECs and NECs showed high expression levels of CD31 protein. In tube-forming assays, NECs and TECs formed round tubes characteristic of cultured endothelial cells. The Huh7 and Hep3B cells with CM from NECs or TECs were co-cultured. Assays of proliferative, migratory, and invasive ability showed that TEC-derived CM markedly increased migration and invasiveness in both Huh7 and Hep3B cells, whereas the effects of NEC-derived CM were extremely weak. **Conclusions:** Our results suggest that TECs accelerate HCC progression through mediators of intercellular communications. We intend to further investigate exosomes contained in TEC-derived CM. **Keywords:** Tumor Endothelial Cell, Hepatocellular Carcinoma, Tumor Microenvironment, Intercellular Interaction

Liver Cancer - AI

PE-145

Developing of Artificial Intelligence on Liver Cancer: Systematic Review

Muhammad Irzaq

Music Education, Alumnus of Padang State University, Indonesia

Aims: Primary liver cancer is a disease in which malignant (cancer) cells form in the liver tissue (HBF, 2022). Along with these developments, technology is getting better at detecting liver cancer. Breakthroughs in artificial intelligence (AI) have inspired the development of algorithms in the cancer setting (Bakrani, 2023). Experts began to study how the use of AL in liver cancer. This study aims to see the development of AL in liver cancer. **Methods:** Articles from 2010-2023 are collected from electronic databases. Then as many as ten selected papers were reviewed to answer the objectives of this study. **Results:** The study results indicate that many researchers are starting to learn about AL and its relationship to liver cancer. The study by Xiong et al. (2023) shows that IB has experienced rapid development and has wide application in diagnosing and treating liver disease, especially in China. Meanwhile, a study by Bakrania et al. (2023) found that due to current limitations in the diagnosis and therapy of liver cancer due to the heterogeneity of the disease, insufficient knowledge of cell origin and barriers to delivery of specific non-toxic drugs to liver tumour cells, AI could revolutionize the field of liver cancer research. Finally, Sharma (2023) said that artificial intelligence tools could develop cancer treatments in less than 30 days. It goes a step further and predicts patient survival rates as well. **Conclusions:** It can be concluded that AL and liver cancer are related and development, and researchers are increasingly studying this relationship. **Keywords:** Artificial Intelligence, Liver Cancer, Systematic, Review

PE-146

Which Is Better? Robot-Assisted Liver Surgery (ROBR) or Laparoscopic Liver Resection (LAPR): Systematic Literature Review

Zulfa Saumia

Universitas Jambi, Indonesia

Aims: Minimally invasive liver surgery is increasing worldwide. It is used for benign and malignant liver diseases. Some experts use laparoscopic liver resection (LAPR) and Robot-assisted Liver Surgery (ROBR). Both of these techniques have advantages and disadvantages. Which of these scenarios would open minor hepatic resections and minimize the risk of surgery? **Methods:** This abstract used a literature study method from recent articles such as Langenbecks Arch Surgery published in 2016, Liver transplantation 2019, etc. **Results:** ROBR can significantly reduce blood loss by about 306 ml, but the operating time is extended to 321 minutes compared to LAPR. Second, postoperative hospitalization decreased after robotic and postoperative pain medication were remarkably lower than LAPR. Thirdly, Robotic-based liver surgery is feasible for patients with primary and secondary liver malignancies. Minor liver resections are good candidates to start this technic. But the enormous benefits of robotic-based liver resections should be expected. The central hepatectomy rate was significantly higher in LAPR (16.6%- P=0.011). In comparison, a parenchyma-preserving approach was favored in ROBR (55% VS 34.1% P=0.019) blood loss was 330 ± 303 ml and 174 ±133 ml for the KOBR and LAPR group, respectively (P= 0.001). ROBR may allow the resection of more liver lesions, especially those in the posterosuperior segments. The surgical procedure is safer for patients and the learning curve taster. The good results obtained so far in terms of postoperative morbidity and the low incidence of post-operative liver dysfunction. Robotic liver resection should

be considered a valuable alternative for patients. **Conclusions:** ROBR is capable of the latest technological developments, but not all developing countries can use this technology, in addition to the high cost and qualified human resources. **Keywords:** ROBR, LAPR, Liver, Surgery

PE-147

Artificial Intelligence (AI)-Powered Spatial Analysis of Tumor-Infiltrating Lymphocytes (TILs) as a Predictive Biomarker for Anti-PD-1 in Advanced Biliary Tract Cancer (BTC)

Yeong Hak Bang[1], Kyunghye Bang[1,2], Jin Ho Shin[3], Hyunseok Yoon[4], Kyu-Pyo Kim[1], Inkeun Park[1], Jae Ho Jeong[1], Heung-Moon Chang[1], Baek-Yeol Ryoo[1], Chiyoon Oum[5], Seulki Kim[5], Yoojoo Lim[5], Gahee Park[5], Chan-Young Ock[5], Changhoon Yoo[1]

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Division of Hemato-Oncology, Department of Internal Medicine, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong Republic of Korea; [3]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [4]Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul Republic of Korea; [5]Lunit Inc., Seoul, Republic of Korea

Aims: Recently, anti-PD-L1 in combination with cytotoxic chemotherapy has shown significant survival benefit in a randomized phase 3 trial for unresectable or metastatic biliary tract cancer (BTC). However, no biomarker including PD-L1 expression has been established to predict clinical outcomes, and there is an unmet need for a novel predictive biomarker for anti-PD-1 or PD-L1 therapy. Here, we assessed TILs using artificial intelligence (AI)-powered spatial analysis in advanced BTC treated with anti-PD-1 beyond 1st line treatment. **Methods:** An AI-powered whole-slide image (WSI) analyzer (Lunit SCOPE IO, Lunit, Seoul, Korea) was used to segment tumor epithelium and stroma, and identification of intratumor TIL (iTIL) and stromal TIL (sTIL). H&E-stained WSI from pre-treatment samples was acquired from Asan Medical Center (n = 166), and a total of 154 samples (92.8%) after quality control were used for the final analysis. Immune phenotypes (IP) were defined as follows: inflamed as high iTIL and sTIL; immune-excluded as low iTIL and high sTIL; immune-desert as low TIL overall. Among them, 20 patients were available for multi-color flow cytometry analysis (FACS) using peripheral blood mononuclear cells, collected at baseline, C1D8, and C2D1. **Results:** All patients (n=154) were treated with anti-PD-1 (pembrolizumab or nivolumab) monotherapy, and 72 of 154 patients (46.8%) were treated as 2nd line. Gemcitabine plus cisplatin (GemCis) was used prior to anti-PD-1 as first-line therapy in all patients. Overall, 15 (9.7%) patients showed inflamed IP. With median follow-up duration of 15.4 months, the inflamed IP group showed better overall survival (17.2 vs. 6.6 months, *P*=0.03), and progression-free survival (PFS; 4.5 vs. 2.6 months, *P*=0.09) along with higher PFS rate at 12 months (33.3% vs. 11.5%, *P*=0.035), and overall response rate (26.7% vs. 8.6%, *P*=0.053) than other phenotype groups. There was no significant difference in median PFS with GemCis among IP groups (*P*=0.74). In the FACS available subgroup, inflamed IP showed higher baseline central memory T (Tcm)+effector memory T (Tem)/Tnaive ratio than other IPs. With the administration of anti-PD-1, Tcm+Tem/Tnaive ratio was increased, while the proportion of PD1+CD8+T, CD39+CD8+T, CD103+CD8+T and Treg were decreased in the inflamed IP group than other phenotype groups. **Conclusions:** Immune phenotype classified by AI-powered spatial TIL analysis was effective to predict the clinical outcomes of patients with advanced BTC treated with anti-PD-1 therapy. **Keywords:** Biomarker, Biliary Tract Cancer

PE-148

Revolutionizing Cancer Diagnosis and Treatment: Harnessing the Power of Deep Learning Technology for Biomarker Discovery

Citra Suardi[1]

[1]PSDKU Informatika, Universitas Ciputra Suarabaya, Ciputra Makassar Campus, South Sulawesi, Indonesia

Aims: In general, the diagnosis of cancer is done using laboratory test techniques and CT scans. However, along with the rapid development of technology, the use of Artificial Intelligence (AI) technology in the health sector, especially in cancer, has shown great potential to improve the accuracy of diagnosis, prediction of response to therapy, identification of relevant biomarkers for certain cancers. Deep Learning (DL) has proven to show enormous capabilities in various fields, including the health sector is a branch of AI that uses neural networks to study data and identify complex patterns. **Methods:** This study combines several studies from world researchers regarding the use of DL for cancer biomarkers. The study design and experimental methods used in the research involve collecting data from different sources in 2018-2023, then processing data on 10 journals which represent research for the last 6 years. **Results:** This research shows that research conducted by world researchers in recent years regarding the use of DL technology in the medical field, especially cancer, has great potential to improve diagnostic accuracy, predict response to therapy, and identify relevant cancer biomarkers and can help doctors and experts. medical. in providing appropriate patient care. However, the development of DL for cancer biomarkers still requires further research and development to improve the accuracy and validity of the models developed and to ensure the safety of the data used. Close collaboration is also needed between researchers, medical experts, and the technology industry to optimize the use of DL in the medical field. **Conclusions:** DL holds promise as a useful tool in the fight against cancer and provides hope for cancer patients around the world. However, it's also necessary to pay attention to aspects of data security, and the accuracy of predictions. With continuous collaboration between researchers and development, DL will further assist the medical field, especially cancer. **Keywords:** Artificial Intelligence, Deep Learning, Cancer, Biomarkers

PE-149

The Accuracy of Microvascular Invasion Prediction Based on Radiomics Methods in Hepatocellular Carcinoma: A Meta-Analysis of Diagnostics Study

Mochamad Afifudin[1]

[1]Department of Clinical Medicine, Islamic University of Indonesia, Indonesia

Aims: Hepatocellular carcinoma (HCC) is one of the most lethal malignancies in the world. The high mortality rate of HCC was associated with high recurrence in postoperative stage. Microvascular invasion has become the prognostic factor of lower survival rate and high-recurrence incidence. The preoperative evaluation by imaging methods as well as the using of machine learning algorithm potentially predicts the presence of microvascular invasion. The aim of this study was to perform meta-analysis about the accuracy of radiomic prediction to microvascular invasion in HCC. **Methods:** Comprehensive literature searched of PubMed, Science Direct, and Google Scholar for between 2016-2021. The articles were diagnostic studies that using imaging methods and logistic regression algorithm to predict the microvascular invasion incidence in patients with hepatocellular carcinoma. The data extraction including true positive, false positive, true negative, and false negative proportion. The meta-analysis was performed by using R Studio with Mada packages. The pooled results that synthesized were log positive likelihood ratio, log negative likelihood ratio, and log diagnostic odds ratio. Those data were analysed by DerSimonian-Laird method. **Results:** Eight studies were included with total 863 number of datasets. The imaging modality were using computed tomography, magnetic resonance imaging, and ultrasound. The meta-analysis showed that log negative likelihood ratio was 0.303 (95% CI 0.204-0.450, *P*=0.325, I2 = 13.405%), log positive likelihood ratio was 3.481 (95% CI 2.790-4.344, *P*=0.445, I2 = 0%), and log diagnostic odds ratio was 13.115 (95% CI 7.010-24.534, *P*=0.439, I2 = 0%). Those data indicates that radiomics method by logistic regression algorithm has fair-very good prediction tools for microvascular invasion in hepatocellular carcinoma patient. **Conclusions:** The radiomics method were feasible to predict macrovascular invasion in hepatocellular carcinoma cases. It has promising application in clinical settings so that physicians have more complete consideration regarding the risk of postoperative recurrency. **Keywords:** Hepatocellular Carcinoma, Radiomics, Diagnosis

PE-150

Ultrasound-Based Deep Learning Model for Detection and Classification of Focal Liver Lesions

Seung Kak Shin[1]*, Young Jae Kim*[2]*, Kwang Gi Kim*[2]*, Hannah Lee*[1]*, Oh Sang Kwon*[1]*, Ju Hyun Kim*[1]*, and Yun Soo Kim*[1*]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Gil Medical Center, Gachon University College of Medicine, Republic of Korea; [2]Department of Biomedical Engineering, Gachon University College of Medicine, Incheon, Republic of Korea

Aims: Abdominal ultrasound is an imaging modality of choice for screening and surveillance of hepatocellular carcinoma (HCC). Experience of ultrasound operators is a factor affecting the sensitivity in detecting focal liver lesions (FLLs) during ultrasound examination. Recently, it has been suggested that the application of artificial intelligence could help to assist physicians in radiologic imaging diagnosis and to reduce individual differences. We aimed to evaluate the usefulness of deep learning-based on liver ultrasound for detection and classification of FLLs including HCC, hepatic hemangioma and cyst. **Methods:** Our proposed deep learning model was based on B-mode ultrasound images of 1383 HCCs confirmed by pathology or computed tomography/magnetic resonance imaging, 1067 hepatic hemangiomas, and 966 hepatic cysts, which was stratified by 5-fold cross-validation method. The DeeplabV3 network was used for the deep learning model for FLLs segmentation and the EfficientNet-B2 was used for the deep learning model for classification. The performances including precision, recall rate, F1-score and area under the curve (AUC) were evaluated. **Results:** In our model, the detection rate for FLLs was 89.1% when the threshold of intersection over union was set to 0.2. In addition, the classification performances for HCCs were 75.4% of recall, 80.5% of precision, 77.9% of F1-score, and 0.854 of AUC, respectively. The classification performances for hepatic hemangiomas were 67.4% of recall, 63.2% of precision, 64.8% of F1-score, and 0.836 of AUC, respectively. The classification performances for hepatic cysts were 91.2% of recall, 86.2% of precision, 88.6% of F1-score, and 0.989 of AUC, respectively. **Conclusions:** We developed an ultrasound-based deep learning model for detection and classification of focal liver lesions. This model may help minimize the difference of operator-dependent detection rate in ultrasound for surveillance of HCC. **Keywords:** Deep Learning, Artificial Intelligence, Hepatocellular Carcinoma, Ultrasound, Focal Liver Lesion

PE-151

Multiparametric MRI-Based Deep Learning for Prediction of Microvascular Invasion Status in Intrahepatic Cholangiocarcinoma

Xian-Ling Qian[1,2,3]*, Geng-Yun Miao*[1,2,3]*, Yun-Fei Zhang*[4]*, Li-Heng Liu*[1,2,3]*, Peng Huang*[1,2,3]*, Fang Wang*[5]*, Chun Yang*[1,2,3†]*, Meng-Su Zeng*[1,2,3†]

[1]Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai, China; [2]Shanghai Institute of Medical Imaging, Shanghai, China; [3]Department of Cancer Center, Zhongshan Hospital, Fudan University, Shanghai, China; [4]Central Research Institute, United Imaging Healthcare, Shanghai, China; [5]Shanghai United Imaging Intelligence Co., Ltd, Shanghai, China

Aims: To compare a deep learning predictive convolutional neural network (CNN) model based on MRI image data with a fusion model that integrates CNN model and clinical model

for predicting preoperative MVI status stratification prediction capability. **Methods:** 444 ICC patients were enrolled and randomized to the training cohort (n=310) and validation cohort (n=134), as well as a time-independent test cohort of ICC patients (n=101). Independent clinical-radiological predictors were ascertained by univariate and multivariate analysis. The optimized CNN model is based on four sub-models using T2WI images, AP images, VP images and DP images. The fusion model combined the independent clinical-radiological predictors and the CNN model. Model predictive efficacy is assessed by receiver operating characteristic curves, calibration curves, and decision curves. **Results:** Clinical model consists of tumor size and intrahepatic duct dilatation, while the CNN model comprises four sub-models. The CNN model outperforms the fusion model in training, validation and test cohorts ($AUC_{training}$, 0.995 vs. 0.994; $AUC_{validation}$, 0.997 vs. 0.974 and AUC_{test}, 0.932 vs. 0.910). The calibration curve and decision curve verify the clinical utility. **Conclusions:** Deep learning predictive CNN model based on MRI image data as a non-invasive computer-aided diagnostic tool for well preoperative risk stratification in ICC patients. **Keywords:** Deep Learning, Intrahepatic Cholangiocarcinoma, Microvascular Invasion, Contrast-Enhanced MRI

PE-152

A Comprehensive Nomogram Based on MRI Radiomics to Predict Microvascular Invasion and Overall Survival in Patients with Intrahepatic Cholangiocarcinoma

Geng-Yun Miao[1,2,3], Xian-Ling Qian[1,2,3]*, Yun-Fei Zhang[4]*, Li-Heng Liu[1,2,3], Fei Wu[1,2,3], Peng Huang [1,2,3], Chun Yang[1,2,3†], Meng-Su Zeng[1,2,3†]*

[1]Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai, China; [2]Shanghai Institute of Medical Imaging, Shanghai, China; [3]Department of Cancer Center, Zhongshan Hospital, Fudan University, Shanghai, China; [4]Central Research Institute, United Imaging Healthcare, Shanghai, China

Aims: Microvascular invasion (MVI) is a predictor of poor prognosis in intrahepatic cholangiocarcinoma (ICC). The aim of this study was to establish a comprehensive model based on MR radiomics for MVI status stratification and overall survival prediction in ICC patients preoperatively. **Methods:** A total of 249 ICC patients were randomized into training and validation cohorts (174:75), and a time-independent test cohort with 47 ICC patients was enrolled. Independent clinical and imaging predictors were identified by univariate and multivariate logistic regression analyses. The radiomic model was based on the robust radiomic features extracted by a logistic regression classifier and the least absolute shrinkage and selection operator algorithm. The imaging-radiomics (IR) model integrated the independent predictors and robust radiomics features. The predictive efficacy of the models was evaluated by receiver operating characteristic curves, calibration curves and decision curves. Multivariate Cox analysis identified the independent risk factors for overall survival, Kaplan–Meier curves were plotted, and a nomogram was used to visualize the predictive model. **Results:** The imaging model comprised tumor size and intrahepatic duct dilatation. The radiomics model comprises 25 stable radiomics features. The IR model shows desirable performance ($AUC_{training}$= 0.890, $AUC_{validation}$= 0.885 and AUC_{test}= 0.815). The calibration curve and decision curve validate the clinical utility. Overall survival predicted by histological and IR model-predicted MVI groups exhibited similar predictive efficacy. **Conclusions:** The IR model and nomogram based on IR model-predicted MVI status may be a potential tool in MVI status stratification and overall survival prediction of ICC patients preoperatively. **Keywords:** Intrahepatic Cholangiocarcinoma, Microvascular Invasion, Overall Survival, Magnetic Resonance Imaging, Radiomics

Liver Cancer - Miscellaneous

PE-153

Outpatient Pattern of Liver Cancer Patients Based on Gate-Keeper System a Case Study of Indonesia

Lintong Hottua Simbolon[1], Rosinta H P Purba[2]

[1]Law, Alumnus University of Lampung, Indonesia; [2]Economics, Learning-Up Institute, Indonesia

Aims: The number of new cancer patients in Indonesia reached almost 400,000 cases in 2020 and 54% of cases occurred in women. The type of cancer is quite specific by sex. Breast, cervical, and uterine cancers are the highest types of cancer that afflict women. While in men, most cases of lung, liver, and colon cancer occur. To access treatment, cancer patients cannot choose health facilities because the gate-keeper system requires tiered health access starting from the smallest at the village level such as the Community Health Center (Puskesmas). Consequently, delay in handling will increase the fatal risk in cancer patients. The C-19 pandemic resulted in limited access to health facilities for cancer treatment. Cancer patients who are forced to come to health facilities for treatment are already at a more advanced stage, so the treatment becomes more severe. **Methods:** This study aims to analyze the outpatient patterns of cancer patients in both formal facilities and traditional practitioners related to the gatekeeper system. We utilize the 2014 Indonesia Family Life Survey (IFLS), a longitudinal survey that has been conducted in five waves since 1993. IFLS 2014 covers only 24 of all 34 Indonesian provinces. However, the covered provinces are also the most populated ones, so the survey is representative of 83% of the Indonesian population. **Results:** Based on the analysis using STATA MP14, it is known that 94% of cancer patients access outpatient services. However, there are 6% of cancer patients do not access outpatient services either in formal institutions or traditional practices. Cancer patients who do not have insurance tend to access health services at the Puskesmas by 31.6%. Based on gender, female cancer patients prefer to access outpatient care at Puskesmas (47.1%) and midwives (21.2%) while male cancer patients prefer private hospitals (24.9) and traditional practice

(24.5%). Only 17.5% of cancer patients are covered by insurance and insurance ownership affects cancer patients' pattern of access to health care. When having insurance, both female (27.8%) and male (20.3%) cancer patients seek treatment at specialist doctors. Nevertheless, there are indications that insurance is not functioning optimally, because female (23%) and male (32%) cancer patients actually seek treatment from traditional practitioners such as shamans or acupuncture. **Conclusions:** Insurance ownership and gate-keeper systems affect the pattern of health care for cancer patients in Indonesia. The complexity of accessing tiered services undermines the freedom to choose services or doctors, leading to indications of the ineffectiveness of government social insurance. Cancer patients prefer to access outpatient services from traditional practitioners because they do not need to undergo complicated referrals to health facilities. Long waiting times increase the death rate from cancer during the C-19 pandemic due to limited access to services and medical personnel. Simplification of access to multilevel health services is needed as socialization of the importance of insurance and community-based prevention programs so that cancer patients can be treated quickly. **Keywords:** Gate-Keeper System, Outpatients Care, Insurance, Shamans for Cancer Treatment

Viral Hepatitis

PE-154

Prediction of Hepatocellular Carcinoma Development in Chronic Hepatitis B Patients Following HBsAg Seroclearance

Jonggi Choi[1], Jina Park[1], Hyeyeon Hong[1], Jiwon Yang[1], Sung Won Chung[1], Won-Mook Choi[1], Danbi Lee[1], Ju Hyun Shim[1], Kang Mo Kim[1], Young-Suk Lim[1], Han Chu Lee[1]

[1]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: Risk of hepatocellular carcinoma (HCC) decreases but remains after HBsAg seroclearance in patients with chronic hepatitis B (CHB). Previous studies focused on predicting the development of HCC in CHB patients without HBsAg seroclearance. The aim of this study was to determine the risk factors for HCC development and develop a prediction model to stratify the risk of HCC after HBsAg seroclearance. **Methods:** We analyzed 2,421 CHB patients with HBsAg seroclearance at Asan Medical Center in Seoul, Republic of Korea, between 1997 and 2022. HBsAg seroclearance was defined as the HBsAg negativity at least two consecutive tests, 6 months apart, regardless of anti-HBs positivity. The primary outcome was HCC development following HBsAg seroclearance. Cox model was used to determine the factors associated with HCC development. Points were assigned to each risk factor based on the Cox model. Median follow-up period was 5.8 years. **Results:** The mean age was 54.6 years, and 64.5% of the patients were male. At the time of HBsAg seroclearance, 414 (17.1%) of patients had liver cirrhosis. During the 17,039 person-years (PYs), 69 of 2,421 patients developed HCC, with an annual incidence of 0.41%/100 PYs. At 5, 10, and 15 years, the cumulative incidence of HCC was 1.7%, 4.3%, and 6.8%, respectively. Liver cirrhosis (adjusted hazard ration [AHR]: 6.2), age over 60 years (AHR: 3.9), and male gender (AHR: 9.2) were independently associated with an increased risk of HCC in multivariable analysis. Risk scores were assigned to age ≥60 years (2 points), 50≤ age <60 (1 point), liver cirrhosis (2 points), male sex (3 points). Low risk (0–2), intermediate risk (3–4), and high risk (5–7) were categorized based on the sum of each point. In the low (n=753), intermediate (n=986), and high risk groups (n=682), the incidence of HCC was 0.04, 0.28, and 1.18/100PYs, respectively. Time-dependent AUROCs of these three groups for predicting HCC development at 5-, 10-, and 15-years were 0.808, 0.856, and 0.879, respectively. **Conclusions:** Liver cirrhosis, older age, and male gender at the time of HBsAg seroclearance were highly associated factors with HCC development after HBsAg seroclearance. **Keywords:** Chronic Hepatitis B, Hepatocellular Carcinoma, HBsAg Seroclearance, Prediction

PE-155

Viral Hepatitis in Asia: Systematic Review

Devi Yulia Rahmi

Department of Management, Universitas Andalas, Indonesia

Aims: Viral hepatitis is the seventh leading cause of mortality worldwide and is the only communicable disease where mortality is increasing (WHO, 2022). Viral hepatitis causes at least as many, if not more, deaths annually than TB, AIDS or malaria combined. There are five main hepatitis viruses: A, B, C, D and E. Most Asians acquire hepatitis B due to vertical transmission from their mothers during birth or later in life via child-to-child transmission (Asian Liver Disease, 2020). This study aims to see the development of viral hepatitis in Asia. **Methods:** This research uses a systematic review method. We collected articles from 2010-2022 from an electronic database (pubmed.gov, springer, science direct, Gleneagles). The keywords used are Viral Hepatitis and Asia. Then as many as ten selected articles were reviewed to answer the purpose of this study. **Results:** Asia has a very high burden of acute hepatitis; thus, a comprehensive study of the current burden and long-term trends of acute hepatitis in Asia is needed (Liu et al., 2022). Hepatitis B is standard worldwide, especially in many parts of Asia and the Pacific Islands. Several countries in Asia are experiencing high development of Hepatitis B. In China, the reason for this increased HBV infection is unknown because hepatitis B has no clear transmission routes in many people in China. However, both neonatal infection and horizontal transmission during early childhood are still the most common routes (Wiki, 2023). In Asia, the burden of acute viral hepatitis was relatively high compared with the other four continents (Liu et al., 2022). **Conclusions:** Viral hepatitis in Asia is increasing, for example, in China and other Asian countries. **Keywords:** Viral Hepatitis, Asia, Systematic Review

PE-156

Nucleotide/Nucleoside Analogues Treatment for Chronic Hepatitis B Patients without Cirrhosis and with Low Viral Load

Chia-Yen Dai[1,2], Tyng-Yuan Jang[1,2]

[1]Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [2]College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

Aims: The biochemical response is an important indicator of prognosis in chronic hepatitis B (CHB) patients receiving nucleotide/nucleoside analogues (NUCs). Among low viral load (HBV DNA of were <2,000 IU/mL) and non-cirrhotic CHB patients, the treatment of NUCs was not generally considered. The present study aimed to evaluate the efficacy of NUCs in these patients. **Methods:** In a single hospital, we recruited 31 non-cirrhotic CHB patients with hepatitis B e-antigen (HBeAg) negative who received NUCs. ALT levels and HBV DNA levels were examined at the first year after anti-HBV therapy. Normal ALT was defined as <19 U/L for females and <30 U/L for males, and the risk factors associated with ALT abnormality were analyzed. **Results:** There were 17 (54.8%) males with a mean age of 61.8 $\pm$10.3 years. 25 (80.6%) patients have fatty liver and 23 and 8 patients were treated with tenofovir alafenamide and entecavir, respectively. After 1-year NUCs therapy, thirty patients (91.7%) had undetectable HBV DNA. There were 7 patients (22.6%) with baseline ALT >40 U/L and 16 patients (51.6%) were ALT abnormal ($\geq$19 U/L for females and $\geq$30 U/L for males). Post-treatment ALT levels significantly decreased, compared to the pre-treatment levels (23.3 U/L vs 33.5 U/L, respectively; P=0.002). The proportion of patients with normal ALT was also significantly higher after treatment, compared to the pre-treatment status of patients (61.3% vs 48.4%, respectively; P=0.003). The only factor associated with ALT abnormality after first-year treatment with NUCs was body mass index (BMI) (odds ratio[OR]/95% confidence interval[CI], 1.80/1.07-3.01, P=0.003). **Conclusions:** Among non-cirrhotic CHB patients with HBeAg negative and low viral load, NUCs could significantly suppress the HBV DNA, improve the ALT level, and increase the proportion of ALT normality after 1-year NUCs treatment. **Keywords:** Chronic Hepatitis B, Cirrhosis, Viral Load, ALT

PE-157

Prevalence of Abnormal LFTs, Pattern of Liver Injury and It's Outcome in Covid-19 Patients - A Study from Tertiary Hospital

Zahabia Sohail[1], Masood Karim[1], Om Parkash[1], Hira Raza[1]

[1]The Aga Khan University Hospital Karachi, Pakistan

Aims: COVID-19 is a highly contagious respiratory disease caused by the SARS-CoV-2 virus. Evidence suggests that it can cause liver damage through various mechanisms, but little is known about the prevalence and clinical significance of abnormal liver function tests (LFTs) in patients with COVID-19. **Methods:** A descriptive cross-sectional study was conducted at the Aga Khan University Hospital, Karachi from 26th February 2020 till June 2020. All the patients above 18 years of age, admitted with confirmed COVID-19 infection were included. Data on patient demographics, clinical symptoms, laboratory test results, length of hospital stay, and clinical outcomes were collected. Statistical analysis of the variables was conducted using SPSS. **Results:** A total of 533 hospitalized patients were included in this study, with a mean age of 53+/-16 years, of which 61.5% were male. The most prevalent comorbidities were hypertension (42%) and diabetes mellitus (36%). LFTs were found to be deranged in 92% of the total patients, with SGOT (81%), GGT (69.4%), and SGPT (66.8%) being the most commonly affected liver enzyme. On comparative analysis, deranged LFTs showed significant correlations with the male gender (p-value 0.012), age group >60 years (p-value 0.001), fever (p-value <0.001), cough (p-value 0.028), shortness of breath (p-value 0.021), hemoglobin levels (p-value 0.003), serum sodium (p-value 0.006), serum CRP (p-value <0.001), serum ferritin (p-value <0.001), serum LDH (p-value <0.001), and length of hospital stay (p-value <0.001). **Conclusions:** The study showed a high prevalence of abnormal liver enzymes in COVID-19 patients, with more cases mild to moderate. Our findings suggest a correlation between abnormal LFTs and various demographic and clinical factors, but further investigation is needed to determine the clinical significance of liver injury in COVID-19 patients. These findings have important implications for patient management and outcomes. **Keywords:** LFTs, Covid-19, Liver Injury

PE-158

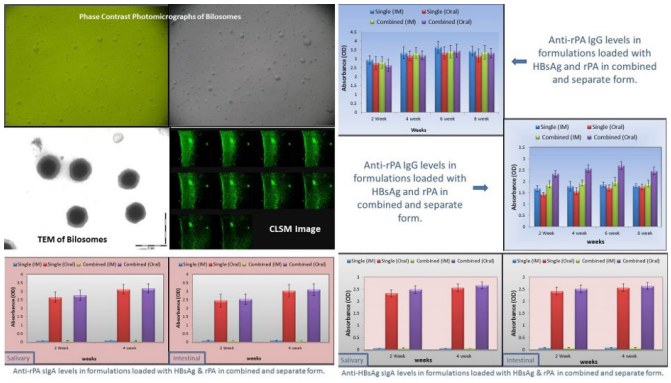
Oral Combination Vaccine against Hepatitis B & Influenza: Development and Characterization

Riya Bhargava[1], Mani Agarwal[2], Mani Bhargava[2]

[1]Himalayan University, India; [2]Signa College of Pharmacy, India

Aims: Vaccination has not only become vital but a lot of revolutionary changes are being observable in the field of vaccine delivery. Vaccine antigens administered by the oral route are often degraded during gastrointestinal transit. Bile salt stabilized vesicles i.e. bilosomes are found to be effective in preventing antigen degradation and enhance mucosal penetration. The aim of the present work was to prepare a combination vaccine system against hepatitis-B (HBsAg) and influenza(r-H1N1Ags). Oral immunization induces both mucosal and systemic immune responses, whereas mucosal responses are not generally observed following systemic immunization. Bilosomes provide needle free, painless approach for immunization, thereby increasing patient compliance and consequently increasing vaccination coverage. **Methods:** Bilosomes containing HBsAg and r-H1N1Ags were prepared by a lipid cast film method. Antigen loaded bilosomes were characterized in-vitro for their shape, size, percent antigen entrapment and stability. Fluorescence microscopy was carried out to confirm the uptake of bilosomes. The in-vivo study comprised of estimation of IgG response in serum and sIgA in various body secretions using specific ELISA. **Results:** Bilosomes formed were

multilamellar and were stable in gastric and intestinal fluids. Fluorescence microscopy suggested that bilosomes were taken up by the gut associated lymphoid tissues. In-vivo data demonstrates that bilosomes produced both systemic as well as mucosal antibody responses upon oral administration at higher dose levels as compared to intramuscular immunization but fail to produce any synergistic effect. **Conclusions:** Thus, HBsAg potentiates the production anti-r-H1N1 antibody. Also measurable sIgA in mucosal secretions were observed. Thus, the bilosomes are a promising carrier for oral combination vaccines. This approach could be adapted for human use because the mucosal surfaces are the initial sites of infection and it therefore seems logical to attempt to develop vaccination strategies that evoke appropriate localized responses to counteract the early events of pathogenesis. **Keywords:** Bilosomes, Hepatitis, Influenza, Combination Vaccine



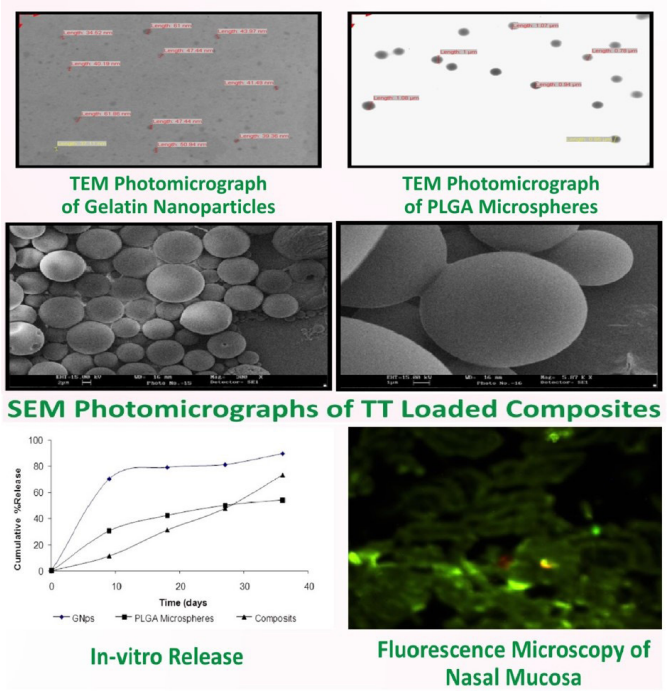
PE-159

Development of Bipolymer Based Novel Nanoparticles in Microsphere System as Vaccine Adjuvant

Prakash Gosain[1], *Saurabh Bhargava*[2]

[1]Manav Bharti University, India; [2]United Institute of Pharmacy, India

Aims: Novel strategies are required for achievement of safe and effective immunization beyond conventional strategies. Frequent booster dosing can be avoided by development of mucosal/ adjuvant vaccine delivery system, which can safely produce high and long lasting immune responses. Mucosal immunization is attractive alternative to parenteral as with appropriate delivery system it is possible to stimulate both humoral and cell-mediated responses. The research work envisaged promotes advantages and overcomes disadvantages of hydrophilic and hydrophobic polymeric systems, by combined hydrophilic (gelatin nanoparticles, GN) with a hydrophobic polymeric system (PLGA microspheres). This combination creates a new biodegradable system for HBsAg delivery. **Methods:** GN & PLGA microspheres were prepared by double emulsification method and composite system was prepared by phase separation method. Antigen loaded composites were optimized and characterized in-vitro for their shape, size, %antigen entrapment and stability. Fluorescence microscopy was carried out to confirm uptake of composites. In-vivo part of the study comprised of estimation of IgG response in serum and sIgA in various body secretions using specific ELISA. External morphology was studied by Scanning &Transmission Electron Microscopy. **Results:** The in-vitro studies exhibited an initial burst release from gelatin nanoparticles, degradation of antigen from PLGA microspheres & a continuous release from composite system. This supports hypothesis to formulate single shot vaccine with such system (to mimic booster dosing). The fluorescence studies showed selective uptake of composites by NALT. **Conclusions:** Humoral response generated by single dose of composites was comparative to marketed formulation that received booster dose. Further, composite system generated the effective sIgA antibody which was not elicited by the marketed formulation. Thus, it could be concluded from present study that bipolymer based composite system are capable to provide sufficient protein stability and can be a promising candidate for development of single shot vaccine, not only against Hepatitis but against all those diseases that invade host by mucosal surfaces. **Keywords:** Nanoparticles, Hepatitis, Microspheres



PE-160

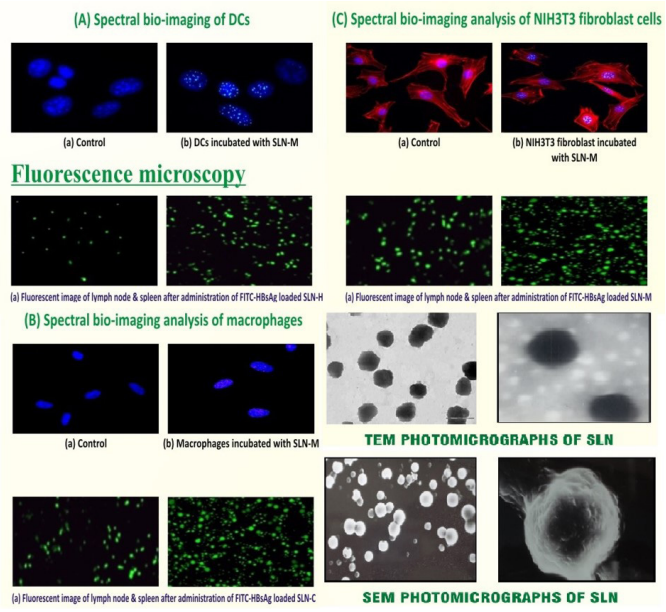
Solid Lipid Based Nanoparticulate System for Effective Vaccine Delivery

Yukti Bhargava[1], *Mani Bhargava*[2]

[1]Signa College of Nursing, India; [2]Signa College of Pharmacy, India

Aims: Search for innovative ways of vaccination has intensified recently with declining vaccine coverage & growing public concern about new virulent disease outbreaks. Work envisaged here explores potential of Solid Lipid Nanoparticles(SLN) in efficient protein delivery through surface modifications using subcutaneous

route(SC). **Methods:** SLN were prepared by Solvent Injection Method. Characterization was done by Electron Microscopy, X-Ray Diffraction Analysis, In-vitro release, Kinetics of uptake by flow cytometer, Evaluation of cell apoptosis, T-cell proliferative assay, TH1/TH2 cytokine profile & Internalization studies by spectral bioimaging. In-vivo study comprised fluorescence studies & estimation of IgG in serum, sIgA in various body secretions using specific ELISA. **Results:** Particulate system is better carrier system for immunization because of less diffusivity & restricted movement. SLNs act as signal for phagocytic cells. Surface modified SLNs can entrap greater amount of antigen, are sustained release & rapidly internalized by antigen presenting cells. In-vitro T-cell proliferation & induction of TH1 type of immune response clearly marks, potential of this novel carrier system. Fluorescence studies showed better uptake of modified SLNs. Higher & more sustained antibody titer obtained with modified SLNs suggests their better immunological potential. Thus, SC immunization could be an efficient alternative approach for vaccination against hepatitis. **Conclusions:** Formulations developed can be further explored for incorporation & delivery of other proteins & peptides should subsequently be subjected to pilot plant scale-up & clinical trial to establish their potential for SC immunization against hepatitis-B**.** **Keywords:** Nanoparticles, Hepatitis, SLN, Vaccine



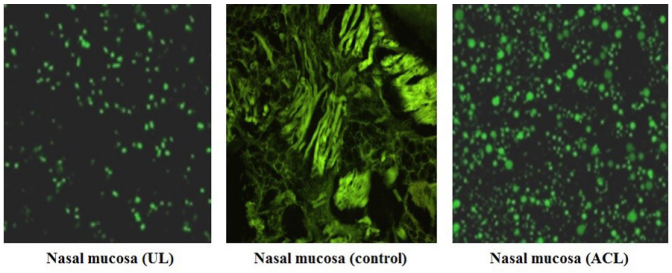
PE-161

Antibody Coated Liposomes for Transmucosal Vaccination

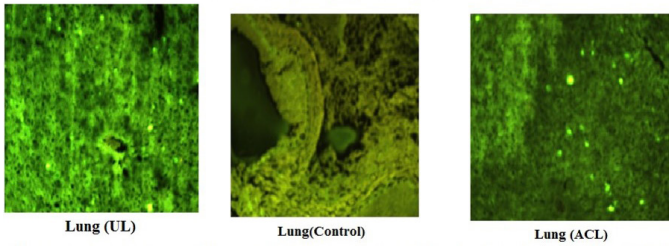
Priyanka Gosain[1], *Saurabh Bhargava*[2]

[1]GTB Hospital, India; [2]United Institute of Pharmacy, India

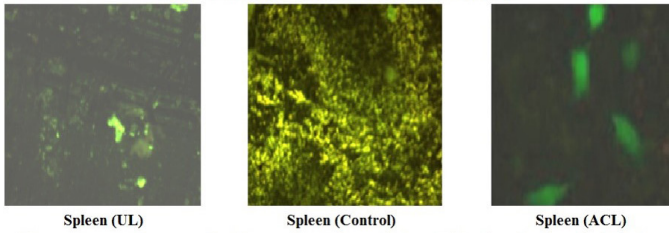
Aims: The critical role of vaccine delivery system in "rational vaccine design" has been widely recognized. Thus research work was envisaged involving development of antibody coated liposome for transmucosal immunization against hepatitis-B which may offer increased uptake of nanoliposome through transmucosal surface of nasal route & sustaining release of HBsAg to evoke relatively high IgA titre in mucosal surface. **Methods:** Liposomes were prepared by lipid cast film method & then IgG antibody was cross linked on the surface. Coated liposomes were characterized in-vitro for their shape, size, % antigen entrapment & stability. Fluorescence microscopy was performed to confirm deposition pattern in respiratory tract. The in-vivo part of the study comprised of estimation of IgG response in serum & sIgA in various body secretions using specific ELISA. **Results:** Observation of fluorescence images of nasal mucosa, lungs & spleen, revealed that these antibody coated liposome, were significantly taken up by mice respiratory mucosal surface, which made them promising carriers for mucosal vaccination. Considerable immune responses were produced by developed system that may be due to induction of MALT as well as contribution of peripheral airways. Higher immunity induced by ACL HBsAg may be attributed to its cationic nature, antibody coating & subsequent mucoadhesive property. **Conclusions:** Thus mucosal immunization with lipid vesicle through nasal administration may be effective in prophylaxis of diseases transmitted through mucosal routes as well as systemic infections. The strategy can be made more appropriate by determination of paracellular transport, nasal mucociliary clearance, mucosal toxicity assessment etc. **Keywords:** Liposome, Hepatitis, Transmucosal



Fluorescence Image of nasal mucosa after the uptake of Rhodamine loaded plain (UL) and antibody conjugated liposome (ACL)



Fluorescence Image of lung after the uptake of Rhodamine loaded plain (UL) and antibody conjugated liposome (ACL)



Fluorescence Image of spleen after the uptake of Rhodamine loaded plain (UL) and antibody conjugated liposome (ACL)

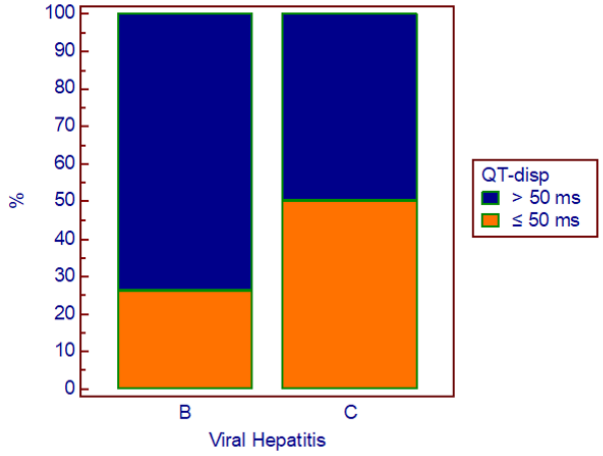
PE-162

QT Prolongation in Patients with Chronic Hepatitis B or C Who Receive Antiviral Therapy: A Cross-Sectional Study

Syania Shabrina[1], Adika Zhulhi Arjana[2], Ninda Devita[3]

[1]Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia; [2]Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia; [3]Faculty of Medicine, Universitas Islam Indonesia, Yogyakarta, Indonesia

Aims: Hepatitis B virus (HBV) and hepatitis C virus (HCV) are major causes of chronic liver disease and hepatocellular carcinoma (HCC). Antiviral therapies can reduce viral load and liver damage, but they may cause QT prolongation, a delayed ventricular repolarization that can lead to abnormal heart rhythms and sudden cardiac arrest. This study aims to assess QT prolongation in patients with chronic hepatitis B or C who receive antiviral therapy. **Methods:** This is a cross-sectional study of 46 patients with chronic hepatitis B or C diagnosed in a tertiary hospital in Indonesia. Patients with a previous cardiac diagnosis were excluded. Hepatitis diagnosis was based on WHO criteria. Electrocardiogram (ECG) examinations were performed, and QT prolongation was defined as QTc> 50 ms. **Results:** We included 46 patients in this study with a mean age of 51.22 years. Most patients (91.3%) were infected with HBV, and 8.7% were infected with HCV. The proportion of patients with QT prolongation was higher in the HBV group than in the HCV group (73.81% vs. 50%; *P*=0.18). The mean QTc interval was also higher in the HBV group than in the HCV group (52.34 ms vs. 49.75 ms; *P*=0.22). There was no significant association between QT prolongation and age, sex, body mass index, viral load, liver enzymes, albumin, bilirubin, or international normalized ratio. **Conclusions:** This study found a high prevalence of QT prolongation in patients with chronic hepatitis B or C who received antiviral therapy, especially in those with hepatitis B. Clinicians should monitor the QT interval in these patients, and further studies are needed to explore the mechanisms and outcomes of QT prolongation. A limitation of our study was that it was conducted in a tertiary hospital, which may have different characteristics and outcomes than primary and secondary hospitals. **Keywords:** Hepatitis B, Hepatitis C, QT Prolongation



PE-163

Liver Fibrosis Disease Classification Based on Hepatitis C Patient Data Using Extreme Learning Machine Algorithm

Rifaldy Fajar, Tiwul Wulandari, Nana Kurnia, Maesyaroh

Computational Biology and Medicine Laboratory, Yogyakarta State University, Indonesia

Aims: Hepatitis C has almost no initial symptoms and has a long treatment period of 7-26 weeks. Therefore, early diagnosis of this disease is required, one of which is a liver biopsy. Liver biopsy is the best standard for diagnosing the development of liver fibrosis, but this method is quite expensive and inconvenient for patients, so in this study, a classification system was made to predict liver fibrosis to help diagnose Hepatitis C based on the Extreme Learning Machine (ELM) algorithm. **Methods:** This research uses a combination of Principal Component Analysis (PCA) feature selection and Synthetic Minority Oversampling Technique (SMOTE) to improve accuracy quality. This study compares two Hepatitis C datasets from Egypt and Germany to be classified using the ELM. This research is divided into three stages, namely pre-processing, classification, and evaluation. In the pre-processing stage, the data will go through two stages the process, the first is scaling using the min-max scaler algorithm and the second stage is oversampling with the SMOTE. In the classification process, classification is carried out based on the calculation of the dataset in the pre-processing stage and featured selection using the ELM. In the evaluation stage, the confusion matrix process is carried out based on four scenarios for the ELM testing needs. **Results:** The combination of SMOTE and PCA was able to increase the evaluation value of the HCV data set from Germany with the initial accuracy, sensitivity, and specificity values of 90%, 44%, and 47% respectively, and then overall increased to 99% while in the HCV for Egyptian patients data set with the same accuracy, sensitivity, and specificity values which were initially 26%, increased to 31% overall. **Conclusions:** The ELM-based HCV classification is very promising to be applied based on the accuracy obtained. However, further research is still needed for better results. **Keywords:** HCV, Liver Fibrosis, Extreme Learning Machine, Classification

PE-164

Prognosis of the Course of Cytomegalovirus Hepatitis in Children Caused by the COVID-19 Pandemic

Manshuk Bakytzhanova, Galina Zhumagalieva

Department of Pediatric Infectious Disease, Astana Medical University, Astana, Kazakhstan

Aims: Cytomegalovirus infection (CMVI) is a common cause of congenital infections and accounts 0.5-2.2% [NiclouxM.Etal, 2020]. The clinical course of CMV hepatitis varies from asymptomatic to severe cholestatic forms characterized by cirrhotic liver lesion. Aim is to search for the outcomes of cytomegalovirus hepatitis in children caused by the COVID-19 pandemic. **Methods:** There

were analyzed 67 medical histories from the Multidisciplinary city children's hospital №3 in 2022 with confirmed CMVI by enzyme-linked immunosorbent assay and polymerase chain reaction. Children were admitted in severe (70%) and moderate (30%) forms, and 80% of infants in the first year of life had comorbidities. The liver lesion was observed in 17 (25%) of 67 patients, which was manifested in all the patients by hepatomegaly in 58% or hepatosplenomegaly in 17% of cases. Icteric syndrome was observed in 5 patients with total bilirubin 255.7 micromole/l, direct 197.4 micromole/l. **Results:** The course of acute CMV hepatitis was favorable in 70.6% of cases. In 3 infants (17.6%) with partial biliary tract atresia, hepatitis was complicated by the liver cirrhosis: an enlarged abdomen with flatulence, a pronounced venous plexus of the abdominal skin, hepatomegaly (+12cm) and splenomegaly (+5cm), with diffuse changes of the liver parenchyma and pancreas. There was one patient with multiple organ failure, ascites, and bilirubin-enzyme and bilirubin-protein dissociation, subsequently the child died due to hepatic encephalopathy and hemorrhagic syndrome. The COVID-19 pandemic complicated course of CMV hepatitis was characterized by process generalization involving all systems. Respiratory organs complications may lead to death. There was pulmonary embolism due to congenital heart defects and bronchopulmonary dysplasia; in the second case the child with pneumonia with the 3 types of respiratory failure and inflammation markers with further development of multiple organ failure against the background of multiple central nervous system defects was noted. **Conclusions:** Prognosis of the course of CMV hepatitis are variable and depend on the promptness of therapy. The SARS-CoV-2 leads to multiple organ failure syndrome with the progression of systemic inflammatory response syndrome.
Keywords: Cirrhosis, COVID-19, Cytomegalovirus

PE-165

Comparison of the Prevalence of Hepatitis in Indonesia with Asian Countries

Nuraliah, MPH

West Sulawesi Research, Empowerment Center, Indonesia

Aims: Hepatitis is a global public health problem, including in Indonesia. Based on Riskesdas, 2013 the prevalence of the Hepatitis B Virus in Indonesia is around 7.1% (around 18 million) and Hepatitis C Virus is around 1.01% (around 2.5 million). This virus is very infectious, especially Hepatitis B and C which can cause Liver cirrhosis, liver cancer, and even death. The aim of this study is to describe the comparison of the prevalence of hepatitis in Indonesia with Asian countries. **Methods:** This type of research is a literature study, in which researchers search for related articles using Google Scholar, secondary data from basic Indonesian health research, and search for articles about programs that have been carried out by the Indonesian government regarding hepatitis in children. The next step is to select articles according to the inclusion and exclusion criteria and then review the articles. **Results:** Based on WHO data, the prevalence of hepatitis B in children under five years of age in Indonesia will reach 1.3% in 2020. This prevalence is the highest in Southeast Asia. Myanmar is in second place with a prevalence of hepatitis B in children under five years of age of 1.11%. Then, the prevalence of hepatitis B in Timor Leste was recorded at 0.72%. The prevalence of hepatitis B in children under five years of age in Laos and Vietnam is 0.68% and 0.64%, respectively. Then, the Philippines has a prevalence of hepatitis B in children under five years of age of 0.38%. Thailand has a prevalence of hepatitis B in children under five years of age of 0.27%. Then, the prevalence of hepatitis B in children under five years old in Cambodia is 0.19%. Singapore and Brunei Darussalam have a prevalence of the disease of 0.13% and 0.1%, respectively. Meanwhile, the prevalence of hepatitis B in children under five years old in Malaysia is 0.06%. The program that has been carried out by the Indonesian government since 2017 is the Hepatitis B immunization program for newborns when the baby is <24 hours old and followed by routine immunization of HB1 at 2 months of age, HB2 at 3 months of age and HB3 at 4 months of age. Hepatitis B early detection activities (DDHB) in pregnant women, and giving Hepatitis B Immunoglobulin (HBIG) <24 hours to babies born to Hepatitis B reactive mothers which are expected to cut the transmission of Hepatitis B Virus from mother to child by up to 95%. For hepatitis C itself, there are currently available antiviral drugs that can cure more than 95% of people with hepatitis C infection, namely with Direct Acting Antiviral (DAA) treatment given orally which is currently accessible in 51 hospitals spread across 25 provinces. **Conclusions:** The government invites all participants to always implement PHBS, carry out Hepatitis B checks on pregnant women, provide complete immunization to infants, detect hepatitis cases early, treat hepatitis infection immediately by carrying out appropriate management or treatment according to doctor's recommendations until recovered and the virus is controlled so it does not transmit to other people.
Keywords: Children, Hepatitis, Asian Countries

PE-166

Effect of Hepatitis in Pregnancy and Prevention of Transmission to the Fetus

Indra Suardi

Department of Midwifery, STIKMAH Tobelo, Indonesia

Aims: Hepatitis is inflammation of the liver cells, which can be caused by infections (viruses, bacteria, parasites), drugs (including traditional medicines), alcohol consumption, excess fat and autoimmune diseases. Hepatitis is the most common liver infection affecting pregnant women. Viral hepatitis is a complication that affects 0.2% of all pregnancies. Mother-to-child transmission is the main route of transmission and contributes to chronic significant HBV infection. Indonesia is one of the countries with the most hepatitis sufferers, among 11 other countries in Southeast Asia. The purpose of this study was to determine the impact of hepatitis on pregnant women in Indonesia and to prevent transmission to the fetus. **Methods:** The method used is an electronic database of published journals. From several journals collected, 4 articles were selected. The article search includes the following criteria, published in the last 10 years from 2013-2023, the research sample is pregnant

women with hepatitis in Indonesia. **Results:** Based on the similarity of the dependent variables, it was found that the prevalence of hepatitis B was 1% and 8% anti-HBs positive in HBsAg negative patients. Hepatitis can cause coagulation defects, organ failure, and increased maternal and newborn mortality, but only hepatitis B and E are believed to be capable of transmitting the infection from mother to fetus. Prevention of hepatitis B can be done by screening during the first pregnancy examination. To reduce the transmission rate of transmission of hepatitis B, it is recommended that pregnant women with positive hepatitis B give birth using the elective cesarean section method. newborn baby. **Conclusions:** In endemic areas, including Southeast Asia, transmission of hepatitis B from mother to baby reaches 25-30% with a risk of infection reaching 60% during life. Thus, it is necessary to prevent transmission. The results of this study are expected to become the basis for policies on hepatitis B prevention, such as promoting hepatitis B vaccination and hepatitis B education to the wider population. **Keywords:** Hepatitis, Pregnancy

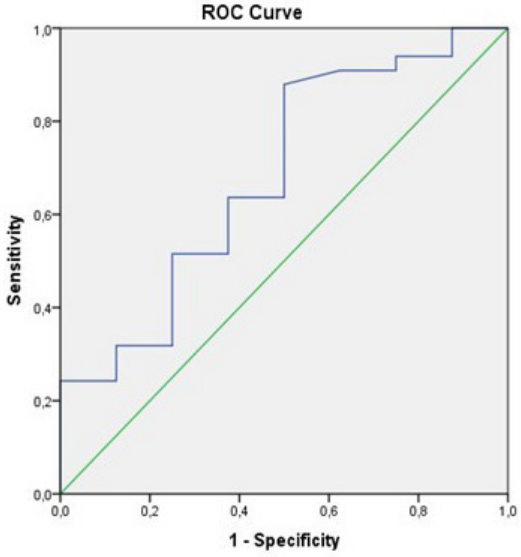
PE-167

Determination of HBsAg Cut off Index (COI) for Diagnosing Acute Hepatitis B

Adika Zhulhi Arjana[1], Arham Zainal Junaid[1], Ninda Devita[2]*

[1]Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia; [2]Faculty of Medicine, Universitas Islam Indonesia, Yogyakarta, Indonesia

Aims: Hepatitis B infection can be hard to diagnose. The serologic test of HBsAg quantitatively can assist the clinician in identifying acute infection status. However, some studies showed that different populations had different cut-off indexes (COI) for diagnosing acute hepatitis B. A population-based study is required to verify this index. This study aims to get the cut-off index for the Indonesian population. **Methods:** All patients suspected of having hepatitis B infection were included in this study. The criteria for diagnosing acute hepatitis B were based on WHO guidelines. All patients were tested for quantitative HBsAg. HBsAg confirmatory is used for confirming the acute hepatitis B status. The data was analyzed using the Receiver Operating Curve (ROC) analysis with the Medcalc statistic program. **Results:** Six hundred and forty-three subjects were included in this study. 88% of samples were confirmed as reactive. The result of ROC curve analysis showed that HBsAg examination with COI 2,255 has AUC 0,682 (95% CI 47,8%-88,5%), *P*=0,095. **Conclusions:** This study's area under the curve (AUC) was 0.682. This means that if the HBsAg examination is done in 100 patients, it will give a correct conclusion in determining the presence or absence of disease in 68 patients. The results of this study differ from the research done by Shao et al. (2012), which states that the initial HBsAg COI of 0.9-1.0 has a sensitivity value of 100% and a specificity of 60.3% and the initial HBsAg COI> 4.0 has a sensitivity value 41,9% and specificity 100% with AUC 0,933 with p-value 0,001.5 The result of Ning et al. (2012) obtained the initial COI of HBsAg 1,455 has specificity value 90,9% with AUC 0,905 (95% IK 84,5% - 96.6%).HBsAg cut-off index in every population could vary; therefore, every laboratory should make the local cut-off index. **Keywords:** HBsAg Quantitative, Cut-Off Index, Acute Hepatitis B



PE-168

Assessment of Liver Enzymes among the Hepatitis A Virus (HAV) Infected Pediatric Patients in Western Nepal

Megh Nath Dahal

Department of Biochemistry, Gandaki Medical College Teaching Hospital and Research Centre, Pokhara, Nepal

Aims: The metabolic activity of liver is due to presence of enormous enzymes. Hepatitis A virus infection being the most important global causes of viral hepatitis especially during childhood that directly alter the normal physiology of metabolism of biomolecules. Study on the alternation of these enzymes may be the marker to understand the severity and complexity of the children infected with hepatitis A Virus Infection. In Our study we approach to understand the level of SGOT, SGPT and ALP among the HAV infected paediatric and observed its severity in association with liver enzymes. **Methods:** Study was done in 90 children (Up to age 14 years) for the period of 1 year presenting with sign and symptoms of Hepatitis A Virus infection coming to OPD and emergency department of Gandaki Medical College teaching hospital and research Centre, Pokhara, Nepal. 50 Healthy children were taken as control. Liver enzymes were analyzed using latest technology and laboratory guideline. Statistical analysis was done for significance. **Results:** The result showed higher level of all three enzymes in HAV infected children; also shows the pattern of enzyme elevation at first visit of the patient. The Method of this study was descriptive investigation with cross sectional approach where 60% children show 8-fold increase in SGPT and 38% shows 6-fold elevation in SGOT transaminase activity similarly 25% children show up to 13 times raised in ALP activity with average SGOT is 45 IU/L, SGPT is 50 IU/L and ALP with average 120 IU/L. **Conclusions:** This study helps us to understand the incidence of Hepatitis A virus infection presenting with clinical features and degree of liver enzyme alteration that would aid the clinician in better treatment and management of the related cases. **Keywords:** Liver Enzymes, Hepatitis A Virus, Pediatric, Prevalence

PE-169

Concomitant Non-Alcoholic Fatty Liver Disease Drives Progression of Overall Liver Disease more than Chronic Hepatitis B Alone in Chinese-Americans

Rouchelle D. dela Cruz[1,4], Neil D. Theise[1,2,3]

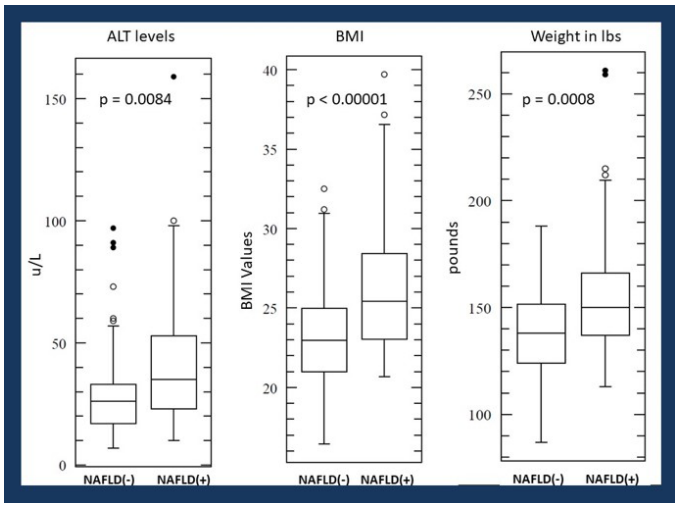
[1]Division of Digestive Diseases, Mount Sinai Beth Israel Medical Center, USA ; [2]Department of Pathology, Mount Sinai Beth Israel Medical Center, USA; [3]Department of Pathology, NYU Langone Medical Center New York, New York, USA; [4]Department of Laboratories, The Medical City, Ortigas Avenue, Pasig City, Metro Manila, Philippines

Aims: This study aims to explore the baseline characteristics, treatment factors and clinical parameters of Chinese-American patients in a single institution diagnosed with chronic hepatitis B (CHB) with and without concomitant non-alcoholic fatty liver disease (NAFLD). **Methods:** Chinese American patients from a single urban referral center (Mount Sinai Beth Israel Medical Center) who underwent biopsies for CHB between January 1, 2008 and Dec 31, 2012 were included in this retrospective study. CHB grading and staging were evaluated using the Modified Ishak on H&E and trichrome slides. All cases were immunohistochemically stained for hepatitis B surface and core antigen for presence and replicative activity of hepatitis B. Liiver biopsy specimens were reviewed, regraded and restaged for NAFLD according to the scoring system designed and validated by Kleiner and Brunt. Subsequent correlation between histological and clinical data was undertaken. Patients were divided into NAFLD (+) and NAFLD (-) groups on pathology. Pathologic and clinical features were compared between the two groups using the student t-test, Fisher exact test or Wilcoxon rank-sum test when appropriate. **Results:** Of the 148 patients, 41 were NAFLD+: 38 with steatosis, 18 with steatohepatitis, 13 with steatofibrosis. Two patients with steatofibrosis had no NAFLD activity but had significant fibrosis. Significantly higher combined necroinflammatory activity (*P*=.00001) and overall combined staging (P =.0015) is seen in the NAFLD+ group as compared to the NAFLD- group. Clinically, alanine transaminase (ALT, *P*=0.0084), body mass index (BMI, *P*<0.00001) and weight in pounds (*P*=0.0008) are significantly higher in the NAFLD+ group. **Conclusions:** Progression of chronic liver disease as measured in overall fibrosis and overall inflammation on pathology is driven by concomitant NAFLD. This may account for persistent serologic features of chronic liver injury in patients who have successful medical suppression of hepatitis B replication. Features of NAFLD on biopsy are associated clinically with higher BMI, weight, and ALT. **Keywords:** Non-Alcoholic Fatty Liver Disease (NAFLD), Chronic Hepatitis B, Concomitant Disease

Table 1. Characteristics of study patients with Chronic Hepatitis B (N=148)

Characteristics	NAFDL (-)	NAFLD (+)	p Value
No. of patients	107	41	
Mean Age ± SD	44.02 ± 12.69	43.51 ± 12.36	0.830
Gender Male Female	 59 48	 26 15	
Mean ALT levels (N=122 with ALT results)	29.1 n = 87	42.9 n = 35	0.0084
Mean BMI* ± SD (N=116)	23.0 ± 2.89 n = 84	26.3 ± 4.22 n = 32	< 0.00001**
Mean Weight ± SD pounds (N=120)	138 ± 20.4	158 ± 34.8	0.0008**
Biopsy Characteristics (N=148) Mean Combined Necroinflammatory Activity	 1.25	 4.27	 0.00001
Mean Combined Staging	2.79	4.07	0.0015

*BMI, body mass index cutoff for Asians & Asian Americans
** adjusted P values from Fisher exact test (categorical data), student t-test or Wilcoxon rank sum test (continuous data)



PE-170

Effectiveness of Phyllanthus Urinaria Leaves Combined with Tenofovir in Treatment of Chronic Hepatitis B

Le Thi Thu Hien[1], *Nguyen Khac Hung Manh*[1]

[1]Thai Nguyen University of Medicine and Pharmacy, Vietnam

Aims: Evaluating the effectiveness of Phyllanthus urinaria (PU) combined with Tenofovir disoproxil fumarate (TDF) in the treatment of chronic hepatitis B **Methods:** Study on a randomized controlled clinical trial in HBeAg (+) chronic hepatitis B patients from 8/2018 to 12/2022. One group received TDF 300 mg, the other group received TDF 300 mg combined with PU 800 mg. **Results:** Percentages of ALT ≤ 40 UI/L after 6, 12, 18 months of PU – TDF group were 82%, 95%, 98% respectively, in comparison to the TDF group with the rates 51%, 75%, 90%, respectively. Percentages of AST ≤ 40 UI/L after 6, 12, 18 months of PU – TDF group were 81%, 94%, 96%, respectively, higher than the TDF group with the rates 68%, 87%, 90% (P<0.05). Early response of HBV DNA after 6 months with HBV DNA reduction rate >1 log copies/mL and >2 log copies/mL in the PU -TDF group were 81%, 66% respectively, which are higher than in the TDF group with the rates of 71% and 52%. The rates of response to reduce HBV DNA below the detection threshold (<250 copies/ml) in the PU-TDF group after 6, 12, 18 months were 22%, 78%, 98% respectively, which are higher than TDF group with the rates11%, 61%, 87% (P<0.05). The rate of the seroconversion from HBeAg (+) to HBeAg (-) in the PU-TDF group after 6, 12, 18 months were 6%, 18%, 36%, respectively, higher than those in the TDF group with the rates of 2%, 9%, 22% (P<0.05) respectively. The rate of HBeAg (-) and anti HBe (+) in the PU-TDF group after 6,12, 18 months were 5%, 14%, 19% which are higher than those in TDF group with the rates of 1%, 4%, 9% (P<0.05). **Conclusions:** The combination of PU and TDF is more effective than TDF alone in the treatment of chronic hepatitis B. **Keywords:** Chronic Hepatitis B, Phyllanthus Urinaria (PU), Tenofovir Disoproxil Fumarate (TDF), Treatment, Effective

PE-171

Indicator of Inflammation: A Case Control Study on C-Reactive Protein (CRP) in Hepatitis Infected

Suresh Jaiswal[1], *Abhisek Lamichhane*[1], *Prakash Khanal*[1], *Man Bahadur Khatri*[1]

[1]School of Health & Allied Sciences, Pokhara University, Kaski, Nepal

Aims: C-reactive protein, an acute phase protein recognized as an important indicator of inflammatory conditions. The aim of the study was to examine the concentration of CRP in people with hepatitis B and healthy people in order to recognize the relationship between infection and inflammation involving factors. **Methods:** A case-control study was carried out on 330 participants of whom 110 were hepatitis B and 220 healthy individuals attending tertiary care centers of Pokhara. A questionnaire was designed to obtain the demography variables like age, sex, and ethnic group. Then, 5 ml of venous samples were collected after taking written consent from the respondent and quantification analysis was performed by nephelometer methods. SPSS version 16 was used for analysis for data. **Results:** In this study, males were 51.8%, 47.7% and females were 48.2%, 52.3% were in the case and control group respectively. 60% of the case participants were CRP positive and only 5.5% of the control participants were CRP positive. Association of CRP with Case and control showed statistically highly significant (p-value 0.000) with an odds ratio of 26.00 in 95% CI of (12.966-52.137). In the case of a group, mean ± S.D. of age and CRP values were 46.77±8.65, and 12.57±14.40 respectively. In the control group, the mean ± S.D. of age and CRP value were 31.05±14.26 and 1.48±2.18 respectively. **Conclusions:** CRP is increased highly in cases so it can be used as an early biomarker which will be helpful in the diagnosis and treatment of inflammatory disease like hepatitis. **Keywords:** Case Control, Hepatitis, C - Reactive Protein, Inflammation

PE-172

C-Reactive Protein (CRP) as an Inflammatory Marker: A Case Control Study on Hepatitis Infected Individuals

Sabina Gaihre, Sharmila Balkuti, Suresh Jaiswal

School of Health & Allied Sciences, Pokhara University, Nepal

Aims: C reactive protein is one of the best members of a group of acute-phase protein used as biomarker of inflammation. CRP is hepatic in origin which increases their concentrations during certain inflammatory disorders. It has widely been used as a biomarker of inflammation in the body. **Methods:** A Case control study was carried out in 244 participants including 122 Hepatitis A infected and 122 non-infected (healthy) individuals for the comparison of CRP concentration using Nephelometry method by MISPA i2. The samples for case were taken from Western regional hospital and for control samples were taken from Pokhara valley through counseling and Questionnaires. **Results:** Among the 122 hepatitis A infected participants 16 individuals had CRP concentration >6mg/L bearing 13.11% positive prevalence rate. Among the healthy 122 participants

only 2 participants had CRP concentration >6mg/L bearing 1.63% of positive prevalence rate. This showed the significance level of *P*=0.001 and OR=9.057 with nine-fold higher prevalence in the case and control. Male participant was found to have higher level of CRP concentration (>6mg/L) in case, among 16 CRP positive, 9(7.4%) were male and 7(5.7%) were female. In control equal prevalence of positive CRP concentration (>6mg/L) was sheen between male and female i.e., 1(.8%). The sex wise distribution showed no significance with the CRP level. In the case 3(2.5%), 4(3.3%), 1(.8%) of the participants were CRP positive in the age group <20, 20-40, 40-60, >60 years respectively. In control 1(.8%) of participants were CRP positive (>6mg/L) in the age group <20 and 1(.8%) in the age group 20-40 years. **Conclusions:** Highest prevalence of the positive CRP concentration was among the case in our study which might be due to the defect in immune system of infected individuals than of non-infected (healthy) individuals. **Keywords:** CRP, Case Control, Inflammation, Nephelometry

PE-173

Utilization of UKS in Preventing the Spread of Acute Hepatitis in Elementary School Students in Indonesia

Ardela Iga Pratiwi

Alumnus of Department of History, Universitas Gadjah Mada, Indonesia

Aims: Hepatitis is a public health problem in developing countries like Indonesia. In Indonesia, hepatitis A accounts for the largest share of acute hepatitis cases being treated. Hepatitis A occurs in a short time so it can cause extraordinary events. One of the efforts that can be made to help reduce the prevalence of hepatitis is through a school health promotion program in preventing hepatitis in elementary school children. This study aims to determine utilization of UKS in preventing the spread of acute hepatitis in elementary school students in Indonesia. **Methods:** This study used electronic data base as a method by reviewing some articles that was collected through google scholar published in 2016 to 2021, keywords hepatitis, UKS, elementary school students and health school program. **Results:** The results showed that the UKS (School Health Clinic) plays an important role in health promotion efforts in schools. The UKS has three programs, namely health education, health services and fostering a healthy school environment. In accordance with its function, the UKS room is not only a health room visited by sick students, but also a health information center room. In accordance with the direction of the Ministry of Health in preventing the spread of acute hepatitis in schools, UKS is intensifying school health promotion programs. One of them, the UKS strengthens the increase in yellow fever surveillance or symptoms of nausea, vomiting, diarrhea that appear in students. UKS routinely conducts training especially in food safety and oversees the management of healthy food in school canteens. **Conclusions:** UKS plays an important role in fortifying students from the threat of spreading acute hepatitis. Therefore, UKS supervisor teachers need to receive regular training to improve knowledge and attitudes, thereby motivating teachers to actively take the initiative to develop various health promotion activities, especially preventing the spread of acute hepatitis to students. **Keywords:** Hepatitis, UKS, Elementary School Students, Health School Program

Cirrhosis and Related Complications

PE-174

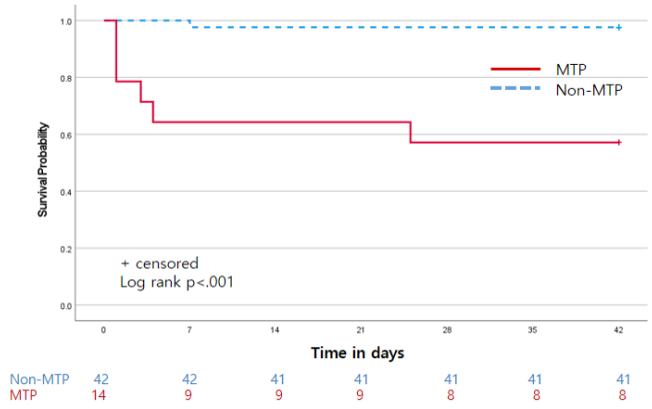
The Impact of a Mass Transfusion Protocol on the Outcome of Patients with Acute Variceal Bleeding: Propensity Score-Matched Analysis

Aryoung Kim, Byeong Geun Song, Myung Ji Goh, Dong Hyun Sinn, Wonseok Kang, Geum-Youn Gwak, Young-Han Paik, Moon Seok Choi, Joon Hyeok Lee

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

Aims: As a study reported that massive transfusion protocol (MTP) improved mortality and morbidity in trauma patients with hemorrhagic shock, some studies on the application of MTP to non-trauma patients were conducted. However, no studies have been conducted on mortality and treatment failure when MTP is used, specifically in acute variceal bleeding (AVB) patients. The current study was designed to investigate whether an MTP affects clinical outcomes in AVB. **Methods:** This was a retrospective cohort study of patients who visited the emergency room of our hospital with AVB and received endoscopic hemostasis between July 2014 and June 2022. Propensity score matching was performed to match patient age, gender, initial systolic blood pressure (SBP) and Model for End-stage Liver Disease (MELD) score. The 42-days mortality rate and treatment failure (death within 5 days, a 3g/dL drop in hemoglobin within any 24 hours, failure of endoscopic hemostasis within the first 24 hours) were assessed as study outcomes. Statistical analyses were performed using Kaplan-Meier curves with log-rank tests and Cox-proportional hazard model for 42-days mortality. **Results:** This study enrolled 218 patients, with 63.8% male, mean age 56 years and MTP protocol was administered to 19 patients (9%). The 42-days mortality rate was significantly higher among those receiving MTP before (42.1% vs 1.5%, *P*<0.001) and after (42.9% vs 2.4%, *P*<0.001). The MTP group had a higher 5-day mortality rate (26.3% vs 0%, *P*<0.001), a 3g/dL hemoglobin drop within any 24 hours (21.1% vs 0.5%, *P*=0.000), and failure of endoscopic hemostasis within the first 24 hours (15.8% vs 0%, *P*<0.001). Only MTP application was an independent predictor of 42-days mortality in two multivariable analyses model of the whole study population. (HR 21.17; 95% CI 3.02-148.40, *P*=0.002, HR 24.19; 95% CI 3.41-171.74, *P*=0.001). Regardless of blood pressure status, patients who received MTP had a significantly higher 42-days mortality rate (SBP<100: 46.2% vs 3.7%, *P*<0.001, SBP≥100: 33.3% vs 0.7%, *P*<0.001). MTP patients with severe liver disease had a significantly higher 42-day mortality

rate (MELD score≥13: 47.1% vs 3.5%, *P*<0.001). **Conclusions:** MTP is a significant risk factor in increasing the 42-days mortality rate of AVB patients and is also linked to treatment failure. Because MTP has a particularly high mortality rate in patients with pre-existing hepatic impairment, it should be used with greater caution. **Keywords:** Acute Variceal Bleeding, Massive Transfusion Protocol, 42-Days Mortality



PE-175

Recurrence of Portosystemic Encephalopathy in Cirrhotic Patients and Its Risk Factors

Zahabia Sohail[1], Masood Karim[1], Abdullah Bin Khalid[1], Bazil Musharraf[1], Muhammad Yasrab[1]

[1]The Aga Khan University Hospital Karachi, Pakistan

Aims: Portal systemic Encephalopathy (PSE) is a common complication of cirrhosis that places a high societal burden of illness and hospitalization. Identifying the patient's risk for PSE may allow closer monitoring to preserve the quality of life and reduce and manage risk factors accordingly. It is important to assess the risk factors for recurrent PSE so that appropriate prevention and prognostication can be done Therefore this study is done to assess, the recurrence of PSE in cirrhotic patients after the first episode of PSE and its risk factors. **Methods:** It is a retrospective study done in the section of Gastroenterology, The Aga Khan University Hospital, Karachi, Pakistan from Jan 1, 2021, till December 31, 2021. Patients who were admitted first time with PSE and admitted within 3 months of index PSE were enrolled in the study. Grading of PSE Grade (I-VI), laboratory tests(Bilirubin, Albumin, Creatinine, and electrolytes), ascites with spontaneous bacterial peritonitis (SBP), gastrointestinal bleeding (GIB), acute kidney injury (AKI), Child-Turcotte-Pugh (CTP) score, and Model of End-Stage Liver Disease (MELD) Score were collected by chart review and analyzed by SPSS version 20. **Results:** Total 61 patients were included in the study and 10 were lost to follow-up. The main comorbids were hypertension 33 (64%) and diabetes 28 (54%). As per etiology HCV (59%), HBV (27%), Alcohol (6%), others (7%). Out of 51 patients, 33 were readmitted with PSE while 22 patients remained stable on follow-up. On comparative analysis of both groups; infection, Meld score, low albumin, and raised total bilirubin showed significant P-value (<0.05). The rest of the parameters were more or less the same in both groups. **Conclusions:** We found ta hat high MELD score, raised total bilirubin level, low Albumin level, and infections were the risk factors for recurrence of PSE. Identification of risk factors during assessment can reduce the recurrence of PSE. We would recommend validating the results of our study on large scale prospectively. **Keywords:** PSE, Recurrence, Cirrhosis

PE-176

Study of Selected Natural Phytomedicines Used in the Treatment of Liver Fibrosis Targeting TGF-β Protein

Dhananjay Yadav

School of Life Science, Yeungnam University, Republic of Korea

Aims: The transforming growth factor-beta (TGF-β) family signaling pathways play essential roles in proliferation, differentiation, migration or cell death, and thus it has diverse and pleiotropic functions including liver fibrosis. In the case of the liver, TGF-β signalling participates in almost all stages from liver injury through inflammation and fibrosis, to cirrhosis and cancer. Therefore, targeting the TGF-β receptor with known natural phytomedicines acts as a ligand and to investigate the best one that could be used in the therapy of liver fibrosis. **Methods:** The three-dimensional structure of TGF-β receptor were retrieved for the present docking study taken from Protein Data Bank (PDB ID: 1VJY). The ligands used in the study were curcumin, osthole, rhein, silymarin and 3D structure of were retrieved from PubChem database. As a result, the ligands were docked to TGF-β receptor using "Autodock 4.2." The study provided the essential hydrogen atoms, atom type charges, and other parameters were calculated. The resulted figures were produced with the help of Discovery Studio Visualizer (Accelrys San Diego, CA, USA). **Results:** The in-silico result shows that the anti-fibrotic activity of rhein a lipophilic anthraquinone to be most effective and can be used as a medicinal agent. Additionally, we reported the amino acid sequences of the protein that were docked with the ligands for each of the compound and noted minimum inhibition constant, Ki and highest negative free energy of binding with the maximum interacting surface. We reported that the binding energy was highest in rhein (-9.17 kcal/mol). The free binding energies were (-5.94 kcal/mol), (-4.63 kcal/mol) and (-4.49kcal/mol) using osthole, Curcumin and silymarin respectively. **Conclusions:** This study may provide the clue that rhein could provide the best therapeutic potential compared with other selected medicinal herbs in the treatment of liver fibrosis. **Keywords:** Phytochemicals, Medicinal Herbs, Fibrosis, Molecular Docking

PE-177

Hydrothorax Treatment in Patients with Liver Cirrhosis

Symbat Kulmaganbetova[1], Talgat Beisenbayev[2]

[1]Department of Liver Surgery, Kyzylorda Oncology Center, Kazakhstan; [2]Department of General Surgery, Aktobe Medical Center, Kazakhstan

Aims: Hepatic hydrothorax occurs in 5–10% of patients who have liver cirrhosis (LC). Almost all patients with hepatic hydrothorax also have ascites. The mechanism of hepatic hydrothorax appears to be the passage of ascitic fluid through defects in the diaphragm. In this composition, we present our experience in the treatment of hepatic hydrothorax with LC. **Methods:** We analyzed 28 patients with hepatic hydrothorax who were treated at the Kyzylorda Oncological Hospital from March 2017 to October 2022. The average age was 41 +/- 4 years, man - 18, woman - 10. According to the etiology of cirrhosis hepatitis B – 11 patients, hepatitis C – 9, and PBC – 8 patients. On the CPT (Child-Pugh-Turcotte) scale patients were class A – 1 patient, class B – 9 patients, and class C – 4 patients. Patients underwent pleural puncture and/or drainage of the pleural cavity. **Results:** Analyzed cases of hydrothorax levels were Grade-2 (moderate) – 14 patients, Grade-5 (severe) – 9. According to the volume of pleural effusion, patients are divided as follows: small - 2 patients, medium - 9, and large - 4. Unilateral hydrothorax was in 24 patients, more often the right-sided (84%) was observed. Bilateral hydrothorax was observed in 12 patients with a predominantly large effusion on the right side. Puncture of the pleural cavity was performed in 14 patients, with 6 patients being punctured repeatedly, and 4 patients punctured 3 times. In addition to puncture of the pleural cavities, these patients underwent complex treatment, including diuretics. Thus, a relapse of hydrothorax was in 20 patients (66.7%). Five patients underwent pleural cavity drainage due to massive hydrothorax. All patients were preparing for related liver transplantation. The pleural drainage of these patients was removed on the 5th and 6th day after transplantation, respectively. There was no mortality from pleural cavity drainage among patients. **Conclusions:** In conclusion, our study demonstrates that pleural puncture remains a safe and effective surgical treatment method for hepatic hydrothorax. Drainage of the pleural cavities is recommended as an auxiliary method for radical methods of treating liver cirrhosis. **Keywords:** Hepatic Hydrothorax, Liver Cirrhosis, Pleural Puncture, Bilateral Hydrothorax

PE-178

Bioactivities and Hepatoprotective Effects of Flavonoid Pectolinarin in the Management of Liver Disorders: A Phototherapeutic Approach in the Medicine

Dinesh Kumar Patel

Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Payagraj, India

Aims: Natural flavonoids are important phytochemical found to be present in the dietary plants and vegetables. Flavonoids have been well known for their cardiovascular, antiviral, antioxidant and anticancer properties. Flavonoids are important class of phytochemical founds in many attractive colored compounds which are having good antioxidant properties and can used as nutraceuticals. Pectolinarin is important flavonoids of Cirsium japonicum which is an important herb of Korea, China and Japan. **Methods:** To know the hepatoprotective effects of Pectolinarin in liver disorders, various experiment have been conducted in the scientific field and data were collected from these databases. Further role of antioxidant in the liver disorders have been also investigated and analyzed through various datasets. However, an integrated method including molecular docking was employed to investigate the interaction between alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), super oxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) and Pectolinarin. **Results:** From the data analysis, it was found that Pectolinarin revealed the beneficial effects on human liver disease conditions, as it showed protective effects against H_2O_2-induced cell death and inhibited ROS generation by oxidative stress. Pretreatment with pectolinarin also inhibited phosphorylation of MAPK. Data also revealed their hepatoprotective activity in through various enzymes test. In-silico docking study revealed that pectolinarin interacted with the pocket region of the ALT, AST, ALP, SOD, catalase and GPx. Molecular docking presented the probable binding modes of inhibitors to liver enzymes and highlighted the key role of hydrophobic interaction for the stability of the docking complex. **Conclusions:** Pharmacological studies have reported the beneficial effects of pectolinarin in liver disorders. These findings put more insights into understanding the interaction of pectolinarin and liver enzymes. **Keywords:** Pectolinarin, Liver Disorders, Catalase, GPx

PE-179

Biological Potential and Hepatoprotective Activity of Tectoridin on the Human Liver System: Molecular Mechanism and Scientific Data Analysis

Dinesh Kumar Patel

Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Payagraj, India

Aims: Isoflavones are flavonoidal class plant derived phytochemical mostly used as natural drugs or dietary supplements in the medicine. Because of their vast therapeutic potential, isoflavones are one of the main target molecule for the drug development. Tectoridin also called 4',5,7-thrihydroxy-6-methoxyisoflavone-7-O-β-d-glucopyranoside have been isolated from the flowers of Pueraria thunbergiana. Tectoridin has various pharmacological importance including hepatoprotective, hypoglycemic and antiallergic activity. **Methods:** Various literature databases have been searched to collect all the needed information for the hepatoprotective activity of Tectoridin in various In-vivo and In-vitro model systems. Other important pharmacological activity data's have been also collected in the present investigation to know

the therapeutic benefit of Tectoridin against human disorders. All the collected datas have been analyzed systematically to investigate the hepatoprotective mechanism of Tectoridin in the liver system. **Results:** Data analysis of the collected information of the present study revealed the importance of Tectoridin in the liver system. Hepatoprotective activity and mechanism of action of tectoridin have been investigated in the scientific research and data analysis of these research work revealed that tectoridin treatment significantly restored all the changes of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and triglyceride (TG). These data analysis showed that tectoridin protect liver against ethanol-induced damage. In another scientific study, hepatoprotective effects of tectoridin on HepG2 cells and mice were investigated and found to showed significant result on HepG2 cells. However, some other scientific research data revealed the importance of Tectoridin on CCl4-induced rats because of their antioxidative and hepatoprotective activities. Tectoridin has been also reported to have potential to modulate beta-oxidation genes in the ethanol-induced mice in some scientific study. **Conclusions:** From the analysis of all these data it was found that Tectoridin have better medicinal power to treat liver disorders and could be used for the treatment of hepatic disorders in the future. **Keywords:** Hepatoprotective Activity, Tectoridin, Liver, Molecular Mechanism

PE-180

Therapeutic Importance of Hispidulin against Nonalcoholic Fatty Liver Disease (NAFLD): Biological Importance in the Medicine

Dinesh Kumar Patel

Faculty of Health Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Uttar Pradesh, India

Aims: Herbal medicine has been used in the history for the treatments of human disorders due to their beneficial potential in the medicine. Hispidulin is the naturally occurring pure phytochemical of medicinal importance found to be present in the Saussurea involucrate and Salvia species. In orders to know the medicinal importance and pharmacological benefit of hispidulin for the treatment of numerous human disorders, here in the present investigation numerous scientific research works have been collected and analyzed. **Methods:** Medicinal application of Hispidulin for the treatment of various form of liver disorders have been investigated in the present work through data analysis of different research work. Effectiveness of Hispidulin for the treatment of nonalcoholic fatty liver disease (NAFLD) has been investigated in this study through data analysis. Molecular study data of different research work have been also investigated to know the effectiveness of hispidulin in the medicine for the treatment of liver disorders. Effectiveness of hispidulin against Cytochromes P450 enzyme and nuclear factor-κB for their better application to treat nonalcoholic fatty liver disorders have been also investigated through scientific data analysis of different research work. However, importance of Cytochromes P450 enzyme and nuclear factor-κB in the medicine has been also investigated. **Results:** Scientific research work data analysis in the present investigation revealed the biological importance of hispidulin in the medicine. Investigation of pharmacological activities of hispidulin revealed their medicinal value in the health sectors. Different scientific research work revealed the importance of hispidulin in the liver disorders through inhibitory mechanism against various enzymes. Enzymatic study revealed the importance of hispidulin on reduced glutathione level, Cytochromes P450 enzyme and nuclear factor-κB in the nonalcoholic fatty liver disease. Molecular study data have been analyzed together with other pharmacological data to know their effectiveness against liver disorders for their hepatoprotective effects. **Conclusions:** Scientific data analysis revealed the therapeutic importance of hispidulin against Nonalcoholic fatty liver disease (NAFLD). **Keywords:** Hepatoprotective, Hispidulin, NAFLD, Nuclear Factor-Kb

PE-181

Validation of Baveno-VII Criteria for Clinically Significant Portal Hypertension in Patients with Compensated Advanced Chronic Liver Disease

Byeong Geun Song, Myung Ji Goh, Wonseok Kang, Geum-Youn Gwak, Yong-Han Paik, Moon Seok Choi, Joon Hyeok Lee, Seung Woon Paik, Dong Hyun Sinn

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

Aims: Baveno VII consensus introduced the non-invasive criteria of clinically significant portal hypertension (CSPH) using liver stiffness measurement (LSM). We evaluated the usefulness of the Baveno VII criteria to predict the risk of decompensation in patients with compensated advanced chronic liver disease (cACLD). **Methods:** We conducted a retrospective cohort study of 1,966 patients with cACLD. Patients were categorized into four groups (CSPH excluded (n = 619), grey zone (low risk of CSPH (n = 699), high risk of CSPH (n = 207)), and CSPH included (n = 441)) according to Baveno VII consensus. Risk of events was estimated using a Fine and Gray competing risk regression analysis, with liver transplantation and death as competing events. We calculated standardized hazard ratios (sHR) to assess the relative risk of decompensation. **Results:** Among 1,966 patients, 178 developed decompensations over a median follow up of 3.06 (interquartile range1.03-6.00) years. Patients with CSPH had the highest decompensation risk, followed by the grey zone high risk group, grey zone low risk group, and those without CSPH with 3-year cumulative risks of 22%, 12%, 3.3%, and 1.4%, respectively (P<0.001). Compared to CSPH excluded group, CSPH included group (sHR 8.00, 95% CI 4.00-16.0), grey zone high risk group (sHR 6.57, 95% CI 3.16-13.6), grey zone low risk group (sHR 2.15, 95% CI 1.04-4.41) had significantly higher risk of decompensation (Gray's test P<0.001). **Conclusions:** Non-invasive diagnosis of CSPH according to the Baveno VII criteria can stratify the risk of decompensation. **Keywords:** Portal Hypertension, Clinically Significant Portal Hypertension, Transient Elastography, Decompensation

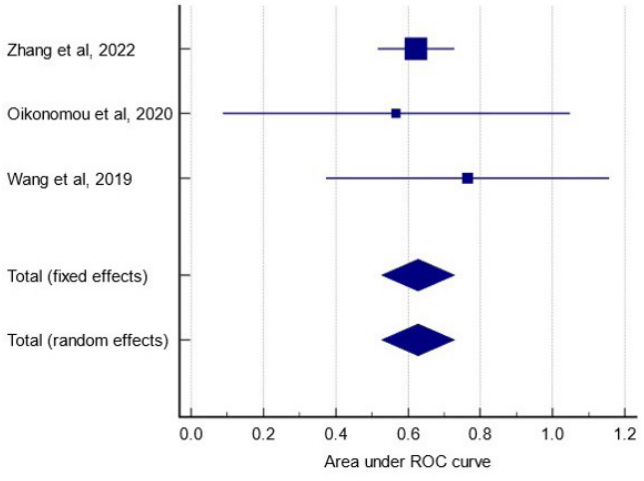
PE-182

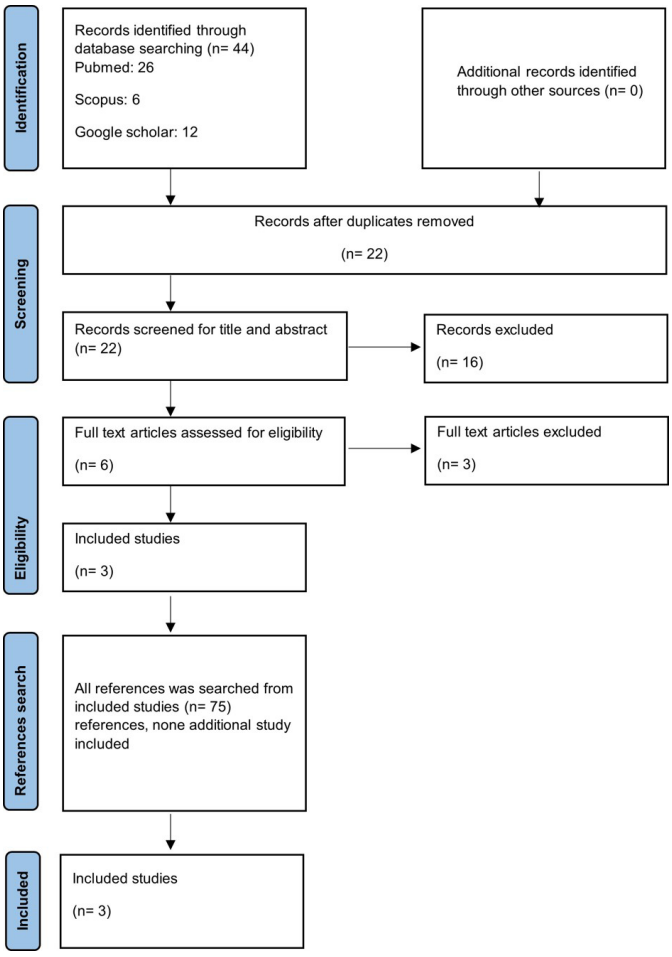
The Performance of CRP to Albumin Ratio in Predicting Mortality of HBV-Related Decompensated Cirrhosis: A Meta-Analysis

Adika Zhulhi Arjana[1], Ninda Devita[2], Umi Solekhah Intansari[1]*

[1]Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Indonesia; [2]Faculty of Medicine, Universitas Islam Indonesia, Indonesia

Aims: Serum albumin is a biomarker of malnutrition–inflammation syndrome, and low albumin levels are linked to poorer survival in many diseases. Albumin has various functions and affects liver disease severity, progression, and prognosis, especially in cirrhosis caused by Hepatitis B Virus (HBV). C-reactive protein (CRP) is another acute-phase protein that reflects the degree of severity. The ratio of CRP to albumin is considered an early indicator of mortality risk. This meta-analysis examined the CRP to albumin ratio in predicting the mortality of cirrhosis patients due to HBV. **Methods:** We searched PubMed, Scopus, and Google Scholar until September 2022 to find how the CRP to albumin ratio could predict the mortality of cirrhosis due to HBV. The pooled area under Receiver Operating Characteristic (ROC) curve was used to assess the performance of the CRP to albumin ratio in predicting mortality. We used a fixed-effect or random-effects model depending on the heterogeneity. **Results:** Out of 44 studies we searched, three studies were included for meta-analysis. A total of 433 patients were included in the analysis, with 87 patients (20%) not survived. All studies showed AUC > 0.5 to predict mortality with no significant heterogeneity. The fixed effect pooled area under the receiver operating characteristic curve was 0.628 (95%CI 0.528 to 0.728, P<0.001). **Conclusions:** Our study suggested that CRP to albumin ratio could be used as a predictor for mortality of cirrhosis patients due to HBV. However, more studies are needed to confirm this early meta-analysis. **Keywords:** CRP to Albumin Ratio, Mortality, HBV, Cirrhosis





PE-183

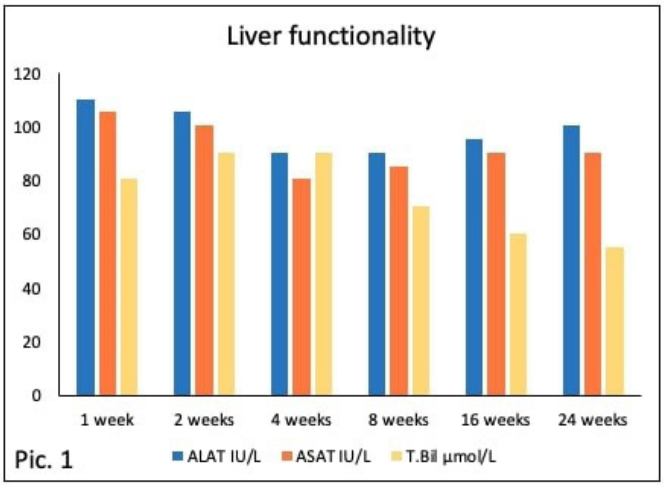
Fetal Liver Stem Cells in Combination with Pancreas Cells as an Alternative Treatment in Patients with Liver Cirrhosis, Complicated by Diabetes Mellitus

Serkulov Alibek[1], Akhmet Seidakhmetov[2], Samat Saparbayev[3]

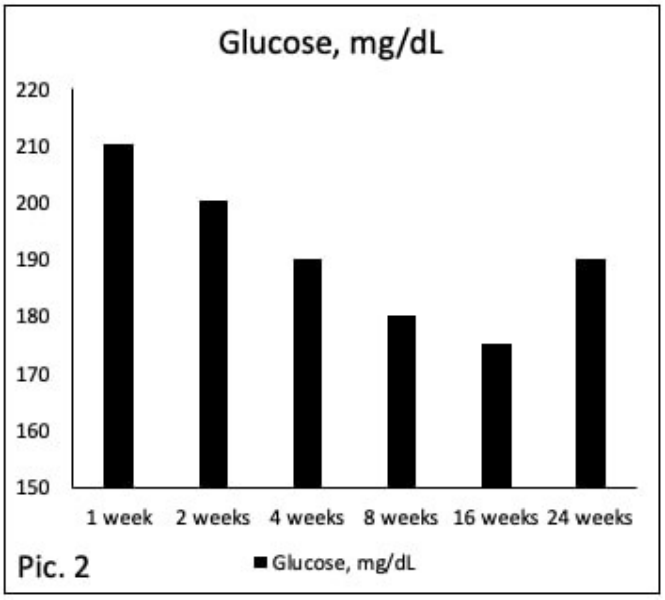
[1]Cell Transplantation Department, Transplant Coordinating Center, Kazakhstan; [2]Internal Medicine Department, JSC National Scientific Medical Center, Kazakhstan; [3]Cell Therapy Department, Aqtobe city Regional Hospital, Kazakhstan

Aims: Liver cirrhosis (LC) is largely associated with diabetes mellitus (DM). More than 80% of patients with LC manifest glucose intolerance and about 30% have type 2 DM. Liver Transplantation (LTx) is the gold-standard treatment for the failure of several solid organs, including the kidneys, liver, heart, and lungs. In past decades, mature hepatocytes, liver progenitor cells, mesenchymal stem cells, and induced pluripotent stem cells have been practiced in cases with liver cirrhosis. Fetal cell transplantation exhibited a promising lifesaving therapy for various end-stage liver diseases and could serve as a life-saving bridge until LTx can be performed.

It is already known, cell therapy using human fetal liver-derived stem cells (FLSC) can provide great potential to conservatively manage end-stage liver diseases. Moreover, the combinational transplantation of FLSC with Fetal Pancreatic stem cells (FPSC) might be a promising therapy in LC+DM cases. Therefore, the present investigation aimed to study and prove the safety and efficacy of human fetal liver-derived stem cells and pancreas stem cell transplantation in patients with end-stage LC complicated by DM. **Methods:** A total of 12 LC+DM patients were enrolled in this open-labeled and controlled study. We used donated tissue from 8 to 14 gestational weeks, which yielded ~2 - 3 × 109 cells with an average viability of 90%. FLSC+FPSC therapy was given three times at one-month intervals. The liver function, adverse events, and survival rates were evaluated during the 48-week or 72-week follow-up period, pic 1. **Results:** Further, there was a decrease in mean MELD score (P<0.01) observed in 6 months follow-up in all patients, pic 3. No significant side effects were observed during the trial. Further, no episodes related to hepatic encephalopathy recurred in any of the subjects following fetal stem cell transplantation. The FLSC+FPSC transfusions significantly increased the survival rates in LC+DM patients; reduced the model for end-stage liver disease scores; increased serum albumin, cholinesterase, and prothrombin activity; increased platelet counts and downregulated glucose level, pic 2. Serum total bilirubin and alanine aminotransferase levels were significantly decreased after the FLSC+FPSC transfusions. **Conclusions:** FLSC+FPSC transfusions are safe in the clinic and may serve as a novel therapeutic approach for LC+DM patients. Therapy using human fetal liver stem/progenitor cells offers a potentially supportive modality to organ transplantation in the management of liver diseases. **Keywords:** Fetal Stem Cells, Liver Cirrhosis, Liver Transplantation, Diabetes Mellitus



Pic. 1



Pic. 2

PE-184

Non Invasive Detection of Esophageal Varices in Patients with Compensated Liver Cirrhosis

E. Tharwa[1], A. Abou-Gabal[1], M. Abdel-Samiee[1], O. El-Abd[2], Eman Abdelsameea[1], E. Abd-Almonem[3], A. Badran[1]

[1]Hepato-Gastroenterology, National Liver Institute, Menoufia University, Egypt; [2]Radiology, National Liver Institute, Menoufia University, Egypt; [3]Clinical Pathology, National Liver Institute, Menoufia University, Egypt

Aims: Varices are present in 30-40 % of patients with compensated cirrhosis (Child-Pugh class A). Although screening endoscopy for esophageal varices (O.V.) is recommended to all patients with cirrhosis, this recommendation is not a result of evidence-based data. We studied the association of (platelet count/spleen diameter ratio, insulin resistance and splenoportal index) and the presence of O.V. in patients with compensated cirrhosis. **Methods:** 124 patients with compensated liver cirrhosis due to chronic hepatitis C virus were studied. After clinical, laboratory ultrasound examinations, all patients underwent screening endoscopy and O.V were reported as present or absent. According to presence or absence of varices; two groups were described: group I without varices and group II with varices. **Results:** Among 124 patients with mean age of (51.81±12.94), 2 groups were described: group I (30 patients) and group II (94 patients) with a male majority (20 patients in group I and 66 patients in group II). In group I and group II: the mean platelet count/spleen diameter ratio was (1022.6±73.36, 608.76±58.44) respectively, the mean insulin resistance value was (2.426±0.618, 3.081±0.474) respectively. The mean splenoportal index (SPI) value was (2.878±0.870, 6.349±0.514) respectively. For platelet count/spleen diameter ratio and SPI, the sensitivity was (95.7%), specificity (83.3%) and accuracy (92.7%). For platelet

count/spleen diameter ratio and insulin resistance (IR), the sensitivity was (70.2%), specificity (86.7%) and accuracy (74.1%). For IR and SPI, the sensitivity was (70.2%), specificity (76.7%) and accuracy (71.7%). For the three predictors combined, the sensitivity was (78.7%), specificity (82.2%) and accuracy (79.5%). **Conclusions:** Low platelet count/spleen ratio and high SPI are very useful non invasive predictors for the presence of O.V. that could be used either separately or combined to decrease the number of upper GIT endoscopies needed in cirrhotic patients management, However, IR as a non invasive predictor is still in need for further evaluation. **Keywords:** Varices, Esophageal, Platelet, Spleen

Table (1) shows the sensitivity, specificity, positive predictive value, negative predictive value and accuracy when we combine (Platelet count /spleen diameter ratio & Splenoportal index), (Platelet count /spleen diameter ratio & IR) and (IR & Splenoportal index).

	Platelet count /spleen diameter ratio & Splenoportal index	Platelet count /spleen diameter ratio & IR	IR& Splenoportal index	Platelet count /spleen diameter ratio & IR& Splenoportal index
Sensitivity (%)	95.7	70.2	70.2	78.7
Specificity (%)	83.3	86.7	76.7	82.2
Positive Predictive Value (%)	94.7	94.3	90.4	93.2
Negative Predictive Value (%)	86.2	48.1	45.1	55.2
Accuracy (%)	92.7	74.1	71.7	79.5

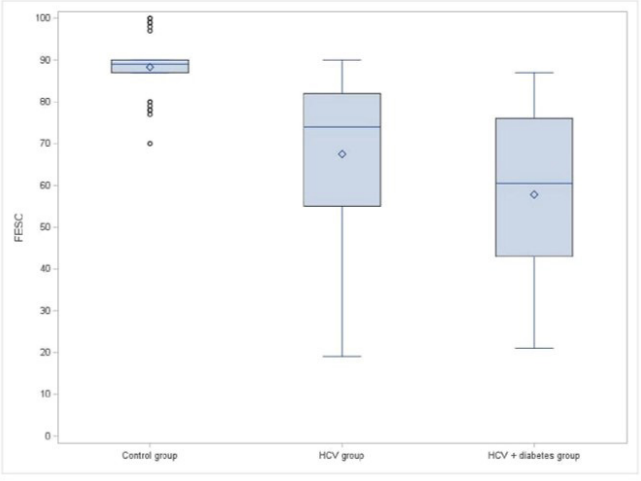
PE-185

Sudoscan for Detection of Small Fiber Neuropathy Changes in Hepatitis C Virus Infected Cirrhotic Patients

El-Sayed Tharwa[1], Anwar Mohamed[1], Mohamed Abdel-Samiee[1], Mohsen Salama[1], Mohamed I. Youssef[2], A. S. Seif[3], Ayman Ahmed Sakr[4], Sally Waheed Elkhadry[5], A.G. Badran[6], Mohammad AbdelElhameed Ahmed Alwaseef[7], Helmy Elshazly[1]

[1]Department of Hepatology and Gastroenterology, National Liver Institute, Menoufia University, Menoufia, Egypt; [2]Department of Internal Medicine, Al-Azhar University, Cairo, Egypt; [3]Tropical Medicine Hepatology and Gastroenterology Department, ShebinElkom Teaching Hospital, Menoufia, Egypt; [4]Department of Tropical Medicine, Faculty of Medicine, Menoufia University, Menoufia, Egypt; [5]Epidemiology and Preventive Medicine Department, National Liver Institute, Menoufia University, Menoufia, Egypt; [5]Specialized Medical Center-Damas Liver Center, GIT and Hepatology, Mansoura, Egypt; [6]Clinical Pathology department, Al-Azhar University, Cairo, Egypt

Aims: Worldwide,130-170 million people are infected with hepatitis C virus (HCV), which represents more than 3 % of the world's population. HCV infection is associated with several extrahepatic manifestations, some of which are neurological and mostly related to immune mechanisms. Hepatitis C Virus (HCV) infection can affect the neurological system and neuropathy is one of these manifestations. HCV infection is associated with diabetes mellitus (DM) type II and diabetic patients are at higher risk of acquiring HCV infection. Sweat function has been proposed to assess early autonomic neuropathy. This study aimed to evaluate small fiber neuropathy in asymptomatic HCV-related cirrhotic patients with or without diabetes mellitus through sweat function assessment by SUDOSCAN test. **Methods:** Three groups were involved: 47 healthy controls, 48 HCV-related cirrhotic patients without DM (Group 1) and 49 HCV-related cirrhotic patients with DM type II (Group 2). All participants were subjected to liver panel tests, renal function tests, cell blood counts, HbA1c, abdominal ultrasound. Sweat function was assessed in all patients and controls by measuring hand and feet Electrochemical Skin Conductance (ESC, µS) using Sudoscan. **Results:** Peripheral neuropathy was detected in none of the controls, 39% of Group 1 patients and in 62% of Group 2 patients ($P< 0.0001$). The mean feet ESC (FESC) was 88.3 ± 6.8 µS in controls, 67.2 ± 19.2 µS in Group 1 and 57.9 ± 19.4 µS in Group 2 ($P< 0.0001$). A significant correlation was observed between FESC and bilirubin, albumin, creatinine, international normalized ratio, transaminases and splenic size. **Conclusions:** In conclusion, mean FESC are decreased in HCV-related cirrhosis with or without DM when compared to the control group, suggesting small fiber autonomic neuropathy based on sweat function assessment. SUDOSCAN seems a valuable noninvasive method for early detection of small fiber neuropathy in asymptomatic HCV-related cirrhosis with or without DM. Long-term follow-up would be useful to evaluate the progression of neurological dysfunction in this population; and future studies are needed to confirm our results in a larger population of hepatic patients with or without cirrhosis of any etiologies, along with a clinical neurological examination. **Keywords:** Small Fiber Neuropathy, Sudoscan, HCV, Liver Cirrhosis



PE-186

Beneficial Effect of White Sesame Oil on Lipid Profile and Liver Enzymes in Male Rats Treated against Thioacetamide-Induced Hepatotoxicity

Ankush Kumar, Prachi Mishra

Department of basic sciences, DAV, A State University, India

Aims: White Sesame Seed Oil (WSSO), a natural product rich in n-3 fatty acid, on lipid peroxidation, antioxidative capacity and membrane deformation of erythrocytes exposed to high glucose is limited. WSSO is a traditional medicine against various disorders including liver diseases. This study was designed to investigate the effect of WSSO on lipid profile and liver enzyme against thioacetamide-induced hepatotoxicity in male Wistar rats. **Methods:** Five groups of male Wistar rats have been used. In group 1 rats received intraperitoneal (i.p.) injection of normal saline while groups 2–5 received thioacetamide (TAA, 75 mg/kg; i.p.) for induction of liver cirrhosis. Group 3 received 50 mg/kg of silymarin. The rats in groups 4 and 5 received 100 and 300 mg/kg of WSSO, respectively. Hepatic damage was assessed grossly and microscopically for all of the groups. **Results:** The statistical results of the present study showed a significant increase in the level of cholesterol, triglycerides and Low density lipoprotein (LDL) in the group treated with TAA compared with control group, also a significant increase in the level of liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT), no difference on high density lipoprotein (HDL) level. The group 4 and 5 that was administrated with WSSO and injected with TAA showed a significant (P<0.05) decrease in the level of cholesterol, triglyceride, LDL and also a significant (P<0.05) decrease in liver enzymes AST and ALT compared with the group that injected with TAA. These groups decreased fibrosis of the liver tissues. Immunohistochemistry assessment against proliferating cell nuclear antigen did not show remarkable proliferation in the WSSO-treated rats when compared with group 2. Moreover, factions of the WSSO extract were tested on Hep-G2 cells and showed antiproliferative activity. **Conclusions:** It is concluded that WSSO has a protective effect against the toxicity of TAA on the liver of male rats. **Keywords:** Thioacetamide-Induced Hepatotoxicity, White Sesame Seed Oil, Rats

PE-187

The Effect of Liver Cirrhosis on the Mental Condition of Elderly Patients

Ardela Iga Pratiwi

Alumnus of Department of History, Universitas Gadjah Mada, Indonesia

Aims: Liver cirrhosis is a chronic and irreversible disease characterized by distortion of the liver architecture and formation of regenerative nodules. Liver cirrhosis is included in the top twenty causes of death in the world. Indonesia ranks third in the highest prevalence of liver disease in Southeast Asia. Liver cirrhosis in elderly patients should receive special attention because it affects the patient's mental condition. This study aims to describe the effect of liver cirrhosis on the mental condition of elderly patients. **Methods:** This study used electronic data base as a method by reviewing some articles that was collected through google scholar published in 2017 to 2022, keywords liver cirrhosis, mental condition, elderly. **Results:** The results showed that elderly patients with liver cirrhosis experienced psychosomatic disorders. Symptoms of psychosomatic disorders in elderly patients with liver cirrhosis include depression, anxiety, insomnia, fatigue and cognitive impairment. The increase in psychological stress correlates with an increase in aspartate aminotransferase, which is an important mediator in the inflammatory process. This shows the role of inflammation in cirrhosis which causes depression in patients. Worsening liver damage increases the risk of hepatic encephalopathy, one of which is characterized by personality changes. Symptoms include confusion, forgetfulness, mood swings and difficulty speaking. **Conclusions:** A psychosomatic approach in elderly patients with chronic diseases such as liver cirrhosis is very important to improve health, quality of life and facilitate the treatment of liver cirrhosis. Thus, the treatment of elderly patients with liver cirrhosis is not enough to only focus on curing the disease, but also on the implications of liver cirrhosis on the patient's mental condition. **Keywords:** Liver Cirrhosis, Mental Condition, Elderly

Other Hepatobiliary Diseases

PE-188

Metformin Ameliorates Liver Fibrosis Induced by Congestive Hepatopathy via mTOR/HIF-1α Signaling Pathway

Xiaowei Dang, Jing Yang, Suxin Li, Shengyan Liu, Yuehui Zhang, Dongqi Shen, Peiju Wang

Department of Hepatopancreatobiliary Surgery, The First Affiliated Hospital of Zhengzhou University, China

Aims: Congestive hepatopathy (CH) is hepatic vascular disease that results in chronic liver congestion, which can lead to liver fibrosis. Newer uses of metformin have been discovered over the years. However, the function of metformin in congestive liver fibrosis is not fully understood. This study investigated the effect of metformin on liver fibrosis in mice model of CH. **Methods:** Partial ligation of the inferior vena cava (pIVCL) was used to establish the mouse model of liver congestion. Metformin 0.1% was added to the daily drinking water of mice, and after 6 weeks, the effect of metformin on liver tissue was studied. We also stimulated hepatic stellate cell (HSC) with $CoCl_2$ to observe the inhibitory impact of metformin on mammalian target of rapamycin (mTOR)/hypoxia-inducible factor-1α (HIF-1α) pathway. **Results:** Metformin attenuated liver congestion; decreased the expression of collagen, fibronectin, α-smooth muscle actin (α-SMA), and HIF-1α; and ameliorated liver fibrosis in pIVCL mice. The proliferation and migration of HSC were inhibited by metformin in vitro, which prevented expression of α-SMA and restrained activation of HSC. The expressions of phosphorylated-mammalian target of rapamycin, HIF-1α, and vascular endothelial growth factor were also decreased. **Conclusions:** Metformin inhibits liver fibrosis induced by CH. This beneficial effect may be a result of inhibition

of HSC activation and mTOR/HIF-1α signaling pathway. **Keywords:** Metformin, Liver Fibrosis, Congestive Hepatopathy, mTOR/HIF-1α

PE-189

Rare Presentation of a Multicystic Biliary Tumour with Features of a Biliary Adenofibroma

Mark Ting-Le Tan[1], Cowan` Ho[2], Leow Wei Qiang[1]

[1]Department of Anatomical Pathology, Singapore General Hospital, Singapore; [2]Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Aims: Biliary adenofibromas (BAF) are exceedingly rare benign liver tumours that have demonstrated the capacity for malignant transformation. Currently, its tumorigenesis remains poorly understood. Herein, we report a case of a multicystic biliary tumour bearing features characteristic of a BAF. **Methods:** A 73-year-old female presented with per rectal bleeding. A 2cm heterogeneous mass in liver segment 5 was incidentally discovered on computed-tomography imaging. She underwent a R0 liver wedge resection, revealing a 2.4cm multiloculated cystic lesion. Histological examination showed a biphasic tumour composed of multicystic locules containing scattered hepatocytes, and a myofibroblastic stroma. The epithelial lining consisted of monotonous cells that were positive for CK19, with areas demonstrating apical snouting. No architectural complexity or high-grade features were observed. On immunohistochemistry, CCND1 and c-erb-B2 were positive. The Ki67 index was 5 to 10%, and p53 staining showed scattered weak nuclear positivity. **Results:** The morphologic features exhibited in our case were similar to prior documented cases of BAF. Only 20 cases have been reported to date, with 8 displaying malignant transformation. These tumours are typically characterised by biliary-type epithelial cells arranged in a tubulo-cystic architecture, with a bland fibroblastic stromal component. A close differential considered was a multicystic biliary hamartoma. Several authors have also proposed that papillary growths, cribriforming glands and nuclear atypia as potential cues that may indicate malignant transformation, although these predictive features have not been validated. These were not observed in our case. Currently, the genomic landscape of BAF has not been well elucidated. Amplifications of CCND1 and c-erb-B2 have been demonstrated in previous cases, which was also reflected on immunohistochemistry in our case. **Conclusions:** The rarity of BAF impedes our understanding of its biological behavior, and efforts to formulate risk stratification tools have been elusive. Further collaborative efforts and expanded genomic profiling with next-generation sequencing are required. **Keywords:** Biliary, Adenofibroma, Multicystic, Hamartoma

Author Index

L

Z

Save the Date

The Asia-Pacific Primary Liver Cancer Expert Association

APPLE

JULY 13 – 15, 2024

Honolulu, Hawaii

Program Co-Chairs

Ghassan Abou-Alfa, MD, MBA
Memorial Sloan Kettering Cancer Center

Linda L. Wong, MD
University of Hawai'i Cancer Center

goto PER®.com

Scan the QR code or visit the link below to explore this program.

gotoper.com/appleab24

Response that matters with the power of LENVIMA®

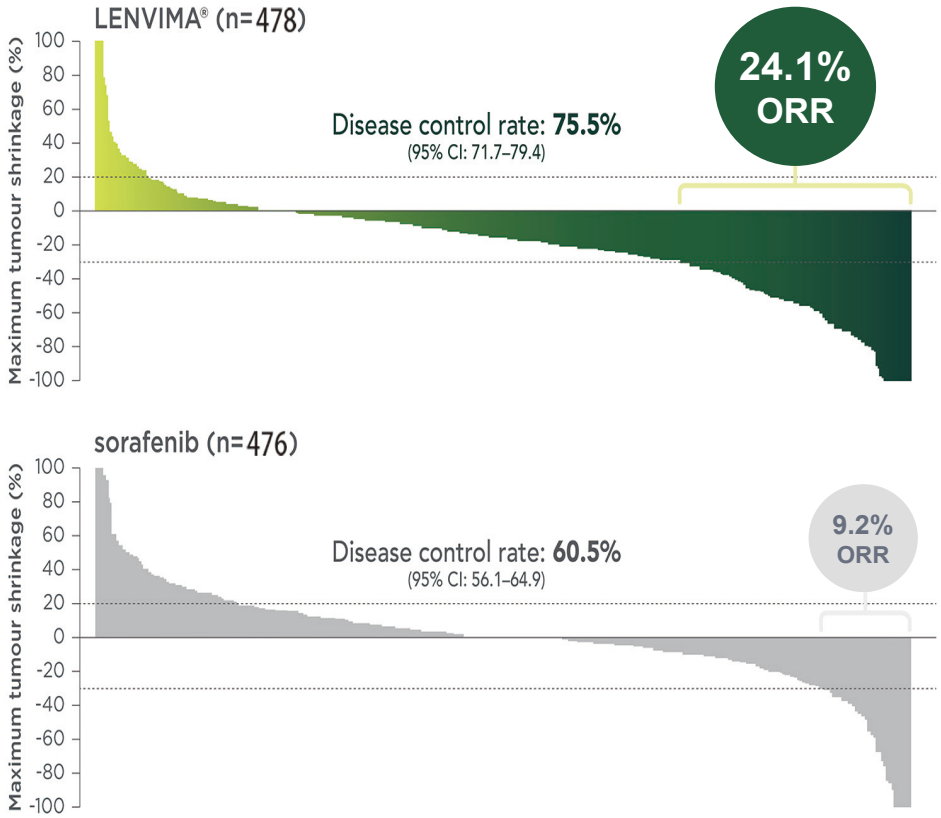
in first-line uHCC therapy

Disclaimer

The information contained herein this material is assured by the regulation of the country where APPLE 2023 is organized. Sponsor does not have any improper interference APPLE 2023 materials Please consult the full local prescribing information for approved information on any products described in APPLE 2023 materials. Eisai does not recommend the use of LENVIMA in any manner other than as described in the approved local prescribing information.

Maximum change in tumour size by mRECIST[1]*

For Healthcare Professionals Only
For Korean Full Prescribe Information, Please get from **HERE**
For other countries, please refer to local prescribing information



~1 in 4 patients achieved **>30% tumour shrinkage** with **LENVIMA®** compared to ~1 in 10 with sorafenib

[ORR: LENVIMA 24.1%(95% CI 20.2-27.9) vs Sorafenib 9.2%(6.6-11.8) OR 3.13(95% CI 2.15-4.56), p<0.0001, investigators' review according to mRECIST]

【Study Design】This was an open-lavel, phase 3, multicenter, non-inferiority trial that recruited patients with uHCC. Patients were randomly assigned (1:1) via an interactive voice-web response system-with region; macroscopic portal vein invasion, extrahepatic spread, or both; Eastern Cooperative Oncology Group performance status; and body weight as stratification factors-to receive oral Lenvatinib (12mg/day for bodyweight≥60kg or 8mg/day for bodyweight <60kg)or Sorafenib 400mg twice-daily in 28-days cycles. The Primary endpoint was overall survival, measured from the date of randomization until the date of death from any cause. The efficacy analysis followed the intention-to-treat principle, and only patients who received treatment were include in the safety analysis. Lenvatinib(median OS 13.6month,95%CI12.1-14.9)was non-inferior to Sorafenib (median OS 12.3month, 95%CI 10.4-13.9) in overall survival in untreated advanced HCC(HR 0.92, 95%CI 0.79-1.06)1

Change in tumour size truncated at 100%. Disease control rate and tumour shrinkage are % of total study groups, including unknown/not evaluable patients not included on these graphs.
*By investigator assessment.
CI: confi dence interval,**mRECIST**: modifi ed Response Evaluation Criteria In Solid Tumours, **ORR:** objective response rate.
uHCC : unresectable hepatocellular carcinoma
Reference 1 : Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018 Mar 24;391(10126):1163-1173.

Eisai

AR-LV-SN-22A-02 / KR-LV-MK-22A-03

LENVIMA® (lenvatinib) capsules

RESPONSE THAT MATTERS

Eisai

ONCOLOGY WITH SOUL

We give our first thoughts to patients and their families and helping to increase the benefits that health care provides.

Eisai Co., Ltd.(www.eisai.com)
4-6-10, Koishikawa, Bunkyo-ku,
Tokyo 112-8088, Japan
Tel: 81-3-3817-3700

AR-LV-SN-21G-01

IMBrave150 : 501patients with unresectable hepatocellular carcinoma who had not previously received systemic treatment were randomly assigned in a 2:1 ratio to receive either atezolizumab plus bevacizumab or sorafenib. The coprimary endpoints were OS and IRF assessed PFS.
HR : Hazard ratio **CI** : Confidence interval **OS** : Overall survival **IRF** : Independent review facility **PFS** : Progression free survival

References 1. Finn et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905. May 14, 2020.
2. AL Cheng, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2021 Dec 10;S0168-8278(21)02241-8.
*descriptive purpose only

M-KR-00001904

*보다 자세한 제품정보 문의 및 제품 관련 부작용 보고는 (주)한국로슈 (02-3451-3600) 로 연락 주시기 바랍니다 *가장 최신 제품정보는 ㈜한국로슈 홈페이지(www.roche.co.kr)에서 확인하실 수 있습니다

㈜한국로슈 서울특별시 서초구 서초대로 411. GT Tower(East) 빌딩 17층 (06615) Tel 02.3451.3600 / www.roche.co.kr

TECENTRIQ® atezolizumab 840 mg | 1200 mg

AVASTIN® bevacizumab

IMBrave150 : 501patients with unresectable hepatocellular carcinoma who had not previously received systemic treatment were randomly assigned in a 2:1 ratio to receive either atezolizumab plus bevacizumab or sorafenib. The coprimary endpoints were OS and IRF assessed PFS.

HR : Hazard ratio **CI** : Confidence interval **OS** : Overall survival **IRF** : Independent review facility **PFS** : Progression free survival

References 1. Finn et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894–905. May 14, 2020.
2. AL Cheng, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2021 Dec 10;S0168-8278(21)02241-8. *descriptive purpose only

M-KR-00001903

*보다 자세한 제품정보 문의 및 제품 관련 부작용 보고는 (주)한국로슈 (02-3451-3600) 로 연락 주시기 바랍니다 *가장 최신 제품정보는 ㈜한국로슈 홈페이지(www.roche.co.kr)에서 확인하실 수 있습니다

㈜한국로슈 서울특별시 서초구 서초대로 411. GT Tower(East) 빌딩 17층 (06615) Tel 02.3451.3600 / www.roche.co.kr

TECENTRIQ® atezolizumab 840 mg | 1200 mg INJECTION FOR IV USE

AVASTIN® bevacizumab

2022년 11월, 국소진행성 또는 전이성 담도암 1차 치료로서 허가 획득

BTC

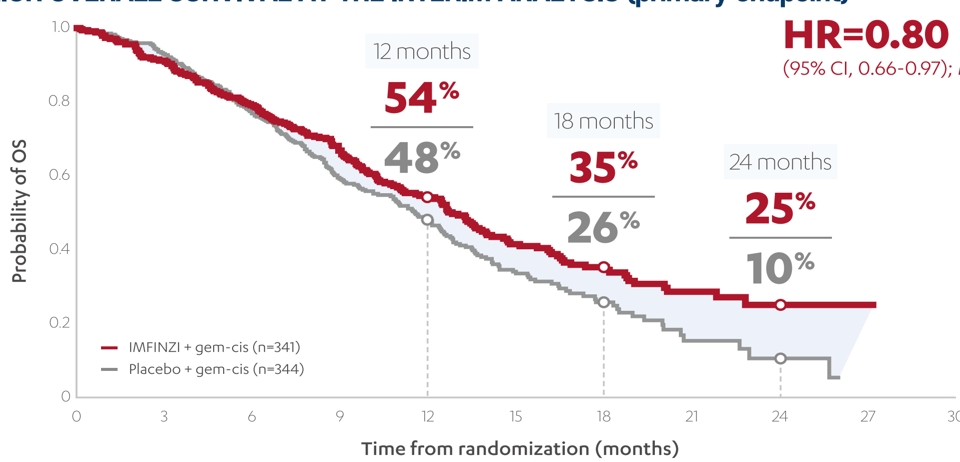
IMFINZI®
durvalumab
Injection for Intravenous Use 50 mg/mL

젬시타빈/시스플라틴 대비 전체 생존기간의 연장이 확인된

담도암 1차 치료 면역항암제 병용요법[1,2]

SUPERIOR OVERALL SURVIVAL AT THE INTERIM ANALYSIS (primary endpoint)[1,2]

HR=0.80
(95% CI, 0.66-0.97); *P*=0.021†



Data cutoff - August 11, 2021

Number of patients at risk

IMFINZI + gem-cis	341	331	324	309	294	278	268	252	238	208	174	151	135	118	93	79	74	57	49	39	29	24	15	12	9	8	4	1	0
Placebo + gem-cis	344	337	329	317	299	283	261	242	220	183	159	143	125	97	78	65	52	40	29	21	15	10	8	4	4	3	0	0	0

Median duration of follow-up: 16.8 months (95% CI, 14.8-17.7) with IMFINZI + gem-cis and 15.9 months (95% CI, 14.9-16.9) with gem-cis.[2]

Median OS was 12.8 months (95% CI, 11.1-14.0) with IMFINZI + gem-cis vs 11.5 months (95% CI, 10.1-12.5) with gem-cis[2]

Adapted from Ref.1

BTC=biliary tract cancer; CI=confidence interval; gem-cis=gemcitabine-cisplatin; HR=hazard ratio; IO=immuno-oncology; OS=overall survival. *histologically confirmed unresectable, locally advanced, or metastatic adenocarcinoma of the biliary tract.[1,2]
†The interim analysis of OS met the prespecified O'Brien-Fleming-type boundary for declaring statistical significance with a 2-sided P value of <0.03. OS at 12, 18, and 24 months was estimated (using Kaplan-Meier curve) and presented by treatment arm.[2]

1. 임핀지 주 국내 허가사항. https://nedrug.mfds.go.kr/index (assessed by 2022-12-01).
2. Oh DY, He AR, Qin S, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. *NEJM Evidence*. 2022. doi:10.1056/EVIDoa2200015 (including Supplementary Appendix and Protocol).

※ 보다 자세한 사항은 제품설명서 전문을 참고하시기 바랍니다.

PRESCRIBING INFORMATION

임핀지주 (더발루맙) [효능·효과] 국소 진행성 비소세포폐암: 백금 기반 동시적 항암화학방사선요법 이후 질병이 진행되지 않은 절제불가능한 국소 진행성 비소세포폐암 환자의 치료 소세포폐암: 확장 병기 소세포폐암 환자의 1차 치료로서 에토포시드 및 카보플라틴 또는 시스플라틴과의 병용 요법 담도암: 국소 진행성 또는 전이성 담도암 환자의 1차 치료로서 젬시타빈 및 시스플라틴과의 병용 요법 [용법·용량] 효능 효과별 권장 용량은 다음 표와 같다. 이 약은 1시간에 걸쳐 정맥 점적 주입한다.

효능 효과	이 약의 권장 용량	투여 기간
국소 진행성 비소세포폐암	이 약 10mg/kg을 2주 간격으로 투여	질환이 진행되거나 허용 불가능한 독성 발생 전까지
소세포폐암	2이 약 1500 mga을 화학요법b,c과 병용하여 3주 간격으로 4주기 동안 투여한 뒤, 이 약 1500 mg 단독요법을 4주 간격으로 투여	질환이 진행되거나 허용 불가능한 독성 발생 전까지
담도암	이 약 1500 mga을 화학요법c,d과병용하여 3주 간격으로 투여한 뒤, 이 약 1500 mg 단독요법을 4주 간격으로 투여	질환이 진행되거나 허용 불가능한 독성 발생 전까지

a 체중 30 kg 이하의 환자는 체중에 따라 이 약 20 mg/kg을 화학요법과 병용하여 3주 간격으로 투여한 뒤, 이 약 20 mg/kg을 단독요법으로서 4주 간격으로 체중이 30 kg을 초과할 때까지 투여한다. b 이 약을 화학요법과 병용할 때에는 에토포시드 및 카보플라틴 또는 시스플라틴의 허가된 용법 용량 정보를 참조한다. c 화학요법과 같은 날 투여하는 경우 이 약을 먼저 투여한다. d 이 약을 화학요법과 병용할 때에는 해당 화학요법제의 허가된 용법 용량 정보를 참조한다. 용법조절: 이 약의 용량 증가나 감소는 권장되지 않는다. 일반적으로 중증 (3등급) 면역 매개 이상사례의 경우 이약의 투여를 보류한다. 생명을 위협하는 (4등급) 면역 매개 이상사례와, 전신 면역 억제 치료가 필요하거나 코르티코스테로이드 시작 12주 이내에 프레드니손 또는 등가량 하루 10 mg 이하로 감량할 수 없는 중증 (3등급) 면역 매개 이상사례의 경우 이 약의 투여를 중단한다. 면역 매개 이상사례가 다음 표에 요약되어 있다. [이 약의 용법 조절 및 관리 권장 사항]

면역 매개 폐렴증/ 간질성 폐질환	2등급	투여 보류c	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3 또는 4등급	투여 중단	
면역 매개 간염	2등급이고, 알라닌 아미노전이효소 (ALT) 또는 아스파르트산 아미노전이효소 (AST)가 정상상한치의 3배 초과, 5배 이하이거나 총 빌리루빈이 정상상한치의 1.5배 초과, 3배 이하	투여 보류c	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3등급이고, ALT 또는 AST가 정상상한치의 5배 초과, 8배 이하 또는 총 빌리루빈이 정상상한치의 3배 초과, 5배 이하		
	3등급이고, ALT 또는 AST가 정상상한치의 8배를 초과 또는 총 빌리루빈이 정상상한치의 5배를 초과	투여 중단	
	다른 요인은 없으며, ALT 또는 AST가 정상상한치의 3배를 초과하고 총 빌리루빈이 정상상한치의 2배를 초과하는 경우		
다음을 동반한 면역매개 간염: 종양이 간에 침범하고 기저 ALT 또는 AST가 정상상한치를 초과	ALT 또는 AST가 기저 상태에서 정상상한치의 1배 초과, 3배 이하였다가 5배 초과 10배 이하까지 증가하거나 AST 또는 ALT가 기저 상태에서 정상상한치의 3배 초과, 5배 이하였다가 8배 초과 10배 이하까지 증가	투여 보류c	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	AST 또는 ALT가 정상상한치의 10배 초과까지 증가 또는 총 빌리루빈이 정상상한치의 3배 초과까지 증가	투여 중단	
면역 매개 결장염 또는 설사	2 또는 3등급	투여 보류c	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	4등급	투여 중단	
	모든 등급의 장 천공	투여 중단	장 천공이 의심되는 즉시 외과 진료
면역 매개 내분비병: 갑상선 기능 항진증, 갑상선염	2~4등급	임상적으로 안정할 때까지 투여 보류	대증적 관리
면역 매개 내분비병: 갑상선 기능 저하증	2~4등급	변경하지 않음	임상 지시대로 갑상선 호르몬 대체 개시
면역 매개 내분비병: 부신 기능 부전, 뇌하수체염/뇌하수체 저하증	2~4등급	임상적으로 안정할 때까지 투여 보류	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량 및 임상 지시대로 호르몬 대체 개시
면역 매개 내분비병: 제1형 당뇨병	2~4등급	변경하지 않음	임상 지시대로 인슐린 치료 개시
면역 매개 신장염	2등급이고, 혈청 크레아티닌이 정상상한치 또는 기저치의 1.5~3배를 초과	투여 보류c	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3등급이고 혈청 크레아티닌이 기저치의 3배를 초과 또는 정상상한치의 3~6배를 초과하거나, 4등급이고 혈청 크레아티닌이 정상상한치의 6배를 초과	투여 중단	

이상사례	중증도 (CTCAE v4.03a)	용법 조절	코르티코스테로이드 요법 및 그 외b
면역 매개 발진 또는 피부염 (유사 천포창 포함)	2등급으로 1주일 초과 또는 3등급	투여 보류c	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	4등급	투여 중단	
면역 매개 심근염	2~4등급	투여 중단	2~4 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량d
면역 매개 근육염/ 다발근육염	2 또는 3등급	투여 보류c,e	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	4등급	투여 중단	
주입 관련 반응	1 또는 2등급	주입을 중단하거나 느리게 주입	후속 주입 반응의 예방을 위해 사전 약물 치료를 고려할 수 있음
	3 또는 4등급	투여 중단	관련 기준, 적절한 임상 진료 지침 및/또는 사회적 지침에 따라 중증 주입 관련 반응 관리
중증 근육 무력증	2등급	투여 보류c	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3 또는 4등급, 또는 호흡 부전이나 자율 신경 실조증의 징후가 있는 모든 등급	투여 중단	
뇌염	3-4등급	투여 중단	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
기타 면역 매개 이상사례f	3등급	투여 보류c	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	4등급	투여 중단	

a 이상사례 표준 용어기준 (Common Terminology Criteria for Adverse Events; CTCAE), 버전 4.03 b 1등급 이하로 개선되면, 코르티코스테로이드의 감량을 시작하여 최소 1개월 간 지속하여야 한다. 악화되거나 개선이 없다면, 코르티코스테로이드의 용량 증가 및/또는 다른 전신 면역 억제제 사용을 고려한다. c 투여 보류 후, 1등급 이하로 개선되고 코르티코스테로이드 용량이 일일 10mg 프레드니손 또는 등가량 이하로 감소되었을 경우, 12주 이내에서 이 약의 투여를 다시 시작할 수 있다. 3등급 이상사례 재발의 경우 이 약을 중단한다. d 코르티코스테로이드 투여에도 불구하고 2~3일 이내에 개선이 없다면, 신속히 추가적인 면역억제 치료를 시작한다. 회복(0등급)되면, 코르티코스테로이드의 감량을 시작하고 최소 1개월 간 지속한다. e 이상사례가 30일 이내에 1등급 이하로 회복되지 않거나 호흡기 기능부전의 징후가 있는 경우에는 이 약 투여를 중단한다. f 면역 혈소판 감소증, 췌장염 포함. 의심되는 면역 매개 이상사례에 대해, 병인 확인 또는 대체 병인을 배제하기 위한 적절한 평가가 수행되어야 한다. 비-면역 매개 이상사례에 대해, 2등급과 3등급 이상사례의 경우 1등급 이하가 될 때까지 이 약의 투여를 보류한다. 4등급 이상사례의 경우 이 약 투여를 중단한다 (예외적으로 4등급 실험실 검사수치 이상의 경우, 수반된 임상 징후 및 임상적 판단에 근거하여 투여 중단을 결정한다). 이 약은 경등도 간장애 환자에서는 용량 조절이 권장되지 않으며, 중등도 또는 중증 간장애 환자에서는 연구되지 않았다. **[투여방법]** 투여 전 이 의약품의 희석에 대한 지시 사항은 사용상의 주의사항, '13. 취급상의 주의사항'을 참고한다. 멸균된 저 단백질 결합 0.2 또는 0.22 마이크로미터 인라인 필터(in-line filter)를 포함하는 정맥 주사 라인을 통해 1시간에 걸쳐 주사액을 정맥 내 투여한다. 같은 주입 라인으로 다른 약물을 동시 투여하지 않는다. 사용하고 남은 약물이나 물품은 관련 규정에 따라 폐기되어야 한다. **[사용상의 주의사항] 다음 환자에는 투여하지 말 것:** 이 약의 주성분 또는 첨가제에 과민증 병력이 있는 환자. **다음 환자에는 신중히 투여할 것:** 자가면역질환 또는 자가면역질환 병력이 있는 환자 **약물이상반응** 1)임상시험에서 보고된 이상사례: 이상사례는 MedDRA의 기관계 분류에 따라 기재되었다. 각 기관계 분류에서, 이상사례는 빈도가 높은 순으로 표기되었다. 각 빈도 군에서, 이상사례는 중증도가 높은 순으로 표기되었다. 또한, 각 이상사례의 해당 빈도 분류는 CIOMS III 협의에 따르며 다음과 같이 정의된다: 매우 흔하게 (≥1/10); 흔하게 (≥1/100 ~ <1/10); 흔하지 않게 (≥1/1,000 ~ <1/100); 드물게 (≥1/10,000 ~ <1/1,000); 매우 드물게 (<1/10,000); 빈도 불명, 즉 이용 가능한 자료로부터 추정될 수 없음. 국소 진행성 비소세포폐암 PACIFIC 연구 PACIFIC 연구 (475명)에서 국소 진행성 절제 불가능한 비소세포폐암 환자로 이 연구 시작 전 1~42일 내에 2주기 이상의 항암화학방사선요법을 완료한 환자들을 대상으로 이 약(10 mg/kg)의 안전성이 평가되었다. 이 환자 집단에서 가장 흔한 이상사례는 기침 (40.2%, 위약군 30.3%), 상부 호흡기 감염 (26.1%, 위약군 11.5%) 및 발진 (21.7%, 위약군 12.0%)이었다. 3 또는 4등급 이상사례의 발생률은 이 약 투여군에서 12.8%, 위약군에서 9.8%이었다. 가장 흔한 3 또는 4등급 이상사례는 폐렴 (6.5%, 위약군 5.6%)이었다. 이 약 투여군의 8.2% 및 위약군의 5.6%에서 이상사례로 인해 투약을 중단하였다. 이 약의 투약 중단으로 이어진 가장 흔한 이상사례는 폐렴증 (4.8%)이었다. 중대한 이상사례는 이 약 투여군 12.8% 및 위약군 11.1%의 환자에서 발생하였다. 가장 흔한 중대한 약물이상반응은 2% 이상의 환자에서 보고된 폐렴증과 폐렴이었다. 치명적인 폐렴증과 치명적인 폐렴은 이 약 투여군과 위약군 간에 유사하게 1% 미만의 환자에서 보고되었다. 확장 병기 소세포폐암 CASPIAN 연구: CASPIAN 연구에서 이전에 치료받지 않은 확장 병기 소세포폐암 환자에게 이 약과 에토포시드 및 카보플라틴 또는 시스플라틴을 병용투여 했을 때의 안전성이 평가되었다 (265명). 이 약과 화학요법을 병용 시의 안전성 프로파일은 이 약 단독요법 및 화학요법의 알려진 프로파일과 일관되게 나타났다. 이 임상연구에서 보고되지 않았더라도, 이 약 또는 화학요법 단독으로 발생한다고 알려진 이상사례는 병용요법 중에도 발생할 수 있다. 담도암 TOPAZ-1 연구 이 병용 요법 임상연구에서 보고되지 않았더라도, 이 약 또는 젬시타빈과 시스플라틴 단독으로 발생한다고 알려진 이상사례는 병용요법 중에도 발생할 수 있다. 젬시타빈 및 시스플라틴의 허가사항을 참조한다. **[저장방법]** 밀봉용기, 2-8℃에서 차광하여 보관 **[포장단위]** 2.4 mL × 1 바이알 / 박스, 10 mL × 1 바이알 / 박스 ※ 만약 구입시 사용기한이 경과되었거나 변질, 변패 또는 오손된 제품인 경우에는 구입처를 통하여 교환하여 드리며, 공정거래위원회 고시 "소비자분쟁해결기준"에 의거 소비자의 정당한 피해는 보상하여 드립니다. 의약품 부작용 발생 시 한국의약품안전관리원에 피해구제를 신청하실 수 있습니다 (피해구제 상담 번호 14-3330, 의약품 부작용 신고/피해구제 상담 번호 1644-6223). 문헌개정연월일: 2022년 12월 26일 수입(수입자): 한국아스트라제네카 서울시 강남구 영동대로517 아셈타워 21층, 전화 02-2188-0800 *보다 자세한 사항은 제품설명서 전문을 참고하시기 바랍니다 aIFZ20230214

한국아스트라제네카 서울 강남구 영동대로 517 아셈타워 21층 전화: (02)2188-0800 팩스:(02)2188-0852

AstraZeneca

KR-12988 I Exp.2025-02(Prep.2023-02)

EPCLUSA®
sofosbuvir/velpatasvir
400 mg/100 mg tablets

Epclusa®는 유일하게 모든 유전자형의 다양한 C형간염 환자군에서 높은 치료 효과를 보인 Pan-Fibrotic, PI-Free DAA입니다.*[1,2]

E fficacy	높은 SVR12 도달률*[1,2]	
P an-genotypic an-fibrotic	**범유전자형** 및 **범섬유증** 치료제†[2]	PAN PAN
C KD	**모든 단계의 신장애 환자**에게 사용 가능‡[2]	
L ow DDIs	비교적 **적은 약물상호작용**§[2,3]	
U nique PI-Free DAA	**유일한 Pan-Fibrotic, PI-Free DAA**[2]	
S imple administration	식사와 관계없이 **12주 복용**¶[2] - 비대상성 간경변(Child-Pugh B 또는 C)이 있는 경우, 리바비린과 병용	
A pill a day	**1일 1회 1정**[2]	

Epclusa®는 만성 C형간염 환자의 치료에 있어 다양한 이점을 보유한 PI-free HCV 치료제입니다.*[1-4]

※ Epclusa®와 관련한 보다 자세한 정보는 제품설명서를 참고하시기 바랍니다.

[적응증[2]] Epclusa®는 단독요법 또는 ribavirin 병용요법으로 만성 C형 간염 바이러스(HCV) 유전자형 1, 2, 3, 4, 5, 6형에 감염된 성인 및 만 12세 이상 또는 체중 30kg 이상 소아 환자의 치료에 사용합니다. **[이상반응[2]]** ASTRAL-1에서 Epclusa®로 12주 동안 치료를 받은 시험 대상자의 5% 이상에서 관찰된 모든 등급의 이상반응에는 두통(22%), 피로(15%), 오심(9%), 무력증(5%), 불면증(5%)이 포함되었으며, ASTRAL-2 및 ASTRAL-3 연구에서 Epclusa® 투여군에서 관찰된 이상반응은 ASTRAL-1 연구에서 관찰된 결과와 일치하였습니다. 1143 연구에서 확인된 이상반응은 성인을 대상으로 한 임상연구에서 확인된 결과와 일치하였습니다. Sofosbuvir의 허가 후 사용 중 심장 장애, 피부 발진 및 혈관부종이 확인되었습니다. Epclusa®를 sofosbuvir가 포함된 다른 의약품과 동시에 투여해서는 안 됩니다.

*Adults treated with SOF/VEL 400/100 mg, without ribavirin, were included. All HCV patients reaching Week 12 or 24 post-treatment were assessed for SVR12/24. Factors associated with not achieving SVR12/24 for virological reasons were evaluated using logistic regression analysis. Overall, 5552 patients were included: 13.3% treatment-experienced; 20.7% compensated cirrhotic; 30.2% genotype 1; 29.5% genotype 2; 32.9% genotype 3; 4.7% genotype 4; 3.7% HIV coinfection; 13.4% current/former intravenous drug use. SVR12/24 in the effectiveness population (n = 5,196; excluding patients who did not achieve SVR12/24 due to non-virologic or unknown reasons) was 98.9%. SVR12/24 in the overall population was 92.6%. All patients with unknown genotype (n = 42), unknown fibrosis score (n = 82) and unknown treatment history (n = 33) achieved SVR12/24 with Epclusa® for 12 weeks.[1] †Epclusa®는 유전자형 1, 2, 3, 4, 5, 6 HCV 환자 및 간경변이 없거나 대상성(Child-Pugh A) 또는 비대상성 간경변(Child-Pugh B/C)이 있는 환자에서 사용 가능합니다.[2] ‡투석이 필요한 환자를 포함하여 신장애 정도에 관계없이 이 약의 용량 조절은 필요하지 않다.[2] §The total percentage of potential DDIs was: 8.6% minor DDIs, 40.5% clinically significant DDIs and 10.0% contraindicated medication. SOF/VEL showed a lower percentage of: minor interactions (1.3% vs.6.6% and 5.9%, P < .001); clinically significant interactions (53.4%, vs. 77.4% and 66.3%, P < .001) and contraindicated medication (1.7% vs. 8.3% and 10.7%, P < .001) compared to GLE/PIB and SOF/VEL/VOX, respectively.[3] ¶간경변이 없거나 대상성 간경변(Child-Pugh A)이 있는 이전 치료 경험이 없는 환자 및 치료 경험이 있는 환자에서 엡클루사 단일요법 12주 또는 비대상성 간경변(Child-Pugh B 또는 C)이 있는 이전 치료 경험이 없는 환자 및 치료 경험이 있는 환자에서 엡클루사와 리바비린 병용요법 12주 복용[2]

AE, adverse event; **DAA,** direct acting antiviral; **DDIs,** drug-drug interactions; **HCV,** hepatitis C virus; **HIV,** Human Immunodeficiency Virus; **PI,** protease inhibitor; **SOF,** sofosbuvir; **SVR12/24,** sustained virological response 12/24 weeks after the end of treatment; **VEL,** velpatasvir

Reference 1. Mangia A, et al. Global real-world evidence of sofosbuvir/velpatasvir as simple, effective HCV treatment: Analysis of 5552 patients from 12 cohorts. Liver Int 2020;40(8):1841-1852. doi: 10.1111/liv.14537. Epub2020 Jun 9. **2.** 엡클루사 식약처 허가사항, 2022. **3.** Sicras-Mainar A et al. Prevalence of the potential drug-drug interactions between pangenotypicdirect-acting antivirals and the concomitant medications associated with patients with chronic hepatitis C virus infection in Spain. Gastroenterol Hepatol 2019;42(8):465 - 475. **4.** Sood A et al. Sofosbuvir-velpatasvir single-tablet regimen administered for 12 weeks in a phase 3 study with minimal monitoring in India. Hepatol Int 2019;13(2):173 - 179.

QR 코드를 스캔하여 Epclusa® PI를 확인하십시오.

GILEAD

YUHAN

KR-EPC-0074_v1.0(12/September/2023)

For the treatement of unresectable hepatocellular carcinoma (uHCC)

Nexavar® (sorafenib) tablets

Stivarga® (regorafenib) tablets

Optimize every step toward extended overall survival (OS) with a uHCC treatment plan[1-3]

References: 1. Finn RS, Merle P, Granito A, et al. Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: additional analyses from the phase III RESORCE trial. J Hepatol. 2018;69(2):353-358. **2.** Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-390. **3.** Bruix J, Qin S, Merle P, et al; on behalf of the RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10064):56-66.

[제품명] 스티바가정40밀리그램(레고라페닙) **[주성분]** 레고라페닙일수화물(별규) 41.49밀리그램(레고라페닙으로서 40.00밀리그램) **[효능·효과]** 1. 이전에 플루오로피리미딘 계열 약물을 기본으로 하는 항암 화학 요법과 항 VEGF 치료제, 항 EGFR 치료제(RAS 정상형 (wild type)의 경우)로 치료를 받은 적이 있는 전이성 직장결장암 환자의 치료 2. 이전에 이매티닙과 수니티닙으로 치료 받은 적이 있는 전이성 또는 절제불가능한 국소진행성 위장관기질종양(GIST) 환자의 치료 3. 이전에 소라페닙으로 치료 받은 적이 있는 간세포암 환자의 치료 **[용법·용량]** 1일 권장 투여 용량은 레고라페닙으로서 160 mg (이 약 40 mg 정제 4정에 해당)이며, 1일 1회 경구 복용한다. 투여 주기는 4주로, 3주 투약하고 1주 휴약한다. 이 약은 매일 같은 시간에 가벼운 식사 후 복용한다. 정제를 물과 함께 통째로 삼켜야 한다. 복용을 잊은 것을 기억하는 즉시 이 약을 복용하되, 전날의 투여량을 보충하기 위해 하루에 2회 용량을 복용해서는 안된다. 이 약의 투여는 질병이 진행할 때까지 또는 수용할 수 없는 독성이 발생할 때까지 지속되어야 한다. 환자 개개인의 안전성 및 내약성에 따라, 일시적 투여 중단 및/또는 용량 감소가 필요할 수도 있다. 용량 변경은 40 mg 1정씩 적용한다. 최소 1일 권장 투여 용량은 80 mg이다. 최대 1일 투여 용량은 160 mg이다. 용량 조절에 대한 자세한 내용은 제품설명서 전문을 참고해주시기 바랍니다. **[사용상의 주의사항] 1. 경고** 1) 임상시험에서 이 약으로 치료 받은 환자에서 치명적인 결과를 동반한 심각한 약물유발 간손상이 발생했다. 대부분의 사례에서, 간 기능 부전은 치료 시작 후 2개월 이내에 발생했으며 간세포 손상 양상으로 특징지어졌다. 2) 임신한 여성에게 이 약 투여 시 태아에게 해로운 영향을 미칠 수 있다. 랫트 및 토끼에서 이 약은 사람의 권장 노출량보다 적은 용량에서 기형 및 배태자 독성을 유발하는 것으로 나타났다. 임신 가능성이 있는 여성 및 남성은 이 약 투여 중 및 투여 후 8주까지 효과적인 피임법을 실시하여야 한다. 임신 중에 이 약을 사용하거나 이 약을 복용하는 동안 임신이 되면, 태아에 미치는 잠재적 위험에 대해 환자에게 알려주어야 한다. **2. 다음 환자에는 투여하지 말 것** 1) 이 약 또는 이 약의 구성성분에 과민증인 환자 **3. 다음 환자에는 신중히 투여 할 것** 1) 간 기능 장애 환자(1. 경고항 참조) 2) 감염 3) 출혈 4) 심장 허혈 및 경색 **4. 이상반응** 이 약의 가장 중대한 약물 이상 반응은 중증의 간 손상 및 출혈, 위장관 천공 및 감염이었다. 임상시험에서 매우 흔하게 나타난 약물이상반응(10% 이상): 감염, 저혈소판증, 빈혈, 식욕 및 음식섭취 감소, 출혈, 고혈압, 발성장애, 설사, 구내염, 구토, 오심, 고빌리루빈혈증, 트랜스아미나아제 상승, 손발피부반응, 발진, 무력증/피로, 통증, 고열, 근육염증, 체중감소 흔하게 나타난 약물이상반응(1%이상 10%미만): 백혈구감소증, 갑상선기능저하증, 저칼륨혈증, 저인산혈증, 저칼슘혈증, 저나트륨혈증, 저마그네슘혈증, 고요산혈증, 탈수, 두통, 떨림, 말초신경병증, 미각이상, 입안건조, 위식도역류질환, 위장염, 탈모, 피부건조, 박리성 발진, 근육 경련, 단백뇨증, 아밀라아제 상승, 리파아제 상승, INR치 비정상 **[전문의약품] [수입 및 판매자]** 바이엘코리아㈜ **[개정년월일]** 2021.12 **보다 자세한 사항은 제품설명서 전문 또는 바이엘 웹사이트, http://www.bayer.co.kr를 참고하시기 바랍니다. 부작용 또는 품질과 관련된 불만사항을 보고하고자 하는 경우 의약전문가(예: 의사 또는 약사), 식품의약품안전처 또는 한국의약품안전관리원에 연락하시기 바랍니다. 혹은 바이엘코리아로도 보고하실 수 있습니다.**

[제품명] 넥사바정 200밀리그램(소라페닙토실레이트(미분화)) **[주성분]** 소라페닙토실레이트(미분화) (별규) 274.0밀리그램(소라페닙으로서 200밀리그램) **[효능·효과]** - 이전의 cytokine 치료에 실패 경험이 있거나, 이러한 치료요법이 적절치 않은 진행성 신장세포암 - 간세포성 암 - 방사성 요오드에 불응한, 국소 재발성 또는 전이성의 진행성 분화갑상선 암 **[용법·용량]** 권장투여용량은 1회 400mg, 1일 2회이며, 공복상태(최소 식전 1시간 또는 식후 2시간째)에 복용한다. 본 약제는 환자에게 더 이상 임상적인 유익성이 없거나 수용할 수 없는 독성이 발생할 때까지 계속 투여해야 한다. 피부학적 독성에 따른 권장용량의 예시는 제품설명서 전문을 확인해 주십시오. **[사용상의 주의사항] 1. 경고** 이 약의 작용 기전 및 임상 사용량보다 훨씬 적은 용량을 투여한 동물시험에서의 관찰 사항에 근거할 때, 이 약을 임부에 투여했을 때 태아에 유해할 것으로 예측된다. 임산부에서는 이 약에 대한 적절한 임상연구를 실시하지 않았다. 임신 가능성이 있는 여성은 이 약을 투여하는 동안에는 임신하지 않도록 해야 한다. 임신 가능성이 있는 환자에게는 중증의 기형(최기형성), 성장 장애, 태아 사망(배아독성)을 포함하여 이 약의 태아에 미치는 잠재적 위험성에 대해 알려주어야 한다. 이 약은 임신 중에는 투여하지 않는다. 임신 중에 이 약을 사용하려면, 태아에 미치는 유익성이 위험성 보다 더 클 때에만 투여토록 한다. 이 약을 투여 받는 동안 수유를 중단해야 한다. **2. 다음 환자에는 투여하지 말 것** 이 약의 주성분이나 부형제에 대해 중증의 과민증이 있는 환자 **3. 주요 이상반응** (1) 간세포암 환자 297명과 신장세포암 환자 451명과 분화갑상선암 환자 207명을 대상으로 하여 총 955명의 환자에 대한 위약 대조 시험한 임상연구의 결과 가장 흔한 이상반응: 설사, 피로, 탈모증, 감염, 수족피부반응, 발진 (2) 여러 임상연구 및 시판 후 조사로부터의 추가 안전성 데이터 중 매우 흔한 이상반응(10% 이상): 감염, 림프구 감소증, 식욕부진, 저인산혈증, 출혈(위장관계, 호흡기계 및 뇌출혈 포함), 고혈압, 설사, 오심, 구토, 변비, 피부건조, 발진, 탈모증, 수족피부반응, 가려움, 홍반, 관절통, 피로, 통증(구강, 상복부, 뼈, 암 통증 및 두통 포함), 발열, 체중감소, 아밀라아제 증가, 리파아제 증가 **[전문의약품] [수입 및 판매자]** 바이엘코리아㈜ **[개정년월일]** 2021.12 **보다 자세한 사항은 제품설명서 전문 또는 바이엘 웹사이트, http://www.bayer.co.kr를 참고하시기 바랍니다. 부작용 또는 품질과 관련된 불만사항을 보고하고자 하는 경우 의약전문가(예: 의사 또는 약사), 식품의약품안전처 또는 한국의약품안전관리원에 연락하시기 바랍니다. 혹은 바이엘코리아로도 보고하실 수 있습니다.**

Bayer Korea Ltd.
Park 1 Tower 2, 108, Yeoui-daero, Yeongdeungpo-gu, Seoul, Korea
TEL:+82-2-829-6600 | http://www.bayer.co.kr/

For Healthcare Professionals Only

DAEWOONG

The new wave of GERD Treatment, P-CAB

FEXUCLUE

Fexuprazan hydrochloride

- Excellent nocturnal symptom control: Longest half-life
- Significantly improved chronic cough of EE
- Rapid and superior heartburn symptom relief
- Take once a day regardless of meal
- Full and fast onset of effect with the first dose
- Less affected by CYP2C19: Low potential of DDI · individual variations

【**Product name**】Fexuclue Tab. 40mg【**Formulation**】Active Pharmaceutical Ingredient: Fexuprazan HCl 40 mg Additives: lactose hydrate (bovine, milk), Yellow No.4, Microcrystalline Cellulose, Magnesium stearate, Opadry Green AMB2 88A610038, Opadry White 03B28796, Croscarmellose Sodium, Yellow Iron Oxide.【**Appearance**】Pale-green, Oblong film-coated tablet with the breaking line on the tablet【**Indication**】Treatment of erosive esophagitis (EE)【**Dosage and Administration**】The Product is administered to adults as follows. • Treatment of erosive esophagitis (EE) - 40 mg is administered orally once a day for 4 weeks. - In the case of patients with untreated esophagitis or symptoms persisting, the administration given for another 4 weeks, The Product can be administered with or without meals.【**Contraindications**】1) Patients who have a history of hypersensitivity to the Product or its components 2) Patients taking a drug containing atazanavir, nelfinavir, or rilpivirine (refer to '5. Interactions') 3) Pregnant and lactating women (refer to '6. Administration to Pregnant and Lactating Women') 4) Patients who have congenital conditions for lactose such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption, as this medicine contains lactose【**The following patients should be administered with care.**】1) Patients with hepatic impairment (no experience of use) 2) Patients with renal impairment (no experience of use) 3) Elderly (refer to '8. Geriatric Use') 4) Patients who have a history of hypersensitivity or allergy to Yellow 4 Tartrazine【**Storage**】Store at temperatures not exceeding 30°C in an airtight container【**Shelf-life**】36 Months【**Availability**】28T/Box (7T/PTP*4), 56T/Box (7T/PTP*8), 28T/Btl, 100T/Btl, 300T/Btl【**Manufactured by**】Daewoong Pharmaceutical Co., Ltd./ 1, Osongsaengmyeong 2-ro, Osong-eup, Heungdeok-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea ※ This medicine has passed strict quality control. If the use-by date or expiration date has passed at the time of purchase, or it the drug is spoiled, contaminated, or damaged, it can be exchanged or refunded through the pharmacy or drug distributor where it was purchased in accordance with the Fair Trade Commission Notice (Consumer Dispute Resolution Standard) ※ Report side effects and apply for damage relief: Korea Pharmaceutical Safety Management Agency (14-3330, 1644-6223)
※ For detailed and up-to-date approval information, please refer to the Ministry of Food and Drug Safety's integrated drug information system (https://nedrug.mfds.go.kr) or the product label.

Boston Scientific
Advancing science for life™

STRIKE FIRST

Your precision strike.
Arming you to target HCC tumors directly and hit them hard with high-dose radiation therapy.

Proven.
Personalized.
Percise.

19F, Lynn Square, 39 Eonju-ro 30-gil, Gangnam-ku, Seoul 06292, Korea

BORYUNG

oral suspension Megace® (megestrol acetate, USP)

Oral Suspension Megace® F (megestrol acetate, USP)

메게이스®가 항상 선생님을 응원합니다.

식욕 개선, 체중 증가, QOL개선을 통해 암환자의 생존률 증가에 도움이 될 수 있습니다.

Megestrol Acetate Original Product입니다.

국내에서 가장 많이 처방되어지고 있습니다.

FDA승인을 받은 유일한 **Megestrol Acetate 제제**입니다.

No Food Effect ✓
식전, 식후 상관없이 편리하게

더 낮아진 점도 ✓
목넘김 개선을 통해복용순응도향상

더 적어진 용량 ✓
1일 5ml만 복용해도 우수한 효과

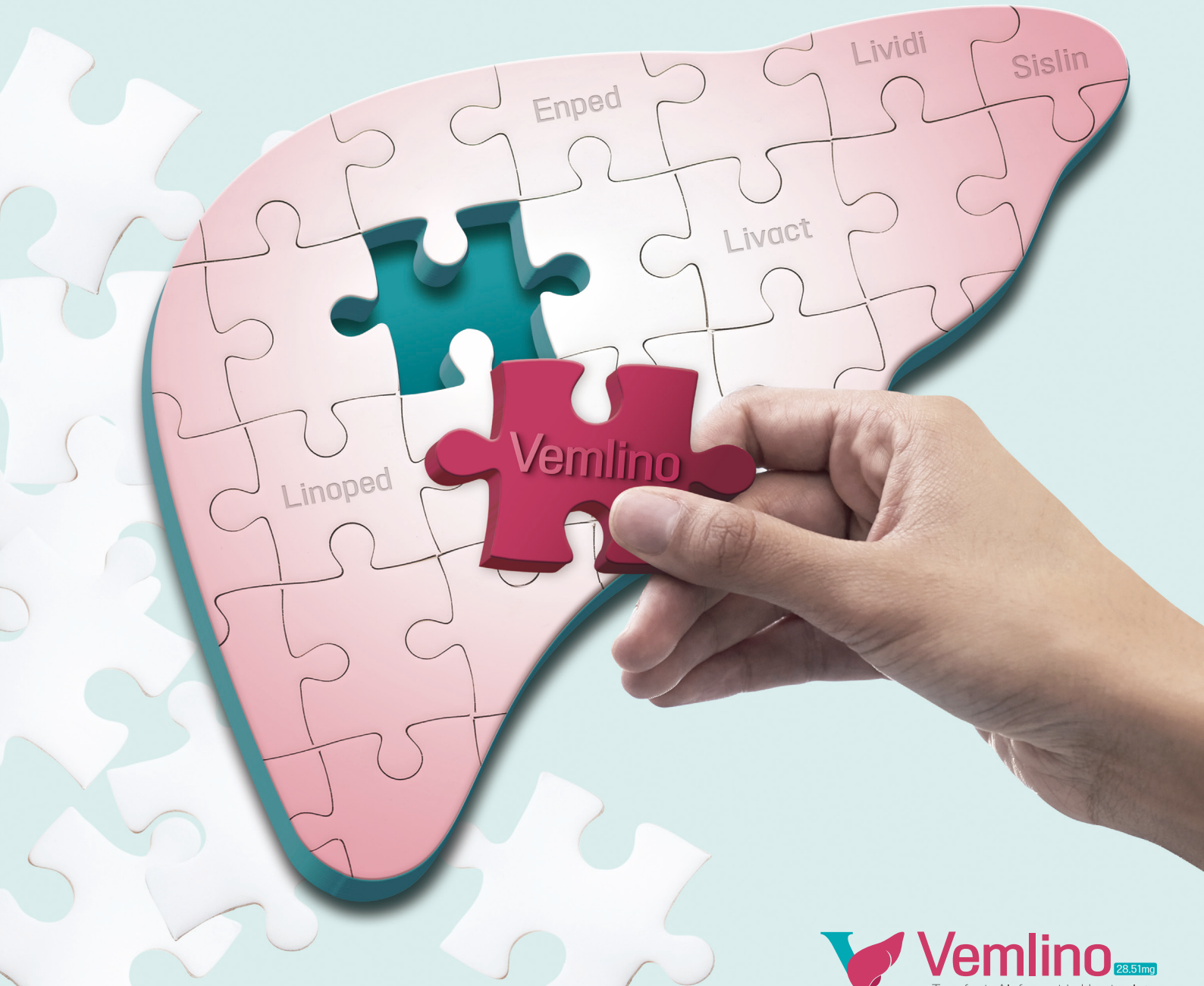
더 빠르고 강해진 효과 ✓
치료기간 단축

Samil

NEXT PIECE FOR BEST PEACE

Experience a better tomorrow with VEMLINO

VEMILINO, Effective for early stage and impaired renal function or decreased bone mineral density of hepatitis B patients.



Vemlino 28.51mg
Tenofovir Alafenamide Hemimalate

Elecsys® PIVKA-II[1]

A sensitive and accurate tool for use as an aid in the diagnosis of hepatocellular carcinoma (HCC)[2]

References
1. Elecsys PIVKA-II (체외 수허 20-8호) *"Sensitivity 86.9%, Specificity 83.7%"*
2. Roche studies No. RD002542 and RD002543

MC-KR-00711

Baraclude® (entecavir) 0.5mg/1mg tablets

15년간의 입증된 증거와 임상 경험을 보유한 CHB 치료제[1]

바라크루드®

VIEW
Values In Evidence and real-World-data

바라 보다. 바로 보다.

• 간경변을 동반한 경우에도[2,3] • HBV DNA 레벨에 관계 없이[4] • 신질환, 골질환의 위험이 있거나 동반한 경우에도[2,5,6]

Reference 1. 바라크루드정 국내허가사항. 식품의약안전처. 의약품통합정보시스템. Available at https://nedrug.mfds.go.kr/searchDrug. Accessed Feb 01, 2021 **2.** 대한간학회. 만성 B형간염 진료 가이드라인 2018. **3.** Chang TT, et al. Hepatology 2010;52:886-93. **4.** Wu IT, et al. Clin Microbiol Infect 2017;23:464-469. **5.** AASLD. Practice Guidance. 2018. **6.** EASL. Clinical Practice Guidelines on the management of hepatitis B virus infection. 2017.

[원료약품의 분량] [0.5mg] 1정(206mg) 중 엔테카비르(별규) 0.53mg(엔테카비르무수물로서 0.5mg) [1.0mg] 1정(412mg) 중 엔테카비르(별규) 1.06mg(엔테카비르무수물로서 1.0mg) [시럽 0.05mg/mL] 100mL 중 엔테카비르(별규) 5.3mg(엔테카비르무수물로서 5.0mg) **[주의]** 제품설명서의 사용상의 주의사항 참조 **[효능·효과]** 활동성 바이러스의 복제가 확인되고, 혈청 아미노전이효소(ALT 또는 AST)의 지속적 상승 또는 조직학적으로 활동성 질환이 확인된 성인(16세 이상)과 2세 이상의 소아 환자의 만성 B형간염 바이러스 감염의 치료 **[용법·용량]** 1. 성인(16세 이상)의 권고 용량: 1일 1회 엔테카비르로서 0.5mg(시럽제의 경우 10mL) 경구투여. 라미부딘 저항성 환자, 즉, 라미부딘 치료에도 불구하고 B형간염 바이러스의 지속적 증식을 경험하였거나, 라미부딘 저항성 변이가 있는 16세 이상의 환자: 1일 1회 공복시 엔테카비르로서 1mg(시럽제의 경우 20mL) 2. 소아의 권고 용량: 제품설명서 참조 **[사용상 주의사항]** 1. 경고 1) 유산증 및 지방증이 있는 중증 간종대 : 간질환에 대한 알려진 위 험인자 들을 가진 환자 2) 항B형간염 요법을 중단한 환자 3) HIV와 HBV에 함께 감염된 환자 2. 다음 환자에게 투여하지 말 것 1) 과민반응이 있는 환자 2) 갈락토오스 불내성, 유당분해효소 결핍증, 포도당-갈락토오스 흡수장애 등의 유전적 문제가 있는 환자
***신부전 환자의 용량 조절 및 자세한 내용은 제품설명서를 참조하십시오.**

Bristol Myers Squibb™ 135-725 서울시 강남구 테헤란로 504 해성1빌딩 12층 TEL : 02 3404 1300 FAX : 02 3404 1380 www.bmsk.co.kr
GC 녹십자

686-KR-2200095 Aug.2022/Jul.2024

Obtained 'Exclusive Marketing Rights'! First Generic of Sorafenib

Soranib was officially approved by MFDS on October 29th, 2020.

Treatment of hepatocellular carcinoma, thyroid carcinoma and renal cell carcinoma

Soranib Tab. 200mg on Market!
(since December 1st, 2020.)
(Sorafenib tosylate(Micronized))

1. **Obtained 'exclusive marketing rights'** by demonstrating bioequivalence to the original product
2. **Accumulated more than 10 years of experience** in prescribing Sorafenib[1–4]
3. **The First-generic to ease the burden of medication cost**
4. **Improved patient convenience** by redesigning the package

HM-Design 2012_01

Hanmi Hanmi Pharm.

Ref. 1) Llovet JM, *et al. N Engl J Med.* 2008;359(4):378-390. 2) Bernard E, *et al. N Engl J Med.* 2007;356:125–34. 3) Robert CK, *et al. Clin Cancer Res.* 2006 Dec;12(24):7271–7278. 4) BroseMS, *et al. The lancet.* 2014 Apr;384(9940):319–328.
SOR-II-2012-01

astellas

Astellas, only PROgraf

프로그랍의 환자 생명 연장을 위한 동행은
앞으로도 계속됩니다.

Prograf® Tacrolimus

NOT A REAL PATIENT.
MAVIRET is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults and children aged 12 years and older. Refer to the full Prescribing Information and Summary of Product Characteristics for further dosing information.

마비렛®정 제품요약정보

[효능·효과] 만성 C형 간염 바이러스(hepatitis C virus; HCV) 유전자형 1, 2, 3, 4, 5, 또는 6 형에 감염된 성인 및 만 12세 이상 청소년 환자의 치료 **[용법용량]** 이 약은 글레카프레비르와 피브렌타스비르가 함유된 고정 용량 복합 정제이다. 이 약의 권장 경구 투여 용량은 1일 1회 동일한 시간에, 3정을 음식과 함께 복용하는 것이다. 이 약은 씹거나, 부수거나, 자르지 말고 통째로 삼켜야 한다. 표 1과 2에 간경변을 동반하지 않거나 대상성 간경변을 동반하고 신장애(투석 환자 포함)가 있거나 없는 HCV 단독 감염 환자 집단 및 HCV/HIV-1 동시 감염 환자 집단에 근거한 이 약에 대한 권장 치료 기간이 제시되어 있다.

표 1. 치료 경험이 없는 환자들에 대한 권장 치료 기간

유전자형	권장 치료 기간	
	간경변 없는 경우	대상성 간경변 있는 경우
1, 2, 3, 4, 5, 6형	8주	8주

표 2. 치료 경험이 있는 환자들에 대한 권장 치료 기간

유전자형	이전 치료 경험	권장 치료 기간	
		간경변 없는 경우	대상성 간경변 있는 경우
1, 2, 4, 5, 6형	인터페론, 페그인터페론, 리바비린 및/또는 소포스부비르	8주	12주
1형	이전 NS5A 저해제 치료경험이 없고, NS3/4A 단백분해효소 저해제1 치료경험이 있을 경우	12주	
	이전 NS3/4A 단백분해효소 저해제 치료경험이 없고, NS5A 저해제2 치료경험이 있을 경우	16주	
3형	인터페론, 페그인터페론, 리바비린 및/또는 소포스부비르	16주	

1. 임상시험에서, 시메프레비르 및 소포스부비르 또는 시메프레비르, 보세프레비르 또는 텔라프레비르와 페그인터페론 및 리바비린의 병용요법으로 투여받음
2. 임상시험에서, 레디파스비르 및 소포스부비르 또는 다클라타스비르와 페그인터페론 및 리바비린의 병용요법으로 투여받음

간장애 환자에 대한 투여: 경증 간장애(Child-Pugh A)가 있는 환자들의 경우, 이 약의 용량 조절은 필요하지 않다. 이 약은 중등증 또는 중증 간장애(Child-Pugh B 또는 C) 또는 비대상성 간경변(hepatic decompensation) 병력이 있는 환자에게는 투여 금기이다. 신장애 환자에 대한 투여: 경증, 중등증 또는 투석을 받고 있는 환자를 포함한 중증 신장애 환자에서 이 약의 용량 조절은 필요하지 않다. 간 또는 신장 이식 환자에 대한 투여: 이 약은 간 또는 신장 이식 환자에 12 주 동안 투여할 수 있다. 이전 NS3/4A 단백분해효소 저해제 치료경험이 없고, NS5A 저해제 치료경험이 있는 유전자형 1 형, 인터페론, 페그인터페론, 리바비린 및/또는 소포스부비르 치료 경험이 있는 유전자형 3 형의 이식환자에서는 16 주의 치료기간을 고려해야 한다. (용법용량 표 2 및 11. 전문가를 위한 정보 2) 임상시험 정보 항 참고) 약물 복용을 놓친 경우: 약물 복용을 놓치고: • 일반적으로 이 약을 복용하는 시간으로부터 18시간 이하 경과한 경우 - 환자에게 해당 용량을 즉시 복용하고, 다음 용량을 원래 복용하던 시간에 복용하도록 조언한다. • 일반적으로 이 약을 복용하는 시간으로부터 18시간 초과 경과한 경우 - 환자에게 놓친 용량을 복용하지 말고 다음 용량을 원래 복용하던 시간에 복용하도록 조언한다. **[주요 사용상 주의사항] 1. 경고** B형 간염 재활성화 위험: HBV/HCV 동시 감염 환자에서 B형 간염 바이러스(hepatitis B virus; HBV) 재활성화 사례(일부에서 간부전이나 사망이 유발됨)가 HCV에 직접 작용하는 항바이러스제로 치료하는 동안 보고되었다. HBV 재활성화는 혈청 HBV DNA 수치 증가로 발현되는 급작스런 HBV 복제 증가가 특징이다. HBV 감염이 해결된 환자들(HBsAg 음성이고 항-HBc 양성)에서, HBsAg가 다시 나타날 수 있다. HBV가 재활성화되면 종종 간기능 검사 수치 이상(즉, 아미노기 전이효소 및/또는 빌리루빈 수치 상승)이 나타날 수 있으며 심할 경우 간부전 또는 사망이 유발될 수 있다. 치료를 시작하기 전에 모든 환자에 대하여 HBV 선별검사를 실시해야 한다. 현재 또는 이전 HBV 감염 환자는 이 약의 치료 중 및 치료 후 간염의 급성 악화(hepatitis flare) 또는 재활성화 확인을 위해 임상적 및 실험실학적 검사(예, HBsAg, HBV DNA, ALT, 빌리루빈 등)로 주기적으로 모니터링해야 한다. HBV의 재활성화가 나타난 경우, 전문가와 상의한다. 당뇨병 환자에서의 사용: 당뇨병 환자는 HCV에 직접 작용하는 항바이러스 치료를 시작한 후, 포도당 조절이 개선되어 잠재적으로 증상이 있는 저혈당을 경험할 수 있다. 직접 작용하는 항바이러스제 치료를 시작하는 당뇨병 환자의 혈당 수준을 특히 처음 3개월 동안 면밀히 모니터링 해야 하며, 필요 시 당뇨병 치료제를 수정해야 한다. 직접 작용하는 항바이러스제 치료가 시작될 때 환자의 당뇨 관리 담당 의사에게 알려야 한다. 간질환이 진행된 환자의 비대상성 간경변/간부전 위험: 이 약을 포함한 HCV NS3/4A 단백질분해효소억제제 함유 요법으로 치료받은 환자에서 치명적인 결과를 가진 환자를 포함하여 비대상성 간경변 및 간부전의 사만 후 사례가 보고되었다. 이러한 사례는 특정할 수 없는 집단에서 자발적으로 보고된 것이었기 때문에, 신뢰할 수 있는 해당 사례의 발생빈도나 약물의 노출과의 상관관계를 확인하는 것이 모두 가능하지는 않았다. 중증의 결과를 보이는 환자의 대다수는 이 약으로 치료를 시작하기 전에 중등증 또는 중증 간 장애(Child-Pugh B 또는 C)로 진행된 간 질환이 있었다. 일부 환자들은 베이스라인에서 경증 간장애(Child-Pugh A 등급)가 동반된 대상성 간경변이 보고되었으나, 기존에 비대상성 간경변의 사례(예 복수, 정맥류 출혈, 뇌병증)을 경험한 바 있었다. 간경변이 없거나 대상성 간경변(Child-Pugh A)을 가진 환자에서 비대상성 간경변 및 간부전이 드물게 보고되었으며, 이들 중 다수에서 문맥고혈압이 있었다. 병용이 권고되지 않는 병용 약물을 복용하는 환자 또는 심각한 간 관련 내과 또는 외과적 동반 질환과 같은 교란요인이 있는 환자에서도 사례가 보고되었다. 보고된 사례는 통상적으로 치료 시작 후 4 주 이내에 발생하였다(중간값 27일). 대상성 간경변(Child-Pugh A)이나 문맥고혈압 등 간 질환이 진행된 환자에서 임상적으로 필요한 실험실적 간 검사를 시행하고, 황달, 복수, 간성뇌병증, 정맥류 출혈과 같은 비대상성 간경변의 징후와 증상이 나타나는지 모니터링 한다. 비대상성 간경변 및 간부전으로 진행된 증거가 있는 환자는 치료를 중단한다. 중등증 또는 중증 간장애 환자(Child-Pugh B 또는 C) 또는 비대상성 간경변(hepatic decompensation) 병력이 있는 환자에게는 투여 금기이다. **2. 다음 환자에는 투여하지 말 것** 1) 이 약의 주성분 또는 구성성분에 과민증이 있는 환자 2) 중등증 또는 중증 간장애 환자(Child-Pugh B 또는 C) 또는 비대상성 간경변(hepatic decompensation) 병력이 있는 환자 3) 아타자나비르, 아토르바스타틴, 심바스타틴, 에티닐에스트라디올 함유제제, 강력한 P-gp 및 CYP3A 유도제[리팜핀, 카바마제핀, St. John's Wort(hypericum perforatum), 페니토인 등]와의 병용 4) 이 약은 유당을 함유하고 있으므로, 갈락토오스 불내성(galactose intolerance), Lapp 유당분해효소 결핍증(Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수장애(glucose-galactose malabsorption) 등의 유전적인 문제가 있는 환자에게는 투여하면 안 된다. **[제조원] (제조의뢰자)** AbbVie Deutschland GmbH & Co. KG, 독일, Knollstrasse 67061 Ludwigshafen (제조 및 포장) **(제조자)** Fournier Laboratories Ireland Limited, 아일랜드, Anngrove Carrigtowhill Co. Cork. **[수입원]** 한국애브비㈜, 서울특별시 강남구 영동대로 421 삼탄빌딩 6층, 전화: (02)-3429-9300 www.abbvie.co.kr **[허가반경일]** 2021년11월16일 *의약품 부작용 신고 및 피해구제 신청: 한국의약품안전관리원 (1644-6223, www.drugsafe.or.kr) *자세한 제품정보는 제품설명서를 참조해 주십시오.

abbvie
서울시 강남구 영동대로 421 삼탄빌딩 6층 Tel. 02.3429.9300
KR-MAVI-220007-220111

MAVIRET®
glecaprevir/pibrentasvir

부광약품

Protect from Various Liver Disease with Legalon® Cap

Original Silymarin 치료제 레가론®,
앞으로도 국내 간 질환 치료에
선생님과 함께하겠습니다.

레가론은 지속적으로 급여처방 가능합니다.

Originality & Worldwide

- 오랜 기간 다수의 간 질환 관련 임상을 통해 효과가 입증된 Original Silymarin 간 질환 치료제입니다.[1-2]

Treatment of Liver disease

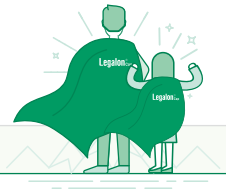
- 다양한 단계의 간 질환에서 간 기능 개선 또는 증상 개선의 효과를 입증하였습니다.[5-11]
  - NAFLD/NASH 환자의 간 기능 수치 감소 및 NASH 환자의 간 섬유화 개선
  - ALD 환자의 간 기능 수치 감소 및 ALD 증상 개선
  - Alcoholic cirrhosis 환자의 인슐린 저항성 감소

Various MoA & All stages

- 간 질환의 전 주기에 걸쳐 다양한 약리 기전을 통해 간 보호 및 치료 효과를 나타냅니다.[3-4]
  - 인슐린 저항성 감소 및 항산화·항염증·항섬유화 효과

Safety & Good tolerance

- 부작용이 거의 없어 안전하고 내약성이 좋습니다.[5-9]



[Reference] 1. Bijak M. Molecules 2017 Nov 10;22(11). / 2. LEGALON Cap. 140 – Insert Paper(KOREA) / 3. Federico A, et al. Molecules 2017 Jan 24;22(2). / 4. Hellerbrand C, et al. Clinical Phytoscience 2017 Jan;2:7. / 5. Zhong S, et al. Medicine (Baltimore) 2017 Dec;96(49):e9061. / 6. Hajaghamohammadi AA, et al. Hepatitis Monthly 2008;8(3):191-5. / 7. Hashemi SJ, et al. Hepatitis Monthly 2009;9(4):265-70. / 8. Wah Kheong C, et al. Clin Gastroenterol Hepatol 2017 Dec;15(12):1940-9.e8. / 9. Saller R, et al. Drugs 2001;61(14):2035-63. / 10. Velussi M, et al. J Hepatol 1997 Apr;26(4):871-9. / 11. Mastron JK, et al. Anticancer Drugs 2015 Jun;26(5):475-86.

[제품정보] 레가론 캡슐 70mg / 140mg **[성분,함량]** 밀크시슬건조엑스산 169.7mg / 339.4mg(실리마린으로서 70mg / 140mg) **[효능,효과]** 다음 질환의 보조 치료 : 독성 간질환, 만성 간염, 간경변 **[용법,용량]** 성인 : 실리마린으로서 초기용량 1회 140mg(또는 실리빈으로서 1회60mg), 1일 3회, 유지용량 1회 70mg(또는 실리빈으로서 1회 30mg), 1일 3회(또는 1회 140mg(또는 실리빈으로서 60mg), 1일 2회)복용한다. **[금기]** 1) 심한 담도 폐쇄 환자 2) 이 약의 과민증 환자 3) 12세 이하의 소아 **[신중투여]** 다음과 같은 사람은 이 약을 복용하기 전에 의사, 치과의사, 약사와 상의 할 것 : 임부, 수유부 [이상반응] 다음과 같은 경우 이 약의 사용을 즉각 중지하고 의사, 치과의사, 약사와 상의할 것. 상담시 가능한 한 이 첨부문서를 소지할 것. 1) 드물게 위통 또는 설사 2) 알레르기 반응 **[일반적주의]** 1) 정해진 용법 ·용량을 지킬 것. 2) 황달의 경우에는 의사 또는 약사와 상의할 것. 3) 1개월 정도 복용하여도 증상의 개선이 없을 경우나 장기복용시에는 의사 또는 약사와 상의할 것.

제조 · 판매
부광약품주식회사
서울특별시 동작구 상도로 7
(02) 828-8114 / www.bukwang.co.kr

기술제휴
MADAUS GmbH
Federal Republic of Germany

VMA-23D008

Vemlia

tenofovir alafenamide 25mg tabletes

B형 간염 치료를 향한 진심,

베믈리아에 담아 동아ST가 선생님들께 다가갑니다.

TDF제제 대비 비열등한 항바이러스 효과[1]

TDF제제로 감소한 BMD, CrCL 호전[2]

2,474원의 저렴한 약가[3]

요일약통 적용을 통해 복약순응도 개선 기여[4]

1. Agarwal K, et al. J Hepatol. 2018, 68, 672–681
2. Lampertico P, et al. Lancet Gastroenterol Hepatol. 2020 May;5(5):441-453.
※상기 자료는 타사 제제(테노포비르알라페나미드헤미푸마르산염)로 실시한 임상자료입니다
3. https://www.health.kr/searchDrug/result_drug.asp?drug_cd=2022122100010 약학정보원, 베믈리아 의약품 상세정보, accessed on April 2023
4. Vervloet M, et al. J Am Med Inform Assoc 2012;19(5):696-704.

동아ST

의약전문가용

신장애, 간장애 환자에서 용량조절이
필요하지 않은 만성B형간염치료제

TAF 타제품 대비
작은 사이즈 낮은 약가

※2023. 4. 약제급여목록표 확인 기준

3월 1일 출시!

테노포벨에이정

성분·함량 Tenofovir Alafenamide Succinate 31.20mg
(Tenofovir Alafenamide로서 25mg)

약가 2,439원/tab (약가기준일:2023.03.01)

효능·효과 성인의 만성 B형 간염 치료

보다 자세한 제품정보는 최신의 제품설명서 또는 의약품안전나라 의약품통합정보시스템(nedrug.mfds.go.kr)을 참고하시기 바랍니다.
·Ref. 의약품안전나라(https://nedrug.mfds.go.kr/index) - 2023.4. 열람

종근당 테노포벨에이정

의약전문가용

간에는
UDCA+BDD
DUO 복합제

4월 8일 출시!

가네듀오캡슐

성분·함량 Ursodeoxycholic Acid 50mg, Biphenyl dimethyl dicarboxylate mixture 125mg
(Biphenyl dimethyl dicarboxylate로서 12.5mg)

약가 221원/cab (약가기준일:2023.04.08)

효능·효과 지속적으로 SGPT가 상승되어 있는 만성 지속성 간염

보다 자세한 제품정보는 최신의 제품설명서 또는 의약품안전나라 의약품통합정보시스템(nedrug.mfds.go.kr)을 참고하시기 바랍니다.
·Ref. 의약품안전나라(https://nedrug.mfds.go.kr/index) - 2023.4. 열람

종근당 가네듀오캡슐

GODEX® cap.

Carnitine Complex의
NAFLD 치료 효과

Beyond ALT/AST normalization effect

- ✔ Carnitine 성분의 **미토콘드리아 회복** 효과
- ✔ 영상학적으로 입증된 **지방간 개선**효과
- ✔ **인슐린 저항성 개선**효과

고덱스®캡슐

| 성상 | 황갈색의 분말이 들어있는 상 · 하 적갈색 불투명의 경질캡슐제 **| 성분 · 함량 |** 1캡슐 중 Carnitine orotate 150mg Liver extract antitoxic fraction 12.5mg Pyridoxine HCl 25mg Riboflavin 0.5mg Cyanocobalamin 0.125mg Biphenyl Dimethyl Dicarboxylate 25mg Adenine HCl 2.5mg **| 효능 · 효과 |** 트란스아미나제(SGPT)가 상승된 간질환 **| 용법 · 용량 |** 통상 성인 1회 2캡슐, 1일 2~3회 복용, 연령, 증상에 따라 적의 증감. **| 사용상의 주의사항 |** 1. 다음 환자는 투여 하지 말 것. 1) 이 약 및 이 약에 포함된 성분에 과민반응이 있는 환자 2) 레보도파를 투여 받고 있는 환자 2. 다음 환자는 신중히 투여할 것. 1) 만성 활동성 간염 환자 2) 간경화 환자 3. 이상반응 1) 간혹 입안마름, 메스꺼움, 발진, 가려움증, 발적 등이 생길 수 있으며, 이러한 이상반응은 투약을 중지하거나 항과민약을 병용투여하면 소실된다. 2) 일과성 황달이 나타날 수 있으나 투약을 중지하거나 황달치료제를 병용투여하면 소실된다. 3) 드물게 구역, 복부팽만, 변비, 메스꺼움, 상복부 불쾌감이 나타날 수 있다. **| 보험코드 |** 693900080 **| 포장단위 |** 100캡슐, 300캡슐(병) / 100캡슐(PTP) **| 저장방법 |** 기밀용기, 실온보관(1~30℃)

고덱스®캡슐 상병코드

B15-19 바이러스성 간염(Viral hepatitis) K70.0 알코올성 지방간(Alcoholic fatty liver) K71.0 독성 간질환(Toxic liver disease) K73.0 달리 분류되지 않은 만성 지속성 간염(Chronic persistent hepatitis, NEC) K74.0 간섬유증(Hepatic fibrosis) K75.8 기타 명시된 염증성 간질환, 비알코올성 지방간염(Other specified inflammatory liver disease, Nonalcoholic steatohepatitis) K77.0 달리 분류된 질환에서의 간장애(Liver disorders in disease classified elsewhere)

셀트리온제약 CELLTRION **국내사업본부** 서울시 송파구 중대로 135 IT벤처타워 서관 17층 **소비자상담실** 080-850-3611~2 www.celltrionph.com

GODEX® cap.

OT2016-07

SK plasma

I.V. Hepabulin SN Inj.

Human Hepatitis B Immunoglobulin for Intravenous Administration

Product Summary[1]

Prescription drug Class No : 634

【PRODUCT NAME IN KOREA】 I.V. Hepabulin SN Inj. **【ACTIVE INGREDIENT AND ITS CONTENT】** Human Hepatitis B Immunoglobulin 200I.U./mL **【INDICATION】** Prevention of Hepatitis B virus re-infection after liver transplantation for hepatitis B induced liver failure **【DOSAGE AND ADMINISTRATION】** Dilute 10,000I.U. of this medicinal product with 5% glucose solution 150mL and administer by intravenous drip infusion according to the following regime • HBV-DNA(-) and HBeAg(-): During operation 10,000I.U., Until week 1 post-operative 10,000I.U./day, Until 1 month post-operative 10,000I.U./week, Month 1 onward 10,000I.U./4weeks • HBV-DNA(+) or HBeAg(+): During operation 20,000I.U., Until week 1 post-operative 10,000I.U./day, Until 1 month post-operative 10,000I.U./week, Month 1 onward 10,000I.U./4weeks. If this medicinal product is to be administered for more than 1 year, it should be administered to maintain the anti-HBs concentration by supervisory of the physician with past experience with this medicinal product. **【PRECAUTIONS】** 1. Warning 1) As this drug is produced from human blood plasma, at the present level of scientific technology the risk of infection by blood borne virus or other kinds of infectious agent (theoretically CJD) cannot be eliminated. Accordingly, appropriate vaccinations such as Hepatitis A vaccination are recommended to hemophilic patients or those with very low immune functions. When medicating, doctors should monitor periodically for any sign of infections. Since human blood is used as the source of the drug the possibility of infection cannot be entirely excluded. In this reason doctors must fully explain the risk and minimize the administration to patients after careful review of the necessity. 2) The risk of thrombosis due to administration cannot be excluded completely, and could occur irrelevant to the risk factor and administration route. In case of patients with risk of thrombosis (elderly, long-term immobile condition, hypercoagulable states, history of venous or arterial thrombosis, use of estrogen, central vein catheter insertion, high viscosity and cardiovascular disease risk factor), it should be administered carefully with lowest concentration at lowest administration rate. Also, the patient should intake water sufficiently before administration. After administration any thrombotic symptoms and the condition of the patient should be observed including evaluating the patient's blood viscosity. 2. Contraindication. Patients with history of allergic reaction to the ingredients of this medicine. **【MANUFACTURER】** SK Plasma Co., Ltd. 157, Saneopdanji-gil, Pungsan-eup, Andong-si, Gyeongsangbuk-do, Korea **【MA HOLDER】** SK Plasma Co., Ltd. 310, Pangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Korea

Revised: 11/07/2017

※ For the latest product information, refer to On-line drug library(https://nedrug.mfds.go.kr/)

1. I.V. Hepabulin SN Inj. Prescribing information. [Cited 2020.06.15] Available from: http://nedrug.mfds.go.kr/

HPS-HA01-202006-02

SK plasma [13494] 310, Pangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Korea TEL +82-80-969-9967 www.skplasma.com

TachoSil®

- Quick onset of hemostasis
- Safe tissue sealing
- Easy handling
- Shorter operation time
- Minimize risk of re-bleeding
- Reduce the likelihood of blood transfusion

[원료약품 및 분량]

Tachosil contains per (1㎠)

- Collagen (sponge) ····· 2.1㎎
- Human Fibrinogen ····· 5.5㎎
- Human Thrombin ····· 2.0 IU
- Riboflavin ····· 18.2㎍

[성상]

한면에 황색 약물이 도포된 백색 스폰지

[표능 및 효과]

1. 기존 치료법으로 조절할 수없는 경우 또는 기존 치료법으로 불충분하다고 예상되는 경우의 출혈 또는 담즙, 림프, 액, 공기 누출
2. 간, 비장, 췌장, 신장, 폐, 부신, 갑상선, 림프절과 같은 실질적 기관 수술시의 지혈 및 조직접착, 또한 이비인후과, 부인과, 비뇨기과, 혈관계, 뼈(예를 들면 해면골)수술, 외상관련 수술시의 지혈
3. 림프, 담즙, 액의 누공의 예방적 처치
4. 폐수술시 일어나는 공기누출의 봉합

[포장단위]

(9.5X4.8X0.5)㎠ X 1매
(4.8X4.8X0.5)㎠ X 2매
(2.5X3.0X0.5)㎠ X 1매

현대약품(주)
충청남도 천안시 풍세면 남관리 200