APASL 2024 Kyoto

The 33rd Annual Meeting the Asian Pacific Association for the Study of the Liver

Summary

Plenary Sessions

APASL 2024 Kyoto

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Summary

Opening Lecture

Opening Lecture

Dr. Masao Omata
The University of Tokyo
Yama-nashi Central Hospital
Japan

RWD (Real World Data) on Elimination and Cure of HCV/HCC

In this occasion of annual Kyoto Meeting 2024 at cherry blossom time, which is the second annual meeting held in Kyoto in 2007, I would like to address our hopes for the future based upon RWD.

The APASL was established in 1979, 45 years ago, and I have been in the field of Gastroenterology and Hepatology over half a century along with the activities of the growing APASL.

I started my career in the department of Prof. Okuda, who started this society with Dr. Powell. Since then, I have conducted basic and clinical studies of viruses and hepatocellular carcinoma.

In this Kyoto meeting, one of the goals is the eradication of viruses, in particular, eradication of HCV. I will address my own experiences how I have tackled with eradication of HCV in high endemic area due to previous infection of Schistosomiasis-Japonica in Yama-nashi with 800,000 population and Mt. Fuji (my homeland).

In addition, I will address the issue of Hepatocellular Carcinoma in two different aspects. One is the introduction of a collaborative study among our APASL colleague; A-HOC (APASL-Hepatology Oncology Consortium) and the other is our RWD (Real World Data) on 30,000 cancer patients of various kinds in our hospital which is the Japanese government Designated Hospital for Cancer Genomic Medicine.

I hope this can be opening remarks for this very exciting and very big pivotal meeting in Kyoto.

I sincerely hope that every attendant of this Kyoto meeting will go back to their own country with many of scientific take-home messages and memories.

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Summary

Presidential Lecture

Presidential Lecture

Dr. Shuichiro Shiina

President, APASL 2024 Kyoto - The Center of Hepatology

(The 33rd Annual Meeting of the Asian Pacific Association for the Study of the Liver)

Professor, Department of Gastroenterology, Juntendo University,

Japan

Ablation for Liver Tumors: Current Status and Future Perspective

Ablation encompasses ethanol injection, radiofrequency ablation (RFA), microwave ablation (MWA), etc. Ablation can be potentially curative, minimally invasive, and easily repeatable for recurrence.

RFA has been the most widely used ablation technique for liver tumors. The new-generation MWA system incorporating antenna cooling and high-power generation has attracted attention. It can create a more predictable ablation zone and a larger ablation volume in a shorter procedure time. Many high-volume centers have introduced new-generation MWA in Japan. However, many studies failed to show that new-generation MWA is superior to RFA in terms of local control and overall survival. In MWA, clinical data have been insufficient compared with those of RFA.

There has been keen competition between surgical resection and ablation for almost 40 years since the era of ethanol injection. In 2021, SURF trial revealed that overall survival and recurrence-free survival were not significantly different between surgical resection and RFA. SURF trial was a multicenter randomized controlled trial in which 49 major centers in Japan enrolled patients with good hepatic function (Child-Pugh scores ≤ 7) and primary HCC of largest diameter ≤ 3 cm, and ≤ 3 nodules during the 6 years of 2009-2015. The registered patients were followed for at least 5 years.

As the result of SURF trial and other comparative studies, the revised Japanese clinical practice guidelines in 2021 treat hepatic resection and ablation equally for patients with ≤ 3 lesions, ≤ 3 cm in diameter.

Recently, the combination of systemic and locoregional therapies has been attracting much attention. Systemic therapy using molecular targeted agents or immune checkpoint inhibitors is used for advanced HCC which cannot be treated by surgery or ablation. On the other hand, some locoregional therapies, such as hepatectomy and ablation, are potentially curative, but they cannot be indicated for advanced HCC. A combination of both therapies is an approach to improve the prognosis of advanced HCC, which is not indicated for curative treatment. Systemic therapy is used to shrink the tumor, and then locoregional therapies are performed to eradicate it. The combination may build a new strategy for advanced HCC.

Ablation is highly operator-dependent. The skills and outcomes are very different from operator to operator. Before the pandemic of COVID-19, we held domestic and international training programs for intermediate and advanced doctors and hands-on seminars for young doctors. These were activities to exchange knowledge and experience and standardize the procedure. During the pandemic, gathering in person was impossible. Since August 2020, we have conducted Japan Ablation Webinar 8 times with a total of 1,566 participants. We have also conducted International Ablation Webinar 4 times with a total of 1,272 participating doctors. Education is important to acquire skills and knowledge for successful ablation.

We established Japan Academy of Tumor Ablation (JATA) in 2023. There are two triggers. One is that SURF trial revealed that there is no difference between hepatectomy and ablation. The other is that ablation for lung, bone, soft tissue, and kidney cancers has become reimbursed with health insurance since September 2022.

In the future, AI is expected to simplify tasks such as selecting an approach route to a target and determining whether the entire tumor has been removed by comparing images before and after resection.

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Post-Graduate Program (Hepatitis B)

Post-Graduate Program (Hepatitis B)

PG1-1

Dr. Wan-Long Chuang

Department of Internal Medicine, Kaohsiung Medical University Hospital,

Kaohsiung Medical University

Taiwan

Chronic Hepatitis B Virus Infection

Chronic hepatitis B virus (HBV) infection is a serious global health issue. Chronic HBV infection might lead to liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). Thus, the goal of treatment for chronic hepatitis B (CHB) is to improve survival and quality of life by preventing transmission, disease progression and HCC. Chronic HBV infection comprises four phases defined as immune tolerant phase, immune clearance phase (HBeAg-positive chronic hepatitis), inactive carrier phase, and reactivation phase (HBeAg-negative chronic hepatitis). Treating the patients with immune active chronic hepatitis B (both HBeAg-positive and negative) is recommended to decrease the risk of liver-related complications. Pegylated interferon and nucleos(t)ide analogues (NAs, including entecavir, tenofovir disoproxil fumarate and tenofovir alafenamide) are the preferred first line agents for CHB treatment. NAs are selected because of convenience, good tolerability, safety, high potency and minimal to no risk of resistance. However, NAs have no direct action on cccDNA, and long-term NAs therapy is required to maintain HBV suppression in HBeAg negative patients. There are several concerns, e.g. financial burden, adherence and willingness, for indefinite long-term NAs therapy. In addition, increase rates of HBsAg loss are observed after cessation of NAs treatment in HBeAg-negative patients. Finite NAs therapy in selected HBeAg-negative CHB becomes a recommendation. Discontinuation of NAs treatment in patients with cirrhosis is not recommended. For HBeAg-positive adults without cirrhosis who seroconvert to anti-HBe on NAs therapy, discontinue therapy after a period of consolidation treatment is suggested. NAs may be discontinued in HBeAg-negative patients without cirrhosis, who achieve long-term virological suppression. Decompensation and severe ALT flare may occur after cessation of NAs, especially in patients with liver cirrhosis. Close monitoring is warranted for the HBeAg-negative patients stopping NAs treatment. If hepatic decompensation developed, re-starting NA therapy should be given immediately. For patients with virological or clinical relapse, treatment indications for naïve CHB patients may be applied.

Post-Graduate Program (Hepatitis B)

PG1-2

Dr. Oidov Baatarkhuu

Department of Infectious Diseases, Mongolian National University of Medical Sciences

Mongolia

Epidemiology, Genotype Distribution, Prognosis and Treatment of Viral Hepatitis C and HCC in Mongolia

In Mongolia, morbibdity from liver cancer is 68.1 per 100 000 population, which is eight times higher than the global average. This is directly associated to the higher rate of morbidity of chronic hepatitis caused by HBV, HCV and HDV. Prevalence of HCV in Mongolia was high. The predominant genotype of HCV among general populations in Mongolia is 1b.

Between 2015 to 2019, 23 (0.5%) and 5,005 patients (99.5%) with genotype 1a and 1b HCV, respectively, were treated with a fixed-dose tablet containing 90 mg ledipasvir and 400 mg sofosbuvir for 12 weeks, and 81 patients (1.6%) with previous experience of interferon (IFN)-based treatment received additional 1,000 mg ribavirin. Most patients (n=5,008; 99.6%) achieved ETR and SVR12 without virologic relapse. Patients with genotype 1a showed low rates of ETR and SVR12 in only 16 patients (69.6%). There was no significant difference in SVR12 rate between patients regardless of IFN experience (n=81; 1.6%), cirrhosis (n=1,151; 22.9%), HCV RNA >6×106 IU/mL (n=866; 17.2%), or liver stiffness >9.6 kPa (n=1,721; 34.2%) (100.0%, 99.3%, 99.4%, and 99.4%, respectively). The most common AEs were headache (n=472; 9.4%), fatigue (n=306; 6.2%), abdominal discomfort (n=295; 5.9%), and skin rash (n=141; 2.8%).

Most patients had advanced HCC – 88 (45.1%) in stage III and 57 (29.2%) in stage IV. The risk factors associated with HCC development were history of acute hepatitis, chronic hepatitis, and the presence of liver cirrhosis. The most common etiology for HCC in our patients was HCV infection which is 46%, HBV infection -34%, co-infection B and C -14% and others which is 6.0%. According to the results of our study over 65% of patients had tumor size more than 5 cm. Single tumors was only found in 15%. The mean AFP level was 196 ng/ml. In 18.5% distant metastasis existed. Regarding tumor stage, there was no patient with stage 1. In addition, the most patients with HCC were diagnosed in advanced stage. In Mongolia HCC treatment modality is very limited. According to the results of our study, 14% of patients received surgical resection, and their survival was the best. 11.8% of patients received RFA and their survival was 11 months. About 55% of patients received TACE and their median survival was 17 months. The prognosis for patients with supportive care was very poor with a median survival of 5 months. Regarding cause of death, about 50% patients died of HCC progression and the others died of liver failure or GI bleeding. Regarding early detection of HCC in Mongolia, AFP is available in all hospitals except inter-soum and soum’s hospitals.

Post-Graduate Program (Hepatitis B)

PG1-3

Dr. George Lau

Humanity and Health Clinical Trial Center, Humanity and Health Medical Group, Hong Kong SAR, China

HBV "Viral Elimination" in Asia-Pacific region-current status and challenges

Humanity and Health Clinical Trial Center, Humanity and Health Medical Group, Hong Kong SAR, China.

In 2016, the World Health Assembly approved the World Health Organisation (WHO) Global Health Sector Strategy on HBV, with a goal of "elimination of HBV as a major health threat" by 2030, targeting a 90% reduction in new HBV infection and a 65% reduction in mortality due to HBV. However, recent data suggested deviation from these goals, with over 890,000 new HBV cases in 2019-2020 and a global HBV-related mortality rate exhibiting minimal change (annualized rate of change < 0.4% between 2015-2019). Two-thirds of the these HBV-related mortality occurred in Southeast Asia and Western Pacific regions. In real-world clinical practice, two major barriers hinder a significant reduction of disease burden due to HBV infection: lack of awareness (among public and policy makers) and under-treatment of those with a risk of developing complications related to HBV infection, with effective anti-viral therapy, namely high resistant barrier nucleos(t)ide analogues (NAs including tenofovir, entecavir, tenofovir alafenamide) or pegylated interferon or both, which have all been demonstrated to enable a drastic reduction in HBV-related morbidity and mortality with long-term follow-up. With the recent availability of low-cost rapid diagnostic tests for HBsAg with negligible false-negative results, which can be utilised for large-scale screening and diagnosis of HBV infection, only an estimated 15-30% of chronic HBV infection have been diagnosed. Hence, to further decrease global viral and disease burden, it is of paramount importance to identify all patients with CHB infection and timely initiate effective antiviral therapy for them. In the meantime, increase public awareness to access hepatitis B test is essential. On the other hand, in accordance with the existing regional treatment guidelines, it was estimated that less than one-tenth of those CHB patients indicated for treatment received anti-HBV therapy. There is also a recent call to expand treatment criteria beyond existing guidelines to extend therapeutic benefits to more patients with CHB infection. Indeed, a cost-effectiveness analysis of expanded antiviral treatment for CHB infection, based on decision-tree Markov state-transition model, suggested expanding treatment to HBV-infected patients with ALT thresholds of 30 U/L and 19 U/L for males and females, with 80% treatment coverage for HBsAg-positive individuals aged 18–80 years. This expanded antiviral treatment with a modified ALT threshold, coupled with lower generic drug costs and a revised medical insurance subsidization policy, particularly in HBV-endemic countries like China, could reduce HBV-related complications and deaths to support the global target of 65% reduction in HBV-related death. With the recent surge of prevalence and emerging association of Metabolic dysfunction-associated fatty liver disease as a co-morbidity factor for CHB patients, future treatment guidelines likely need to be modified accordingly. In future, we believe that a collaborative effort of all authoritative liver societies to revise and expand HBV treatment guidelines considering the drastically reduced cost of anti-viral therapy, along with universal screening for HBsAg positivity, will contribute to a meaningful reduction in disease burden due to HBV infection in Asia-Pacific region.

Post-Graduate Program (Hepatitis B)

PG1-4

Dr. Tai-Chung Tseng

Department of Medical Research, National Taiwan University Hospital, Taipei

Taiwan

Role of HBcrAg in Predicting Long-Term Outcomes for Patients with Chronic Hepatitis B

Hepatitis B virus (HBV) infection poses a significant global health challenge. Individuals with chronic hepatitis B (CHB) infection face diverse adverse events, including the risk of severe hepatitis flare, potentially leading to acute-on-chronic liver failure (ACLF), cirrhosis, hepatocellular carcinoma (HCC), and other complications. Conversely, some individuals experience favorable outcomes, such as spontaneous clearance of hepatitis B surface antigen (HBsAg) or hepatitis B e antigen (HBeAg). Serum hepatitis B core-related antigen (HBcrAg) quantification is a valuable biomarker for covalently closed circular DNA (cccDNA) levels, providing crucial information for clinical management.

In the early phase of chronic HBV infection, HBeAg-positive patients are considered "immune-tolerant" due to active viral replication without significant liver damage. Our recent findings revealed that elevated HBcrAg levels (>100 million U/mL) correlate with a reduced likelihood of spontaneous HBeAg seroclearance in HBeAg-positive patients, particularly in the immune-tolerant subgroup. This insight aids physicians in deciding whether to initiate antiviral treatment or await spontaneous HBeAg seroclearance.

Functional cure, indicated by HBsAg seroclearance, is associated with lower HBcrAg levels, especially in those with HBsAg levels >1000 IU/mL. The reduction of HBcrAg precedes the decline of HBsAg, suggesting the need to target cccDNA for successful treatment. A delayed decline in HBsAg levels suggests additional agents targeting HBsAg derived from integrated HBV DNA may be necessary for achieving functional cure.

Current guidelines recommend antiviral therapy for immune-active CHB patients but not for inactive CHB patients due to their different HCC risk. However, more than half of the HBeAg-negative CHB patients find themselves in the "grey zone" (GZ). We developed a novel GZ-HCC risk score (EXPLORE) considering age, sex, platelet count, ALT levels, and hepatitis B core-related antigen. This is the first risk prediction model demonstrating that an HBcrAg-based HCC score outperforms HBV DNA-based HCC scores in HBeAg-negative GZ patients. The model has been validated in an independent Japanese cohort. Furthermore, we propose a GZ-HCC score of 8 to categorize GZ patients into high- and low-risk groups, aligning their HCC risk levels with those of immune-active CHB and inactive CHB patients, respectively.

In conclusion, HBcrAg is a valuable biomarker for predicting clinical outcomes, and its integration with various viral markers enables customized therapeutic approaches for CHB patients with distinct risk profiles.

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Summary

Post-Graduate Program (Hepatitis C)

Post-Graduate Program (Hepatitis C)

PG2-1

Dr. Necati Örmeci

İstanbul Health and Technology University

Turkey

Management of HCV Infection

Hepatitis C virus (HCV) infection is a one of the major healths problem which cause of chronic liver disease, with approximately 71 million chronically infected individuals worldwide. Main target is to achive sustained virological response which indicates HCV RNA undetectable by sensitive assey 12 weeks or 24 weeks after the treatment by direct acting antivirals. The goal of therapy is to cure HCV infection in order to:

(i) prevent the complications of HCV-related liver and extrahepatic diseases, including hepatic necroinflammation, fibrosis, cirrhosis, decompensation of cirrhosis, HCC, severe extrahepatic manifestations and death; (ii) improve quality of life and remove stigma; iii) prevent onward transmission of HCV treatment as prevention.

All treatment-naïve and treatment-experienced patients with recently acquired or chronic HCV infection should be treated without delay. Patients with significant fibrosis (METAVIR score F2 or F3) or cirrhosis (METAVIR score F4), including decompensated cirrhosis; Clinically significant extrahepatic manifestations (e.g. Symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma);HCV recurrence after liver transplantation; Patients at risk of a rapid evolution of liver disease because of concurrent comorbidities (non-liver solid organ or stem cell transplant recipients, HBV and human immunodeficiency virus [HIV] coinfections, diabetes); İndividuals at high risk of transmitting HCV (people who inject drugs [PWIDs], men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, patients on haemodialysis, incarcerated individuals) should be treated urgently. There are some contraindications for the treatment with direct acting antivirals of HCV infection: * The use of certain cytochrome P450/P-gp-inducing agents. *HCV protease inhibitor,such as grazoprevir, glecaprevir or voxilaprevir, are contraindicated in patients with decompensated (Child-Pugh B or C) cirrhosis and in patients with previous episodes of decompensation. *We should be aware of drug drug interactions, co-morbid diseases and severity of liver disease before the treatment of HCV infection.Systematic testing for HCV resistance prior to treatment in DAA-naïve individuals is not recommended. Symply sofosbuvir +velpatasvir for 12 weeks are given to the patients with all genotypes, with naive /treatment experienced with or without compensated cirrhosis. Or glycaprevir +piprentasvir for 8 weeks is given to the patients with all genotypes with treatment naive with or without compensated cirrhosis. Glicapravir+Piprentasvir are given to patients with all genotypes,treatment experienced , compensated cirrhosis. Genotype/subtype determination-based treatment should be made according to AASLD, EASL or APASL guidelines.

Post-Graduate Program (Hepatitis C)

PG2-2

Dr. Saeed Hamid

Department of Medicine Aga Khan University

Pakistan

Simplified treatment guidelines and service Delivery models to drive Elimination of HCV.

Global data suggest that only a few countries are on course to eliminate HCV infection by 2030. To achieve this, the following needs to be done:

- Simplification of HCV Guidelines
- Simplification of the service delivery models.
- Decentralization.
- Task shifting
- Training and enabling prescribers other than physicians
- Removing access issues to DAAs
- Financing of national programs.
- Political will.
- Projecting success stories.

This talk will cover these aspects in detail, based on the recent Lancet Commission report On Viral Hepatitis Elimination.

Post-Graduate Program (Hepatitis C)

PG2-3

Dr. Lai Wei

Hepatopancreatobiliary Center, Beijing Tsinghua Changgung Hospital,

School of Clinical Medicine, Tsinghua University

China

Community engagement, Protection of rights and interests, and Gender equality in HCV elimination

World Health Organization called for elimination for chronic hepatitis as a public health threat. Specific targets include that newly acquired infection reduce by 90%, and liver-related mortality reduced by 65%. Historical barriers are overcome including screening test and programs, safe and effective drugs, linkage to care, treat all. However, some social barriers still delay elimination, that is civil society engagement, protection of rights and interests, and gender equality. Asia Pacific region is so diversity regarding economic, social development and with multi culture, therefore, we face potential challenge for community engagement, protection of rights and interests, and gender equality in hepatitis C elimination.

Community engagement is to develop relationships that enable stakeholders to work together to address chronic hepatitis related issues and promote well-being to achieve elimination impact in the community. Some organizations and people engages, they are community health worker, civil society organization (CSO), health centre committee. Finally, we can achieve community-led monitoring (CLM) and meaningful engagement to focus on local fact-finding to solve problem and meet the needs of local communities. Community engagement should be people-centred and involved with person affected by hepatitis C virus (HCV).

Protection of rights and interests maybe a bigger challenge in Asia Pacific region. Common international problem in HCV elimination is a deficiency of financial resources as indicated Ukraine and Georgia study. There still is need for effective fighting the epidemics and guarantee equal access to treatment for every person. More investments is required.

Gender equality maybe the biggest challenge in Asia Pacific region due to significant diversity of culture. Korea study that Global Gender Gap Index (GGGI) was significantly associated with the incidence of both chronic hepatitis B and C in under 5 years. For HIV infection, GGGI score was significantly associated with the pregnant women with unknown HIV status, no early infant diagnosis, and final transmission rate, which imply more study is needed.

Community engagement, protection of rights and interests, and gender equality should be improved in Asia Pacific region for hepatitis C elimination.

Post-Graduate Program (Hepatitis C)

PG2-4

Dr. Yoshiyuki Ueno

Department of Gastroenterology, Yamagata University Faculty of Medicine

Japan

Post-Graduate Program (Hepatitis C)

Viral hepatitis infection has been a great threat to human health globally. Although remarkable breakthrough has been made in the past several decades for prevention and treatment of viral hepatitis, still this infectious disease is increasing its risk. Actually, 905,700 people were diagnosed with and 830,200 people died from liver cancer in 2020. Moreover, the number of new cases and deaths from liver cancer could rise by >55% by 2040. Thus, HCC remains to be global risk for next decades. Of course, viral infection is a major cause of HCC in many countries. With this line, WHO aimed to set the global elimination of viral hepatitis by 2030. WHO's global hepatitis strategy, endorsed by all WHO Member States, aims to reduce new hepatitis infections by 90% and deaths by 65% between 2016 and 2030. However, except for few countries or regions, our actual achievement has been behind the track. In this session, our current status and future strategy will be summarized to keep our mission on the planned goals.

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Summary

Post-Graduate Program (MAFLD)

Post-Graduate Program (MAFLD)

PG3-1

Dr. Ian Homer Y. Cua
Hepatology Society of the Philippines
Philippines

Understanding the Name Changes to Fatty Liver: From NAFLD to MAFLD and MASLD

The evolution of nomenclature in the realm of fatty liver diseases has witnessed a shift from the traditional term NAFLD to MAFLD and, more recently, MASLD. This transformation reflects an understanding of the conditions, emphasizing their intricate connection with metabolic factors.

NAFLD was introduced to differentiate fatty liver conditions not attributed to alcohol consumption. However, as research delved deeper into the underlying mechanisms, it became apparent that the term fell short of encapsulating the broader metabolic implications associated with these liver disorders. This realization led to the emergence of MAFLD, a term that encompasses the intricate interplay between fatty liver and metabolic dysfunction.

MAFLD signifies a paradigm shift in diagnostic criteria by incorporating metabolic risk factors like obesity, insulin resistance, and dyslipidemia. Unlike NAFLD, which primarily focused on excluding other liver pathologies, MAFLD offers a more inclusive approach, recognizing the dynamic relationship between metabolic health and fatty liver conditions. This evolution aligns with the understanding that these diseases are not isolated incidents but rather components of a larger metabolic syndrome.

More recently, in 2023, the term MASLD was introduced. In addition to recognizing the metabolic factor of FLD, MASLD also aims to eliminate the stigma surrounding the disease and recognize the overlap of MASLD and alcoholic liver disease. Understanding these name changes is pivotal for healthcare practitioners as it shapes diagnostic approaches, treatment strategies, and research frameworks. The transition from NAFLD to MAFLD and MASLD signifies a departure from a singular focus on the liver to a more holistic consideration of metabolic health. It emphasizes the need for comprehensive evaluations, recognizing the bidirectional relationship between metabolic dysfunction and fatty liver conditions.

In conclusion, the shift from NAFLD to MAFLD and MASLD in nomenclature highlights a refined understanding of fatty liver diseases, acknowledging their close ties with metabolic dysfunction. These changes pave the way for a more comprehensive and precise approach to diagnosis and management, recognizing the intricate interplay between liver health and overall metabolic well-being.

Post-Graduate Program (MAFLD)

PG3-2

Dr. Takumi Kawaguchi

Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine.

Japan

Etiology and Usefulness of MAFLD in the Asian-Pacific region

MAFLD is a major public health problem in the Asian-Pacific region. Excess energy intake and a sedentary lifestyle are major causes of hepatic steatosis. These unhealthy lifestyles also cause the accumulation of lipids in visceral adipose tissue, leading to adipose tissue inflammation. Adipose tissue produces proinflammatory cytokines including TNF-α, IL-1β, and IL-6, which flow into the liver through the hepatic artery. These adipose tissue-derived factors promote the development of MAFLD.

Besides visceral adipose tissue, the gut is a major etiological organ of MAFLD. Dietary factors including excess fructose intake induce dysbiosis, leading to low-grade intestinal inflammation and an impairment of gut barrier function called leaky gut. A leaky gut facilitates the translocation of lipopolysaccharides and microbial metabolites to the liver through the portal vein. This influx causes the production of pro-inflammatory cytokines and attracts immune cells through activation of Kupffer and liver sinusoidal endothelial cells in the liver.

Risk factors for MAFLD in Asians are like those in Westerners. In addition, a feature of Asians is non-obese MAFLD. In non-obese Asian individuals, possible etiologies of MAFLD are the following: visceral obesity, dysbiosis, sarcopenia, hypothyroidism, hypopituitarism, and hyperuricemia. Furthermore, another possible etiology is genetic predisposition including polymorphism in PNPLA3 (patatin-like phospholipase domain-containing protein 3), TM6SF2 (transmembrane 6 superfamily member 2), GCKR (glucokinase regulator), MBOAT7 (membrane bound O-acyltransferase domain containing 7), and HSD17B13 (hydroxysteroid 17-beta dehydrogenase-13).

MAFLD is a disease concept that actively encloses high-risk patients through inclusion criteria. In fact, various Asian-Pacific clinical studies demonstrated that MAFLD identifies patients with significant hepatic fibrosis and at high risk of HCC. In addition, MAFLD has been reported to identify patients at higher risk for atherosclerotic cardiovascular disease better than NAFLD. The superiority of MAFLD over NAFLD seems to be due to the presence of metabolic dysfunction rather than moderate alcohol consumption. Furthermore, MAFLD is more associated with various extrahepatic diseases including reflux esophagitis, colorectal adenoma, the recurrence of esophageal squamous cell carcinoma, chronic obstructive pulmonary disease (COPD), and psoriasis rather than NAFLD. Thus, MAFLD is useful to identify patients at risk of both liver-related events and extra-hepatic events.

In this session, I will introduce the etiology of Asian-Pacific MAFLD according to the APASL guidelines. I also mention the impact of MAFLD on the identification of patients at risk of hepatic events as well as extra-hepatic events in the Asia–Pacific region.

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Summary

Post-Graduate Program (Fibrosis/Cirrhosis)

Post-Graduate Program (Fibrosis/Chirrosis)

PG4-1

Dr. Norifumi Kawada

Department of Hepatology Graduate School of Medicine Osaka Metropolitan University

Japan

Molecular and Cellular Mechanisms of The Development and Regression of Liver fibrosis

Since chronic liver diseases progress to fibrosis and even cirrhosis regardless of their etiology, elucidating the molecular and cellular mechanisms of liver fibrosis is an important issue for the development of therapeutic strategies. Research on liver fibrosis progressed with the discovery of hepatic stellate cells, and in 1985, after Dr. Scott Friedman determined that hepatic stellate cells produce extracellular matrix substances such as collagen in the liver, detailed mechanistic analyzes of activation and deactivation process of hepatic stellate cells have been carried out for about 40 years. Furthermore, recently, cell-cell interactions and more detailed cell classification have been performed using single cell RNA-seq analysis, and the overall picture of liver fibrosis/cirrhosis has progressed, including functional analysis of hepatocytes. Furthermore, progress is being made in elucidating why liver cancer develops from liver cirrhosis, and the cascade involved in the transformation of fibrotic hepatocytes into hepatocellular carcinoma. One of the molecule involved in this cascade is cytoglobin, a stellate cell-specific globin in the liver. Although no anti-fibrotic treatment has been developed to date, it has become clear that removal of the etiological cause triggers regression of fibrosis. In this lecture, molecular and cellular mechanisms of the development and regression of liver fibrosis will be discussed.

Post-Graduate Program (Fibrosis/Cirrhosis)

PG4-3

Dr. Gamal Shiha

Gastroenterology and Hepatology Dept., Faculty of Medicine, Mansoura University,

Egyptian Liver Research Institute and Hospital (ELRIAH)

Egypt

Hepatocellular Carcinoma Risk prediction score (GES) in chronic hepatitis C patients with compensated advanced chronic liver disease (cACLD) after achieving SVR

Introduction

We designed and validated a scoring system known as the General Evaluation Score (GES) for Hepatocellular Carcinoma (HCC) risk stratification. Our objective was to assess the efficacy of this score within a substantial prospective cohort comprising individuals with cured hepatitis C, with compensated advanced chronic liver disease, and achieved a sustained virological response following direct-acting antivirals.

Methods:

This prospective study, conducted at the Egyptian Liver Research Institute and Hospital between January 2018 and October 2019, enrolled 463 consecutive patients with advanced fibrosis (≥F3) who attained sustained virological response. Prior to antiviral therapy initiation, all patients underwent abdominal ultrasound and multislice computed tomography for HCC surveillance. Subsequent follow-ups occurred every 6 months post-treatment, utilizing ultrasonography, alpha-fetoprotein, and additional multislice computed tomography every 12 months.

Results:

Of the 463 patients included, 197 (42.5%), 114 (24.6%), and 152 (32.8%) were stratified as having low, intermediate, and high-risk scores, respectively, before treatment initiation. The incidence rate of HCC was 2.61 per 100 person-years (95% CI = 1.73–3.80), with 25 cases developing HCC during the follow-up period. The respective HCC incidence rates in the low, intermediate, and high-risk groups were 0.97% (95% CI: 0.31–2.34), 1.68% (95% CI: 0.53–4.05), and 5.57% (95% CI: 3.35–8.74). A significant positive correlation was observed between higher risk scores and increased HCC incidence ($p < 0.001$). Harrell's c-statistic for this model was 0.728.

Conclusion:

This prospective study underscores the predictive capability of GES in anticipating HCC occurrence and effectively categorizing patients into low, intermediate, and high-risk groups

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Summary

Post-Graduate Program (ACLF)

Post-Graduate Program (ACLF)

PG5-1

Dr. Teerha Piratvisuth

NKC Institute of Gastroenterology and Hepatology

Faculty of Medicine, Prince of Songkla University

Thailand

Prognostic predictors in patients with Acute-on-chronic liver failure (ACLF)

Acute-on-chronic liver failure is a severe form of acutely decompensated cirrhosis with high mortality rate, 28-day mortality rate >20%. Prognostic predictors can guide the optimal strategies for managing individual patient properly. The number of organ system failure is associated with severity and mortality of ACLF-patients. The ACLF grades, based on the number of organ failures (liver, kidney, brain, coagulation circulation, respiration) enable to categorize patients with a range of 28-day and 3-month mortality risks. There are currently a few scoring system for predicting mortality rate in patients with ACLF. The CLIF-C ACLF score was developed by combining the CLIF-C score with age and white cell count for predicting 28-day and 90-day mortality better than those of the MELD score, MELD-Na score and Child-Pugh score. The AARC score was developed for patients with ACLF diagnosed using the APASL for predicting short-term mortality. The NACSELD only based on failure of 4 organ systems (brain, kidney, circulation, reparation) defined by the physicians' response to the problem. The NACSELD may underestimates the risk of death in patients with ACLF. The COSHH Score was developed for patients with HBV-related ACLF. The newly proposed models and nomograms for predicting prognosis in patients with ACLF have shown some improvement on the CLIF-C ACLF score, but they require further validation. Inflammation severity has been shown as the most important predictor of ACLF.

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Summary

Post-Graduate Program (Portal Hypertension)

Post-Graduate Program (Portal Hypertension)

PG6-1

Dr. Xiaolong Qi

CHESS Center, Center of Portal Hypertension, Department of Radiology,

Zhongda Hospital, School of Medicine, Southeast University

China

Emerging non-invasive methods for evaluation of cirrhotic portal hypertension

Clinically significant portal hypertension (CSPH) is associated with symptomatic gastro-oesophageal varices (GOV), the development of hyperdynamic circulation, and patients with compensated advanced chronic liver disease at risk of clinical decompensation. Hepatic venous pressure gradient (HVPG) measurement and esophagogastroduodenoscopy are the gold standard methods for assessing CSPH (HVPG ≥10 mm Hg) and GOV, respectively. However, they are limited by their invasiveness in clinical practice. In recently years, there are a lot of new technologies focuses on the development of non-invasive approaches to the diagnosis and serial monitoring of portal hypertension.

Imaging techniques used for portal hypertension include ultrasound, computed tomography (CT) and magnetic resonance (MR). Elastography techniques measure liver and spleen stiffness by quantifying the velocity of an induced shear wave, including transient elastography, point-shear wave elastography, and two-dimension shear wave elastography; and MR elastography. Liver stiffness measurement has been proved to be sufficiently accurate to identify CSPH and safe to screen high-risk varices combined with platelet count in clinical practice. Laboratory tests and serum markers need to be interpreted critically because some of their individual components can be affected by a variety of comorbidities. Artificial intelligence (AI) has made great strides in the field of medicine. Information of CT and MR imaging can be integrated and applied to detection of cirrhosis and portal hypertension by AI.

In summary, a wide spectrum of novel non-invasive tests have emerged and represent a major advantage in the assessment of portal hypertension. However, there are still many challenges to integrating non-invasive screening methods into clinical practice, and more data are needed to establish consensus on standard practice and implementation.

Post-Graduate Program (Portal Hypertension)

PG6-2

Dr. Hideki Kobara

Department of Gastroenterology and Neurology, Faculty of Medicine, Kagawa University

Japan

Current Endoscopic Gastrointestinal Interventions and Management

Endoscopic submucosal dissection (ESD) has been an attractive minimally invasive surgery during the past two decades. Currently, pure Endoscopic Full-Thickness Resection (EFTR) is focused as next-advanced technique. Meanwhile, post-ESD or EFTR defects, and iatrogenic perforation must be carefully managed to prevent and rescue adverse events.
Here, I would like to introduce these current gastrointestinal interventions and our ongoing research.

Post-Graduate Program (Portal Hypertension)

PG6-3

Dr. Hitoshi Maruyama

Department of Gastroenterology, Juntendo University

Japan

Role of HVPG in the management of portal hypertension

Cirrhosis is the most advanced stage of chronic liver disease. It is accompanied with a risk of developing serious complications, including variceal bleeding, ascites, icterus, and hepatic encephalopathy. These events limit quality of life and long-term outcomes, therefore, patients with these conditions need to be properly monitored.

Hepatic venous catheterization is a safe and an established technique which enables measurement of hepatic venous pressure gradient (HVPG) by either jugular approach or femoral approach. Hepatic venogram is useful to demonstrate the typical appearance of cirrhosis and non-cirrhotic portal hypertension, which could be obtained by using either iodinated contrast material or carbon dioxide.

Portal hypertension is the principal pathophysiology of cirrhosis, and a HVPG is a representative marker for the severity of the condition. A HVPG of 10 to 12 mmHg is the threshold level for the development of esophageal varices, ascites, and the occurrence of variceal bleeding, and a HVPG higher than 16 mmHg suggests an increased risk of death. Moreover, a HVPG higher than 20 mmHg is the best independent prognostic marker for acute variceal bleeding, and thus indicates the presence of much more severe status. In addition, a HVPG is an effective marker to offer the treatment direction of TIPS for variceal rebleeding in cirrhosis, and to predict the prognosis after TIPS placement for refractory ascites. Thus, hepatic venous catheterization has a wide range of role in the management of portal hypertension This presentation overviews recent studies regarding HVPG and summarizes the evidences.

APASL 2024 Kyoto

The 33rd Annual Meeting the Asian Pacific Association for the Study of the Liver

Summary

Post-Graduate Program (HCC)

Post-Graduate Program (HCC)

PG7-1

Dr. Takahiro Kodama

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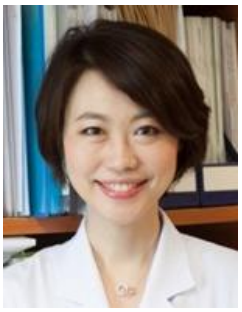
Japan

Discovery of therapeutic and biomarker for HCC through basic and translational research of tumor microenvironment

HCC is a dismal disease with the third highest mortality rate among all cancer types. Its molecular entity is very complex and further clarification of its heterogeneous nature is required for prognostic improvement. With the progress of next-generation sequencers over the past decade, the genomic and epigenomic abnormalities in HCC have been well-documented with a large number of cases, and the whole picture has become clear. On the other hand, the recent development of innovative technologies such as single-cell analysis and spatial omics analysis has begun to open a new era in cancer research. In the tumor microenvironment, not only cancer cells but also various immune cells and stromal cells exist, and these form a complex network that leads to cancer formation and progression. In recent years, various drugs have been developed and made available for HCC. Importantly most of them, such as angiogenesis inhibitors and immune checkpoint inhibitors, target the tumor microenvironment rather than the cancer cells themselves, indicating the importance of understanding cancer as such an ecosystem to truly overcome cancer. One of the treatment goals of HCC therapy is personalized therapy with a variety of molecular-targeted drugs and their efficacy biomarkers. Recent advancement in HCC pharmacotherapy allows us to utilize 8 different therapeutic regimens but the efficacy of each drug is still limited. Further research efforts to discover novel drug targets and develop efficacy biomarkers are desired in the HCC field. In this presentation, I would like to share recent knowledge of the HCC tumor microenvironment and show our latest discoveries of therapeutics and biomarkers for HCC through basic and translational research. I also would like to discuss with the audience the future perspective of HCC research.

Post-Graduate Program (HCC)

PG7-2



Dr. So Yeon Kim

Department of radiology, Division of Abdominal Imaging,

University of Ulsan College of Medicine, Asan Medical Center

Korea

Cutting-Edge Imaging of HCC

The role of imaging in hepatocellular carcinoma (HCC) is distinctive, offering noninvasive diagnostic capabilities unparalleled in many other solid tumors. Recent updates to major clinical guidelines, including those established by the Asian Pacific Association for the Study of the Liver (APASL), have underscored the pivotal role of magnetic resonance imaging (MRI) employing hepatobiliary agents and contrast-enhanced ultrasonography (US) in the diagnosis and management of HCC. These updates introduce nuanced variations in contrast agent selection and HCC definition, reflecting the dynamic landscape of regional medical practices and evolving technologies. Furthermore, contemporary guidelines have embraced the incorporation of alternative surveillance tools in specific patient cohorts, acknowledging the limitations of traditional gray-scale US approaches. Beyond its diagnostic utility, imaging serves as a powerful tool for elucidating tumor biology and prognostic assessment, providing clinicians with invaluable insights into disease progression and treatment response. This presentation will delve into the intricacies of the pivotal guidelines governing the management of HCC, while exploring the diverse array of imaging modalities and features critical for predicting clinical outcomes and optimizing patient care.

Post-Graduate Program (HCC)

PG7-3

Dr. Yi-Hsiang Huang

Taiwan Liver Cancer Association (TLCA),

Institute of Clinical Medicine, College of Medicine, National Yang Ming Chiao Tung University,

Healthcare and Services Center, Taipei Veterans General Hospital

Taiwan

Post-Graduate Program (HCC): Treatment guidelines update

HCC is prevalent in Asia Pacific countries and its incidence is expected to rise in the next decade. The treatment of HCC depends on tumor stage and liver function reserve. BCLC is widely adopt as the staging system for HCC in most countries. The goal of treatment for early stage HCC is to curative resection or ablation for the tumor and avoid recurrence as possible. Several strategies have been established to be able to decrease the risk of recurrence, such as antiviral treatment for underlying chronic hepatitis B or C, and most recently adjuvant immunotherapy for high risk patients. For intermediate stage HCC, TACE is no longer the only option. Due to the heterogenous nature of BCLC B tumors, the outcome of TACE is varied depends on tumor burden and radiologic patterns. Due to the advance of systemic therapy, some patients with intermediate stage HCC have the potential to be curative conversion by atezolizumab/bevacizumab followed by locoregional treatment or surgical resection. TACE combined with immunotherapy, lenvatinib or sorafenib may also prolong the survival for BCLC B HCC. For advanced stage HCC, systemic therapy is the key treatment. Immunotherapy either by atezolizumab/bevacizumab, or tremelimumab/durvalumab is the standard of care if there is no contraindication for immunotherapy. Although there is no phase 3 clinical trial to support the optimal treatment as 2L after immunotherapy, different mechanism of action and tolerability of adverse event are the key considerations for the choice of subsequent treatment

Post-Graduate Program (HCC)

PG8-1

Dr. David C. Madoff

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USA

Role of Interventional Oncology in the Management of Hepatocellular Carcinoma

The treatment of patients with hepatocellular carcinoma (HCC) requires a careful balance of adequate oncologic control and the preservation of both liver function and performance status. Over the last few decades, the emerging field of interventional oncology has introduced a variety of minimally invasive, safe and effective therapies, expanding the armament of available treatment options (1). The Barcelona Clinic Liver Cancer staging system, updated in 2022, is the most widely adopted treatment classification which aims to match patients with the therapies that will yield the best outcomes based on these factors (2). Thermal ablation has been recommended for patients with very early-stage or early-stage disease and transarterial chemoembolization (TACE) has been recommended as the gold standard therapy for patients with intermediate grade disease (3,4). An important addition to the updated BCLC staging system is that transarterial radioembolization (TARE) is now included in the treatment of both early- and intermediate stage HCC (2,5). Technical innovation brings newer ablative and embolotherapy techniques into practice, while clinical innovation continues to expand the indications of these treatments outside of the formal paradigm (1). Clinical trials incorporating locoregional therapies in combination with immunotherapy, potentially leading to synergistic effects and improved survival outcomes, are now underway (6). This presentation will provide a brief overview of the varied interventional procedures being used in clinical practice and will review how they can be used to cure very early and early-stage disease, to facilitate surgical resection, to bridge or downstage tumors for liver transplantation, and extend survival as palliative interventions in patients with intermediate or advanced disease.

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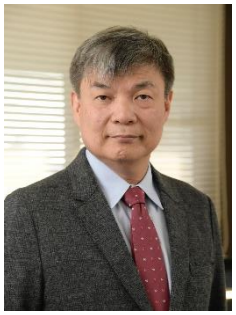
Post-Graduate Program (HCC)

PG8-2



Dr. Takumi Fukumoto

Department of HBP Surgery, Kobe University

Japan

Current status of multidisciplinary treatment for advanced HCC in Kobe University

Past two decades, the greatest advances in the treatment of HCC have been achieved in chemotherapy with tyrosine kinase inhibitors and/or immune checkpoint inhibitor. Another important advance have been observed in radiotherapy. Particle radiotherapy enables curative treatment even for patients with large HCC and impaired liver function. These advances changes the therapeutic landscape, however optimal strategy is still unclear. We herein demonstrate the current status of multidisciplinary treatment for advanced HCC with the advent of the era of combined immunotherapy in Kobe University.

Methods: Study1, Hepatectomy with tumor thrombectomy (n=142) vs sorafenib (n=85) for HCC patients with PVTT. Study 2, Treatment results of systemic chemotherapy including lenvatinib (n=142), atezolizumab/bevacizumab (n=125), and tremelimumab plus durvalumab (n=19) treatments, and the conversion rate to local treatment of systemic chemotherapy. Study3, Treatment results and best candidate of reductive hepatectomy for HCC patients with extrahepatic metastases (n=32) and/or multiple bilobar metastases (n=107). Study 4, Liver resection (n=19) vs particle radiotherapy (n=31) for HCC patients with inferior vena cava tumor thrombus.

Results: Study1, By propensity-match, MST of HCC patients with Vp3/4 underwent hepatectomy (15.1 months) was significantly better than sorafenib (4.5 months). Study 2, Response rate of lenvatinib, atezolizumab/bevacizumab, and tremelimumab plus durvalumab for advanced HCC by mRECIST or RECIST were (33.0%, 13.9%),(37.7%, 29.5%),(10.5%, 10.5%), respectively. Conversion rate was only 4.9% (n=14). Study 3, MST of HCC patients with extrahepatic metastases were 11.8. Among them, MST of patients with intrahepatic maximal tumor size <100 mm and tumor number ≤2 was 39.0 months. MST of multiple bilobar metastases was 18.0 months. Among them, MST of patients with bilirubin <1.0 mg/dl nor albumin >3.0 g/dl was 20.0 month. Study 4, The 1- and 3-year survival rates were 68%, 25% in the particle radiotherapy and 34%, 14% in hepatectomy.

Conclusions: Hepatectomy still plays an important role in the multidisciplinary approach for HCC. Best candidate for new treatment modalities and best combinations of existing and new one should be elucidated.

Post-Graduate Program (HCC)

PG8-3

Dr. Kazuomi Ueshima

Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine

Japan

Optimizing the treatment sequences in chemotherapy of hepatocellular carcinoma

Systemic chemotherapy for hepatocellular carcinoma has made remarkable progress, and eight regimens of nine drugs are currently available. However, the sequences in which these regimens should be selected are controversial. First, in first-line treatment, combination immunotherapy is the first choice, but the BCLC Guidelines and the Japanese Clinical Practice Guidelines for Hepatocellular Carcinoma do not state and recommend clearly which should be used first: durvalumab plus tremelimumab or atezolizumab plus bevacizumab. The same applies to second-line treatment and beyond; no clear guidelines have been provided. Although these situations are partly unavoidable due to the lack of evidence, no clear treatment strategy is a serious problem in clinical practice. In the presentation, I will talk about the optimal treatment strategies based on the evidence obtained to date.

Post-Graduate Program (HCC)

PG8-4

Dr. Masafumi Ikeda

Department of Hepatobiliary and Pancreatic Oncology at the National Cancer Center Hospital East

Japan

Post-Graduate Program (HCC) Systemic therapy

Systemic therapy has become mainstream for hepatocellular carcinoma (HCC), with the development of molecular-targeted agents, such as sorafenib and lenvatinib as first-line treatment and regorafenib, ramucirumab and cabozantinib as second-line treatment, and of immunotherapies, such as atezolizumab plus bevacizumab, durvalumab plus tremelimumab and durvalumab monotherapy. In Japan, a total of 8 regimens are now available for unresectable HCC. Combined immunotherapies are firstly selected if patients have no contraindication for immunotherapies, such as autoimmune diseases. Molecular-targeted therapy is selected when immunotherapy is not indicated or proves ineffective. And, it is necessary to select the appropriate treatment taking into consideration the patients' clinical condition, expected treatment efficacy, and adverse effects of the treatment.

The indications for systemic therapy are currently expanding, although advanced-stage HCC was a good indication for systemic therapy previously. Systemic therapy is indicated for intermediate-stage HCC that is trasarterial chemoembolization (TACE) refractory or TACE unsuitable. When performing non-curative-intent TACE, combination therapy of TACE and systemic therapy is expected to be a future treatment strategy, because phase III trial of TACE with durvalumab plus bevacizumab vs. TACE with durvalumab plus placebo vs. TACE with placebos (EMERALD-1) was press-released to meet the primary endpoint for progression-free survival. Furthermore, the indication might be expanding for early-stage HCC, because perioperative adjuvant therapy of atezolizumab plus bevacizumab demonstrated significantly better recurrent-free survival after curative surgical treatment or ablation (IMbrave050). Therefore, systemic therapy is now available for any stage of the disease. While previously, local therapies used to be the main treatment strategy for HCC, systemic therapy in combination with local therapies is being actively tried at present. Systemic therapy is currently promising topics of development of novel treatments for HCC.

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Summary

APASL Targets for this Century

APASL Targets for this Century

TC1-2

Dr. George Lau

Humanity and Health Clinical Trial Center, Humanity and Health Medical Group,

Hong Kong SAR, China

APASL clinical practice guideline on systemic therapy for hepatocellular carcinoma- 2024

Since the inception of the first Asian-Pacific Association for the study of liver (APASL) hepatocellular carcinoma (HCC) working party in 2007 and the publication of its first guideline published in 2010 and then revised in 2017, major advances in systemic therapy for hepatocellular carcinoma (HCC) have been made. Despite the availability of effective HCC surveillance and preventive measures, most of the HCC still present at advanced stage as reflected by the high mortality-incidence ratio across Asian-Pacific region. Most of these patients diagnosed with HCC are therefore beyond curative measures such as surgical resection, local ablation or liver transplantation. Even for those patients who are eligible to have curative measures in accordance to various HCC treatment guidelines, recurrence is still a very common clinical problem. The major etiology of the HCC in Asian-Pacific region are chronic hepatitis B and C infection, compounded by the recent rise of metabolic dysfunction-associated fatty liver diseases (MAFLD). In country like China, the incidence of HCC is not rising but account for close to half of the global annual cases. Most if not all are related to chronic hepatitis B infection.

In the recent few years, new targeted therapy and immune-checkpoint inhibitors have been registered as systemic therapy for hepatocellular carcinoma either as first-line or second-line therapy for unresectable or not eligible for locoregional therapy. The gravity of chronic hepatitis B and C as etiology of hepatocellular carcinoma in Asia-Pacific region, is of great relevance as the response to immune-checkpoint inhibitors are much higher, as compared to targeted therapy. Recently, new data is also emerging with the use of systemic therapy to prevent HCC after curative attempt with resection or local ablation therapy. The purpose of this clinical guideline is to provide an up-to-date recommendation based on clinical evidence and experience from regarded key opinion leaders in the field of hepatocellular carcinoma. Three key questions will be addressed, namely (1) which patients with HCC should be considered for systemic therapy? (2) which systemic therapy should be used? and (3) how should a patient planned for systemic therapy be managed and monitored?

APASL Targets for this Century

TC1-4

Dr. Jacob George

Robert W. Storr Professor of Hepatic Medicine at the Storr Liver Centre,

Westmead Institute for Medical Research, University of Sydney

Australia

Looking ahead: MAFLD in the APASL region

At its core, APASL's main objective is to advance the science and practice of Hepatology, particularly for patients in the Asia Pacific region. In 2024, the APASL pillars focussed on viral hepatitis elimination, liver cancer, acute on chronic liver failure through AARC, the APASL-ACLF Research Consortium (AARC), and MAFLD, through the APASL-MAIDEN (Metabolic fatty liver Disease consortium; maiden-apasl.com) consortium. While we have made tremendous progress over the past decades through vaccination against hepatitis B, curative treatments for hepatitis C and suppressive treatments for hepatitis B, the frontier that has now received the attention it deserves is MAFLD, projected to be the most common liver disease worldwide, with Asia at its epicentre. The Asian Pacific region harbours a majority of the world's population, with just two countries, India and China the most populous. The region is witnessing an economic transformation becoming the engine for global growth, but at the same time, being home to a rising global burden of oversight/obesity and type 2 diabetes. These diseases drive a systemic physiological response driven by insulin resistance, which in the liver drives fat deposition (MAFLD) and in pre-disposed individuals, a low grade chronic inflammatory response that leads to hepatic inflammation (steatohepatitis), cirrhosis and its feared complications, liver failure and liver cancer (both hepatocellular and cholangiocarcinoma). However, MAFLD is more than a liver disease and is just one part of systemic metabolic dysfunction, the harbinger of cardio-reno-vascular disease, diabetes and extrahepatic cancer. Managing the consequences of these diseases, a very large proportion of health budgets in Asian Pacific countries will be consumed unless effective policy action and settings are undertaken. While effective pharmacotherapies for weight loss and type 2 diabetes are emerging or are clinically approved, at a population level, they are expensive. Hence, preventive frameworks focussing on food quality, food quantity and physical activity needs to be prioritised. For those with MAFLD, clinical pathways to identify those with significant liver disease, referral pathways to tertiary care and treatment is required. APASL as the peak body for Liver Disease in our region is well placed to lead these initiatives by developing pan-national educational toolkits that can subsequently be individualised to cater to local needs.

APASL 2024 Kyoto

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Summary

APASL Award Session

APASL Award Session

AC1-2

Dr. Tatsuo Kanda

Division of Gastroenterology and Hepatology, Nihon University School of Medicine

Japan

Recent advances of viral hepatitis, and current situation of hepatitis A and E in Japan

Compared with before, it is easier to control of chronic hepatitis B virus and C virus (HBV and HCV) infection by the development of nucleos(t)ide analogues and direct-acting antivirals, respectively. We may also pay attention to other hepatitis viruses. In Asian countries, infection of hepatitis A virus (HAV) and hepatitis E virus (HEV) are common diseases. The increase of number of these patients could follow the improvement of hygiene environment.

In 2018, there was an outbreak of HAV infection in Japan, and hepatitis A is also considered a sexually transmitted disease. Patients with hepatitis A should be receiving attention, and this disease needs to be prevented more than ever. Despite the development of an effective vaccine against hepatitis A, universal vaccination has not yet been performed in Japan.

In Japan, until the early 2000s, acute HEV infection was considered rare until reports emerged confirming the existence of HEV genotype 3 and 4 infections. Until now, vaccines against hepatitis E have not yet become available in Japan. The Japanese National Health Insurance System does not approve anti-HAV and anti-HEV drugs.

Recently, we discovered several effective drugs against HAV infection and their mechanism by drug repositioning, in silico screening (Sasaki-Tanaka R, et al. J Virol. 2022 Sep 28; Sasaki-Tanaka R, et al. J Virol. 2023 Feb 28; Sasaki-Tanaka R, et al. Int J Mol Sci. 2023 Jun 3; Int J Mol Sci. 2022 May), etc. Although the use of off-label ribavirin for HEV infection was shown to be effective, the development of antivirals against HAV and HEV infection is urgently required.

The Japan Agency for Medical Research and Development (AMED) Hepatitis A and E viruses (HAV and HEV) Study Group has recently published the recent advances in research and clinical practice recommendations for hepatitis A. Here, the recent advances in research and clinical practice recommendations for HAV and HEV infections in Japan will be presented.

In conclusion, we should also promote and develop the antivirals against HAV and HEV infection.

APASL Award Session

AC1-3

Dr. Qin Ning

State Key Laboratory for Diagnosis and Treatment of Severe Zoonotic Infectious Diseases, Department and Institute of Infectious Disease, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. Clinical Study Centre for Viral Hepatitis, Hubei Province

China

Functional cure of CH-B in Real World

Evidence from randomized controlled trials (RCT), e.g. OSST, Endeavor and Anchor study, as well as other relevant clinical studies has shown that sequential combination therapy with immunomodulators (e.g. peg-interferon) and NUC in virally-suppressed patients with chronic hepatitis B (CHB) can improve functional cure (HBsAg loss), as compared to NUC continuous monotherapy. Moreover, several strategies can be used to predict functional cure or identify patients likely to benefit from the sequential treatment with immunomodulators (e.g. peg-interferon), including baseline-guided therapy using pretreatment HBsAg level, response-guided therapy using early decline in HBsAg level, and HBVcrue crab model using end-of-therapy HBsAb level and HBcrAg level. We further have conducted two multicenter real-world studies---COST study and OCEAN study in China, aiming to investigate the efficacy and long-term outcome of sequential peg-interferon treatment in patients undergoing long-term NUC treatment who had HBV DNA undetectable and HBsAg level <3000IU/mL. The interim analysis of COST study demonstrated consistent results of the RCT studies. We are currently conducting a nationwide questionnaire survey on the application of functional cure strategies for patients with CHB.

APASL Award Session

AC1-4

Dr. Ashok Choudhury

Additional Prof, Hepatology and Liver Transplant

Institute of Liver & Biliary Sciences- A Deemed University. New Delhi, India

Functional cure of CH-B in Real World

Evidence from randomized controlled trials (RCT), e.g. OSST, Endeavor and Anchor study, as well as other relevant clinical studies has shown that sequential combination therapy with immunomodulators (e.g. peg-interferon) and NUC in virally-suppressed patients with chronic hepatitis B (CHB) can improve functional cure (HBsAg loss), as compared to NUC continuous monotherapy. Moreover, several strategies can be used to predict functional cure or identify patients likely to benefit from the sequential treatment with immunomodulators (e.g. peg-interferon), including baseline-guided therapy using pretreatment HBsAg level, response-guided therapy using early decline in HBsAg level, and HBVcrue crab model using end-of-therapy HBsAb level and HBcrAg level. We further have conducted two multicenter real-world studies---COST study and OCEAN study in China, aiming to investigate the efficacy and long-term outcome of sequential peg-interferon treatment in patients undergoing long-term NUC treatment who had HBV DNA undetectable and HBsAg level <3000IU/mL. The interim analysis of COST study demonstrated consistent results of the RCT studies. We are currently conducting a nationwide questionnaire survey on the application of functional cure strategies for patients with CHB.

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Summary

HBV1 Challenges for Elimination of CCC HBV DNA

HBV1 Challenges for Elimination of CCC HBV DNA

HBV1-1

Dr. Man-Fung Yuen

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Clinical utility of novel biomarkers for hepatitis B infection

During the process of viral replication of hepatitis B virus (HBV) from the viral template, the covalently closed circular (ccc) DNA, there are production of viral nucleic acids, namely, HBV DNA and intermediate HBV RNA. Viral translation activities of different genomic regions of HBV also produce several mRNAs which would be transcribed into various viral antigens including HBsAg, HBcAg and HBeAg. Of note, HBsAg can also be generated from integrated HBV DNA. In the past, conventional measurements of serum viral biomarkers in patients with chronic hepatitis B (CHB) mainly include HBsAg, HBeAg and HBV DNA. It has been shown that measuring these conventional biomarkers have clinical significance for the disease monitoring and treatment. For example, serum HBsAg has predictive value for spontaneous and treatment-induced HBsAg seroclearance. However, existing nucleos(t)ide analog (NA) treatment has negligible effects on HBsAg level. Whereas baseline HBsAg levels before initiation of novel treatment predicts antiviral response including HBsAg seroclearance. Recently, a new entity of measuring several viral antigens, collectively named as hepatitis B core-related antigen (HBcrAg) which include HBcAg, HBeAg and p22cr becomes available. It was found that HBcrAg correlated well with cccDNA and other serum and intrahepatic viral markers. HBcrAg profile also relates to the development of CHB complications including hepatocellular carcinoma and cirrhosis, treatment outcome, disease relapse after treatment cessation and chance of HBV reactivation in occult HBV patients receiving immunosuppressive therapy. In addition, a certain proportion of occult HBV patients can be identified by the detectable HBcrAg levels in the blood where both HBsAg and HBV DNA remains undetectable. The detectability rate has been significantly increased by using the second version of the assay. Recently, there is another novel assay development measuring phosphorylated and non-phosphorylated forms of HBcAg in the serum. Clinical usage of this new assay is being actively explored. HBV RNA is another novel HBV biomarker; its roles are overlapping with HBcrAg in some areas. HBV RNA measurement correlates with disease outcome, treatment response and HBV reactivation. HBV RNA seems to be prominently useful in patients who are on NA treatment. In conclusions, development of novel HBV biomarkers is able to provide additional and essential disease assessment and treatment guidance for CHB disease. Standardization and increased availability of these assays are highly encouraged.

HBV1 Challenges for Elimination of CCC HBV DNA

HBV1-2

Dr. Masao Honda

Department of Clinical Laboratory Medicine

Kanazawa University Graduate School of Medical Science

Japan

Identification of host factors that were essentially involved in hepatitis B virus persistence

Background & aims: Hepatitis B virus (HBV) infection is difficult to cure owing to the persistence of covalently closed circular viral DNA (cccDNA). We performed single-cell transcriptome analysis of newly established HBV-positive and HBV-negative hepatocellular carcinoma cell lines and found host factors that were crucially involved in HBV persistence. Methods: The cccDNA levels were measured by Southern blotting and real-time detection polymerase chain reaction in various hepatocytes including PXB cells by using an HBV-infected model. HBV capsid was investigated by super-resolution microscopy, proximity ligation assay, and time-lapse analysis. The binding partners of host factors were examined by liquid chromatography-tandem mass spectrometry, immunoblotting, and enzyme-linked immunosorbent assay. Results: We found that four factors that were crucially involved in HBV persistence. One of the four host factors was dedicator of cytokinesis 11 (DOCK11), known as a guanine nucleotide exchange factor (GEF) for Cdc42. The cccDNA levels were strongly increased by DOCK11 overexpression and repressed by DOCK11 suppression. Interestingly, DOCK11 functionally associated with retrograde trafficking proteins in the trans-Golgi network (TGN), Arf-GAP with GTPase domain, ankyrin repeat, and pleckstrin homology domain-containing protein 2 (AGAP2), and ADP-ribosylation factor 1 (ARF1), together with HBV capsid, to open an alternative retrograde trafficking route for HBV from early endosomes (EEs) to the TGN and then to the endoplasmic reticulum (ER), thereby avoiding lysosomal degradation. Clinically, DOCK11 levels in liver biopsies from patients with chronic hepatitis B were significantly reduced by entecavir treatment, and this reduction correlated with HBV surface antigen levels. Conclusions: HBV uses a retrograde trafficking route via EEs-TGN-ER for infection that is facilitated by DOCK11 and serves to maintain cccDNA. Therefore, DOCK11 is a potential therapeutic target to prevent persistent HBV infection.

HBV1 Challenges for Elimination of CCC HBV DNA

HBV1-3

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Department of Gastroenterology, Graduate School of Biomedical & Health Sciences,

Hiroshima University

Japan

Analysis of HBsAg and cccDNA reduction by nucleotide analogue and pegylated interferon combination therapy

Once HBV enters human hepatocytes, its genome is carried into the nucleus where it forms covalently closed circular DNA (cccDNA), similar to a minichromosome. This translocation of the HBV genome into the nucleus makes it difficult for either the host immune response or present antiviral therapies to eliminate the virus. Combined antiviral treatment using pegylated interferon (PEG-IFN) and nucleotide/nucleoside analogues (NAs) are currently used to suppress cccDNA levels in patients with chronic HBV infection. Although add-on therapy and sequential therapy using PEG-IFN have been attempted in chronic hepatitis B patients following long-term NA therapy, it has not been clarified which PEG-IFN therapy is most effective in reducing HBs antigen (HBsAg) levels. In this study, we investigated the change in HBsAg levels after PEG-IFN therapy (approval number: E-704) and conducted basic research on reduction of cccDNA in liver tissues by NA plus PEG-IFN combination therapy. The subjects included 21 HBeAg-negative chronic hepatitis B patients who had undergone NA therapy for more than one year at our hospital and related facilities. Sequential or add-on therapy using PEG-IFN was performed, and HBsAg levels were measured for up to 5 years after completion of PEG-IFN treatment. Furthermore, we performed add-on therapy on HBV-infected human hepatocyte chimeric mice and examined changes in intrahepatic HBV RNA and cccDNA levels. HBsAg level was reduced by a median of 0.48 LogIU/ml during PEG-IFN therapy. More than 1 Log HBsAg reduction was observed in 9 patients 5 years after the completion of PEG-IFN therapy. Five patients with sequential therapy and 2 patients with add-on therapy achieved HBsAg loss. ALT elevation during PEG-IFN therapy and lower serum IL-8 level at the end of PEG-IFN therapy contributed to HBsAg reduction at 1 year after completion of PEG-IFN therapy (P=0.038, P=0.044). ALT elevation during PEG-IFN therapy, platelet levels at the start of PEG-IFN therapy, and serum IL-8 levels at the end of PEG-IFN therapy were associated with HBsAg reduction at 5 years after PEG-IFN therapy (P=0.034, P=0.049, P=0.041). To confirm high HBsAg reduction by IFN treatment, we measured intrahepatic HBV markers using HBV-infected chimeric mice with add-on therapy. After add-on therapy, intrahepatic HBV RNA and cccDNA levels had decreased to less than 1/50 and 1/2 of that in untreated mice, respectively. Sequential therapy might be more effective in reducing HBsAg levels than add-on therapy, but add-on therapy has the potential to reduce intrahepatic cccDNA levels.

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Summary

HBV2 Novel Detection Methods for HBV Markers

HBV2 Novel Detection Methods for HBV Markers

HBV2-1

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Japan

Rethinking the disease status of chronic hepatitis B: The roles of novel detection methods for HBV markers

Beyond widely available diagnostic tests used in the management of HBV, that includes quantitative (q) HBV DNA and qHBsAg, novel detection methods for HBV markers are scrutinized for their clinical utility in recent years, aiming to rigorous evaluation of functional cure (undetectable HBsAg and HBV DNA) and to appropriate risk stratification for hepatocellular carcinoma (HCC). Among them, ultrasensitive measurement of HBsAg or HBcrAg by iTACT (Immunoassay for Total Antigen including Complex via preTreatment) technology and specific detection of middle (M)-proteins in HBsAg of genotype C by the antibody against O-glycosylated residue (HBsAgGi) are promising candidates.

iTACT system have been applied to HBsAg or HBcrAg detection, the latter of which is a composite of HBcAg, HBeAg, and p22Cr. iTACT improves the detectability ten times more sensitive than the second-generation (standard) HBsAg and conventional HBcrAg assays, that is, the lower limit of quantification (LLOQ) of HBsAg and HBcrAg assays as 0.0005 IU/mL and 2.1 log U/mL, respectively. Consequently, even after HBsAg seroclearance (SC) in chronic hepatitis B (CHB) patients documented by standard assay, HBsAg and HBcrAg became detected in 36.8 % and 68.9% with iTACT, respectively1). Though chronological decline in the detectability of HBsAg and HBcrAg by iTACT after SC were also demonstrated, these results raise a number of important issues; the definition of functional cure should be reconsidered firstly, and more importantly, the clinical significance of low-leveled expression of HBV protein in patients with conventional SC deserves thorough investigation with regard to the persisting HCC risk2) and HBV reactivation.

HBsAgGi measurement system detects HBsAg associated with infectious particles. In a cross-sectional analysis by the recent literature3), low HBsAg (< 3 log IU/ml) and high HBsAgGi (>3 log ng/ml) was associated with HCC development in genotype C chronic HBV patients. Moreover, HBsAgGi decreased significantly by 48-week NA therapy. Still preliminary, discrimination of infectious virions with M-HBsAg from non-infectious subviral particles is likely advantageous for the accurate evaluation of disease status in CHB.

Implementation of novel detection methods for HBV markers into clinics may not only add a new aspect in disease status, but also revolutionize the strategy of monitoring CHB patient by updating the concept of functional cure.

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HBV2 Novel Detection Methods for HBV Markers

HBV2-2

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Japan

Novel biomarkers for the management of chronic hepatitis B

The hepatitis B core-related antigen (HBcrAg) is a novel HBV serum biomarker that plays an essential role in reflecting intrahepatic covalently closed circular DNA (cccDNA) in chronic hepatitis B (CHB). We describe here the clinical application of highly sensitive HBcrAg and HBsAg assays in CHB patients, with a particular focus on current and novel therapies targeting intrahepatic HBV replication. (1) HBcrAg can be detected in clinical cases where serum HBV DNA is undetectable during anti-HBV therapy such as nucleos(t)ide analogues (NAs). (2) The combination of HBcrAg and HBsAg would be useful for the cessation of NA therapy. (3) Decreased HBcrAg levels have been significantly associated with promising outcomes in CHB patients, reducing the risk of progression or recurrence of hepatocellular carcinoma. (4) Recently, a fully automated, novel highly sensitive HBcrAg assay (iTACT-HBcrAg) has been developed (J Hepatol 2021). The sensitivity of iTACT-HBcrAg (2.1 Log U/mL) was approximately 10-fold greater than that of the conventional G-HBcrAg. The iTACT-HBcrAg as well as iTACT-HBsAg (cut-off value: 0.0005 IU/mL) should be of increased benefit for monitoring anti-HBV therapy in HBeAg-negative patients and early detection of HBV reactivation, as an alternative to HBV DNA. (5) Finally, we introduce a novel compound destabilizing HBV-RNA. In brief, drug screening from 30,000 library compounds using HepG2.2.15 cells and HBV-infected PXB cells was performed to optimize the hits that reduced the amount of HBsAg in the culture supernatant, especially those with potent anti-HBV activity, to obtain SAG compounds (SAG-comp; IC50= 1.4 nM). The SAG-comp, a novel anti-HBV therapeutic agent, is an orally available and well-tolerated drug that potently suppresses HBsAg. It can destabilize HBV-RNA and may induce functional cure in combination therapy with NA. In such anti-HBV therapies aiming for functional cure, monitoring HBcrAg and HBsAg would be useful for determining the therapeutic efficacies of novel anti-HBV drugs targeting HBV-RNA and its related-proteins. In conclusion, HBcrAg and HBsAg, especially when measured by the recently developed iTACT assay, may be the most appropriate surrogate marker, over other HBV biomarkers, for the management of CHB patients.

HBV2 Novel Detection Methods for HBV Markers

HBV2-3

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HBV RNA – is it ready for clinical use?

Pregenomic HBV RNA is a new diagnostic biomarker to monitor the disease of chronic hepatitis B. It reflects the transcriptional activity of intrahepatic cccDNA. In untreated patients, the level of HBV RNA correlates well with other HBV viral markers including HBV DNA and HBcrAg. The key clinical usage of HBV RNA is among patients under nucleos(t)ide analog treatment, as HBV DNA is often undetectable in these patients. The presence of HBV RNA indicates residual viral activity, which is associated with an increased risk of hepatocellular carcinoma. The value of HBV RNA to predict virological relapse after stopping nucleos(t)ide analog is controversial, but detectable HBV RNA is found to associate with an increased risk of hepatitis flare. With the development of new therapeutics for chronic hepatitis B, HBV RNA can be a biomarker for target engagement particularly for capsid assembly inhibitors.

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Summary

HBV3 Functional Cure of CH-B in Real World

HBV3 Functional Cure of CH-B in Real World

HBV3-1

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Advancing towards the functional cure of HBV

As a therapeutic goal for the treatment of hepatitis B, the 'clearance of HBs antigen' is currently the goal. However, this achievement is challenging with the nucleoside analogs, which are widely used. Consequently, there is an active pursuit in the development of novel therapeutic agents. At present, the most promising approach is RNAi-based drugs, which can decrease the HBsAg levels. As an alternative approach, we focused on compounds that inhibit the degradation of the host factor Smc5/6 protein, which plays a role in suppressing the transcription of viral RNA from cccDNA. Through a screening of compounds, we identified two compounds that suppress the degradation of Smc5/6 protein complexes and show potential in suppressing the expression of viral RNA and viral proteins. Both compounds are utilized in the treatment of diseases other than HBV, raising expectations for their practical application through so called “drug repositioning”. Simultaneously, this inhibition of Smc5/6 protein degradation suggests a potential link to the suppression of HBV-related oncogenesis. This presentation will provide an overview of these mechanisms and discuss remaining challenges in HBV treatment after achieving a functional cure.

HBV3 Functional Cure of CH-B in Real World

HBV3-3

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Functional cure of CH-B in Real World

Evidence from randomized controlled trials (RCT), e.g. OSST, Endeavor and Anchor study, as well as other relevant clinical studies has shown that sequential combination therapy with immunomodulators (e.g. peg-interferon) and NUC in virally-suppressed patients with chronic hepatitis B (CHB) can improve functional cure (HBsAg loss), as compared to NUC continuous monotherapy. Moreover, several strategies can be used to predict functional cure or identify patients likely to benefit from the sequential treatment with immunomodulators (e.g. peg-interferon), including baseline-guided therapy using pretreatment HBsAg level, response-guided therapy using early decline in HBsAg level, and HBVcrue crab model using end-of-therapy HBsAb level and HBcrAg level. We further have conducted two multicenter real-world studies---COST study and OCEAN study in China, aiming to investigate the efficacy and long-term outcome of sequential peg-interferon treatment in patients undergoing long-term NUC treatment who had HBV DNA undetectable and HBsAg level <3000IU/mL. The interim analysis of COST study demonstrated consistent results of the RCT studies. We are currently conducting a nationwide questionnaire survey on the application of functional cure strategies for patients with CHB.

HBV3 Functional Cure of CH-B in Real World

HBV3-4

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Role of Immunomodulatory Therapy for Functional Cure of CHB

The functional cure of hepatitis B virus (HBV) is defined as the seroclearance of HBsAg (hepatitis B surface antigen) and HBV DNA after a defined period of antiviral therapy. Several barriers hinder the achievement of a cure for HBV, including the presence of reservoirs for HBV replication and antigen production, which stem from the mini-chromosome of covalently closed circular DNA (cccDNA) and integrated HBV DNA within the host's genome. High viral burden (both HBV DNA and HBsAg), as well as impaired host innate and adaptive immunity against HBV, are additional obstacles. Currently, standard HBV treatments, such as one-year pegylated-interferon-α (PEG-IFNα) and long-term nucleos(t)ide analogues (NAs), seldom lead to a functional cure of HBV. Switching from an NA to IFN after achieving HBV DNA suppression increases the chances of HBsAg clearance, primarily in individuals with low HBsAg levels. While novel antiviral drugs targeting various stages of the HBV life cycle have shown promising results, including those that inhibit viral entry, translation, and HBsAg secretion, as well as modulate capsid assembly or target cccDNA transcription and degradation, the quest for an HBV cure extends to innovative immunomodulatory approaches. These approaches encompass immune checkpoint inhibitors (ICI), metabolic modulation of T cells, therapeutic vaccines, adoptive transfer of genetically engineered T cells, and stimulation of innate and B-cell immune responses. These strategies are explored in combination with existing agents to enhance the likelihood of achieving an HBV cure. Ultimately, any curative regimens developed must prioritize safety and affordability to make meaningful progress toward the global goal of eliminating hepatitis B.

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Summary

MAFLD1 Asian MAFLD: Clinical Features

MAFLD1 Asian MAFLD: Clinical Features

MAFLD1-1

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MAFLD in Patients living with HIV; PLWH

Metabolic syndrome and metabolic dysfunction-associated fatty liver disease (MAFLD) are emerging problems and play important role in the higher morbidities and mortality in patients living with HIV (PLWH). The high MAFLD burden among PLWH is one of a major concern issue according to the novel MAFLD criteria and it needs to identify those patients at risk for chronic liver disease. Generally, the prevalence of MAFLD varies from 10-36% depended on the criteria of diagnosis and investigating tools1-5. Most of them are lean MAFLD with younger age in comparison to those MAFLD with diabetes or obesity. Current antiretroviral treatments for example tenofovir alafenamide fumarate (TAF) and particularly its combination with integrase inhibitors (INSTIs) appear to have the significant consequences on metabolic dysfunction by increasing insulin resistance3, 6, 7. In addition, an unhealthy lifestyle, with a high calories dietary intake especially processed foods, high carbohydrates, saturated fatty acids, high fructose added beverages, as well as less physical inactivity, are key triggers for the progression of fatty liver to steatohepatitis, and advanced liver fibrosis. Finally, we review the current recommendation of treatment in this special population at risk of MAFLD8-10.

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MAFLD1 Asian MAFLD: Clinical Features

MAFLD1-2

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How to follow up of patient with act Metabolic dysfunction-associated fatty liver disease (MAFLD)

Metabolic dysfunction–associated fatty liver disease (MAFLD) is the most common cause of chronic liver disease worldwide. MAFLD includes a wide spectrum of liver injury including simple steatosis and non-alcoholic steatohepatitis (NASH) that may lead to serious complications such as liver cirrhosis and liver cancer.

The identification of Nonalcoholic steatohepatitis (NASH) or NAFLD is clinically important because NASH indicates an increased risk for fibrosis progression and the need for aggressive treatment and closer follow-up. Population based study suggests that NAFLD is becoming an important cause of HCC, and these rates are increasing by approximately 10% per year. So we needs follow up guideline of patients with NAFLD but there is no accepted consensus on the optimal strategy for monitoring patients with NAFLD and their response to treatment.

According to The Asian Pacifc Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease, patients with NAFLD may

need a FibroScan yearly or once every three years. The frequency is dependent on your previous FibroScan results. It is important to distinguish mild (F1-F2) from advanced or severe (F3-F4) fibrosis, as patients with severe fibrosis have a greater risk of complications and need to undergo screening for hepatocellular carcinoma with NAFLD.

MAFLD1 Asian MAFLD: Clinical Features

MAFLD1-4

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Metabolic dysfunction-associated fatty liver disease: clinical features and implications

In 2020, the term metabolic dysfunction-associated fatty liver disease (MAFLD) was introduced. This was followed by the term metabolic dysfunction-associated steatotic liver disease (MASLD) in June 2023, which effectively retired the old term non-alcoholic fatty liver disease (NAFLD). While both of the new terms are a clear step forward, there are nuances between them that deserve considerations. The criteria to define metabolic dysfunction for MASLD is present in a large proportion of the general population, even among those without hepatic steatosis. Among those with normal body weight, many would be considered as having metabolic dysfunction based on the criteria, although only a small proportion actually have insulin resistance. These suggest that the criteria to define metabolic dysfunction for MASLD may be too relaxed. Furthermore, patients diagnosed with MAFLD based on presence of type 2 diabetes have been shown to have more severe liver fibrosis and greater risk of cardiovascular, cancer and all-cause mortality compared with patients with MAFLD who are diagnosed based on the other two criteria. This is an important consideration in our strategy to tackle the disease of interest. Last but not least, the introduction of a new entity called MASLD and increased alcohol intake (MetALD) encroaches into the field of alcohol-related liver disease and may embroil the disease of interest with unresolved issues surrounding alcohol-related liver disease. Differences aside, the adoption of either term is a clear recognition that the disease of interest is part of the bigger problem related to excess adiposity, insulin resistance and low-grade meta-inflammation. A paradigm shift is needed, where primary prevention should be the prevention of the onset of metabolic dysfunction instead of the prevention of cardiovascular disease or advanced chronic liver disease. There must be an increasing focus on lifestyle habits for promoting and preserving metabolic health during the entire life course at the individual level and beyond.

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Summary

MAFLD2 The Prognostic Event for MAFLD: CVD or Extrahepatic Cancers?

MAFLD2 The Prognostic Event for MAFLD: CVD or Extrahepatic Cancers?

MAFLD2-1

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Treatment strategies of MASLD with a view to suppression of cardiovascular diseases and liver-related events

AASLD indicated that the most common cause of death in patients with MASLD is related to cardiovascular diseases (CVDs). Liver-related mortality was reported to be the second or third cause of death, and cancer-related mortality was among top three causes of death. In Asia, the incidence rates of these events still remain unclear. We retrospectively investigated the incidence of three complications (CVDs, malignancy except for liver cancer, and liver-related events) in 550 Japanese patients with biopsy-proven MASLD for median follow-up of 6.0 years. The yearly incidence rates of CVDs, malignancies, and liver-related events were found to be 1.04%, 0.83%, and 0.30%, respectively. Especially, in malignancy except for liver cancer, the incidence rates of colon cancer were 25.0%. The impacts of diet and exercise, and diabetes therapeutics with high evidence levels for suppression of CVDs should be evaluated in patients with MASLD. Regarding diet and exercise treatment, the subjects of retrospective cohort study were 203 Japanese patients with SLD diagnosed by abdominal ultrasonography. All of them were introduced the personalized diet and exercise treatment. A diet of 25 to 30 kcal/kg multiplied by ideal body weight daily and aerobic and resistance exercise (exercise intensity of 4 to 5 metabolic equivalents daily, respectively) were performed for 6 days. Treatment efficacy was evaluated in terms of the rate of decrease of liver function tests, glycolipid metabolism markers, physical findings, image findings, and CVD risk score (Suita score) at 6 months compared to baseline, and these parameters improved significantly. Regarding diabetes therapeutics, histological impacts at 5 years after the start of SGLT2 inhibitors were investigated retrospectively in 6 Japanese patients with MASLD and T2DM, and liver biopsies were obtained at the points of pretreatment, 3 years, and 5 years after the start of treatment. The primary outcome was liver histopathological changes at 5 years (defined as decrease in MASLD activity score of one point or more without worsening in fibrosis stage, compared to the pretreatment). 2 patients were performed the additional treatment of GLP-1 receptor agonist after the point of 3 years, and evaluated as histological worsening. Histological improvement, no change, and worsening were 50, 17, and 33% at 5 years, respectively. None developed CVDs events. In conclusion, the most common event in Japanese patients with MASLD was CVDs. Personalized medicine with diet and exercise, and diabetes therapeutics are expected to improve the pathology of MASLD, including the suppression of CVDs and liver-related events.

MAFLD2 The Prognostic Event for MAFLD: CVD or Extrahepatic Cancers?

MAFLD2-2

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Prognostic event for MAFLD: CVD or Extrahepatic cancers

The diagnosis of Metabolic Associated Fatty Liver Disease (MAFLD) is based on the presence of hepatic steatosis associated with metabolic conditions such as type 2 diabetes mellitus (T2DM), obesity or metabolic dysregulation. The underlying metabolic disequilibrium, potentially manifesting as diabetes mellitus, hypertension, and hyperlipidaemia, is the same process that drives vascular atherosclerosis and increases the risk of carcinogenesis in multiple organs of the body.

Hence it is no surprise that major adverse cardiovascular events (MACE) and extraintestinal cancers are the 2 commonest complications and causes of mortality in patients with MAFLD, constituting higher risks compared to liver complications such as cirrhosis and liver cancer.

We will review the risks for non-hepatic metabolic complications in patients at different stages of MAFLD and also the evidence for non-invasive tests (NIT) that can predict these life-threatening complications. Active management such as surveillance and aggressive management will be discussed.

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The Prognostic Event for MAFLD: CVD or Extrahepatic Cancers?

The metabolic dysfunction associated fatty liver disease (MAFLD) is a systemic disease that affects various extrahepatic organs. The prevalence varies from 30-40% and increases to 70% in patients who also have diabetes. Recent evidence has suggested an increase in the risk of chronic kidney disease as almost two-fold which is independent of the other cardiorenal risk factors. Apart from these, MAFLD is also associated with extrahepatic chronic complications. A very close association of MAFLD with diabetes, insulin resistance and obesity also confer a higher risk of hepatocellular carcinoma (HCC) including other extrahepatic malignancies. Mechanisms such as insulin resistance, metabolic stress causing disruption of the regulatory pathways for instance, nuclear factor-kappa B (NF-jB), phosphatase and tensin homolog (PTEN), and microRNAs have been observed to be associated with the development of HCC. The role of lipopolysaccharide-mediated signalling of the toll-like receptor 4 (TLR-4) which further perpetuates the hepatic inflammation and gut dysbiosis causing disrupted metabolism of bile acids has also been causally linked to the development malignancies in patients with MAFLD. The microbiota cause conversion of primary to secondary bile acids such as deoxycholic acid. These secondary bile acids are hepato-toxic and cause worsening of inflammo-fibrosis in MAFLD patients. Dietary intake of high fat and fructose intakes along with genetic factors (e.g., PNPLA3 polymorphisms) have shown to cause progression of the disease increasing the hepatic lipid accumulation. This perpetuates hepatic fibrosis. Accumulation of fat at ectopic locations and adipose tissue dysfunction have also been implicated in the development of MAFLD. Secretion of various hepatokines such as retinol-binding protein-4, fetuin-A, fibroblast-growth factor 21 and inflammatory cytokines, tumor-necrosis-factor alpha, C-reactive protein and interleukin-6 cause hepatic gluconeogenesis, glycogen synthesis and insulin resistance which together drives complications in these patients.

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Summary

MAFLD3 Asian MAFLD: Basic Understanding (Molecular Pathogenesis)

MAFLD3 Asian MAFLD: Basic Understanding (Molecular Pathogenesis)

MAFLD3-1

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Japan

Metabolic Dysfunction-Associated Liver Cancer

Metabolic dysfunction caused by abnormalities in hepatic lipid metabolism is associated with an increased risk of developing liver cancer. The molecular mechanisms underlying the progression of MASLD/NAFLD-associated liver cancer (MALC) are not fully understood. Animal models are extensively used for examining the molecular events under the conditions that mimic human disease. Several mouse models for liver cancer associated with metabolic disease have been established by using specific diets, chemotoxic agents, genetic engineering, or combinations thereof. Mice fed methionine- and choline-deficient diets are conventional models of nonalcoholic steatohepatitis, but they undergo weight loss. Although high-fat diets (HFDs) promote hepatic lipid accumulation, long-term exposure is required for tumor development. Streptozotocin, a compound selectively eliminating β cells in the pancreas and resulting in type 1 diabetes, in combination with HFDs induces steatohepatitis and liver cancer without overweight or insulin resistance. Pten conditional knockout (KO) mice on HFDs also recapitulate MALC but not metabolic syndrome. Several congenital mutations are implicated in regulation of food intake and body weight in the hypothalamic nuclei, and these genetic mutations are the most common known monogenic causes of obesity in human. As reported in the previous studies, this regulator-KO mice exhibit obesity, insulin resistance, and dyslipidemia, and they develop steatohepatitis, liver fibrosis, and then well-differentiated liver cancer, suggesting this mouse model may be the best fit for reproducing the features of MALC. Cross-species comparison of gene expression signatures provides a powerful approach to evaluating the biological similarity between human patients and mouse models and to elucidating the molecular system in the common phenotype. Although there have been several comparative studies on human and mouse metabolic liver disease, the cross-species subtyping of liver cancer is focused in our studies. Here, we performed integrative transcriptome analysis of liver cancer resected from human patients and metabolic dysfunction-associated mice, and identified a subtype of liver cancer closely associated with metabolic syndrome, which was characterized by overexpression of several specific genes associated with metabolic dysfunction. We investigated the clinical significance of these metabolic molecules as a specific biomarker for this subtype and the correlation between the expression and metabolic dysfunction in our laboratory. Targeting these pathways may be a useful therapeutic strategy for the subtype-specific liver cancer.

MAFLD3 Asian MAFLD: Basic Understanding (Molecular Pathogenesis)
MAFLD3-2

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Roles of SGLT2 Inhibitor in MAFLD-related HCC

MAFLD is becoming a leading cause of hepatocellular carcinoma (HCC) in the Asian-Pacific region. In the Japanese clinical practice guidelines for NAFLD/NASH, sodium-glucose co-transporter 2 inhibitor (SGLT2i) is recommended for patients with NAFLD and diabetes mellitus. However, the effects of SGLT2i on HCC remain unclear.

First, we examined the expression of SGLT2 in human HCC cell lines and found that SGLT2 occurred and localized on mitochondria in Hep3B and Huh7 cells. Furthermore, SGLT2i significantly suppressed the proliferation of these HCC cell lines. To investigate the pathogenesis, we employed multi-omics analysis of metabolomics and absolute quantification proteomics (iMPAQT). This multi-omics analysis revealed that SGLT2i mainly altered the following metabolisms; 1) oxidative phosphorylation metabolism, 2) fatty acid metabolism, and 3) purine and pyrimidine metabolism. Moreover, SGLT2i altered the phosphorylation of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC), which are sensors of intracellular ATP levels and regulators for beta-oxidation in mitochondria. Thus, We found that SGLT2i may suppress the proliferation of HCC cell lines via the regulation of electron transport systems, beta-oxidation, and nucleic acid synthesis.

HCC is known to release various chemokines/cytokines to modulate the tumor microenvironment and regulate the proliferation and invasion of HCC cells. Next, we investigated the direct effects of SGLT2i on tumor-releasing chemokines/cytokines in human HCC cell lines. Hep3B and Huh7 cells were treated with SGLT2i or a control vehicle for 24 h. Then, the culture media were collected and subjected to 48 chemokine/cytokine assays using the human cytokine screening 48-plex panel (Bio-Plex Pro, Bio-Rad Laboratories, Inc., Hercules, CA). We first demonstrated that SGLT2i directly downregulated the three tumor-releasing chemokines such as C-X-C motif chemokine ligand (CXCL) 1, CXCL8, and CXCL10 in Hep3B and Huh7 cells. Based on the previous studies, these changes in chemokines may exert antitumor effects through alterations in tumor characters and tumor immunity. We also found that SGLT2i downregulated tumor-releasing macrophage colony-stimulating factor (M-CSF) in Hep3B and Huh7 cells. This downregulation of M-CSF may exert antitumor effects through the polarization of M1 macrophages.

In conclusion, SGLT2i directly suppressed the proliferation of HCC cells through alterations in mitochondrial oxidative phosphorylation metabolism, fatty acid metabolism, and purine and pyrimidine metabolism. SGLT2i also indirectly suppresses HCC by modulating the tumor microenvironment. I will introduce both direct and indirect molecular mechanisms for the effectiveness of SGLT2i on the suppression of HCC.

MAFLD3 Asian MAFLD: Basic Understanding (Molecular Pathogenesis)
MAFLD3-3

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The role of intestinal TM6SF2 in MAFLD

Metabolic dysfunction-associated steatohepatitis (MASH) is associated with the loss-of-function variant of Transmembrane 6 superfamily member 2 (TM6SF2). While TM6SF2 is primarily expressed in the liver and small intestine, the role of intestinal TM6SF2 dysfunction in MASH development remains unclear. In this study, we utilized systemic, liver-specific, and intestine-specific Tm6sf2 knockout mouse models to investigate the impact of TM6SF2 deficiency on MASH progression. We subjected the knockout mice and wildtype littermates to high-fat high-cholesterol (HFHC) or choline-deficient high-fat diet (CD-HFD) for 2 months to induce MASH. Additionally, fecal microbiota transplantation was performed in germ-free mice, and the therapeutic potential of microbiota modulation was examined by co-housing intestine-specific Tm6sf2 knockout mice with wildtype controls. We characterized the gut microbiota using shot-gun metagenomic sequencing and performed untargeted/targeted metabolomics using liquid chromatography-mass spectrometry.

Our results showed that systemic Tm6sf2 knockout mice exhibited more severe steatohepatitis compared to liver-specific Tm6sf2 knockout mice, indicating the involvement of extra-hepatic TM6SF2 deficiency in MASH formation. Interestingly, intestine-specific Tm6sf2 knockout mice developed spontaneous MASH when fed a normal chow diet, which was further exacerbated by HFHC or CD-HFD supplementation. This MASH development in Tm6sf2ΔIEC mice was accompanied by impaired gut barrier integrity and dysbiosis of the gut microbiome. We observed an enrichment of the metabolite lysophosphatidic acid (LPA) in the stool, portal vein, and liver tissues of Tm6sf2ΔIEC mice, which in turn promoted hepatic lipid accumulation and pro-inflammatory cytokine secretion. Moreover, intestinal cells of Tm6sf2ΔIEC mice secreted higher levels of arachidic acid, which induced intestinal barrier dysfunction, enrichment of pathogenic bacteria, and LPA secretion. Importantly, transplantation of stools from Tm6sf2ΔIEC mice into germ-free mice induced steatohepatitis, while co-housing Tm6sf2ΔIEC mice with wildtype controls ameliorated MASH development, resulting in reduced lipid accumulation and inflammation.
In conclusion, our findings demonstrate that intestinal TM6SF2 deficiency leads to gut dysbiosis and barrier dysfunction, thereby facilitating the translocation of LPA into the liver and promoting MASH. Manipulation of the gut microbiota represents a potential therapeutic strategy for preventing TM6SF2 deficiency-induced MASH.

MAFLD3 Asian MAFLD: Basic Understanding (Molecular Pathogenesis)

MAFLD3-4

Dr. Jian-Gao Fan

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Therapeutic management of MAFLD/MASLD

The global incidence and prevalence of non-alcoholic fatty liver disease (NAFLD) and its severe form non-alcoholic steatohepatitis (NASH) have been steadily increasing over the past 2 decades, with a huge disease and economic burden. Recently, NAFLD and NASH have been renamed and redefined as metabolic dysfunction associated fatty liver disease (MAFLD)/metabolic dysfunction associated steatotic liver disease (MASLD) and metabolic dysfunction associated steatohepatitis (MASH)), which result from an imbalance between metabolic and inflammatory stress (mainly as a consequence of adipose tissue dysfunction and insulin resistance) and the defence and repair mechanisms of the steatotic liver. Once MAFLD/MASLD progresses to end-stage of liver disease, treatment efficacy becomes limited and may require liver transplantation. Early detection and intervention are crucial. Lifestyle modification is consequently the cornerstone of its management. Timely consideration of bariatric surgeries should be given to patients meeting specific criteria. A multidisciplinary approach is warranted, starting from the concept that steatotic liver and steatohepatitis are at the centre of the cardiovascular-liver-metabolic syndrome. In some cases, pharmacological treatment can complement lifestyle modification. Several drugs used to treat the cardiometabolic co-morbidities have some potential efficacy in resolution of MASH and slowing down progression of liver fibrosis, and some drugs have demonstrated efficacy on histological endpoints that are likely to translate into long-term clinical benefits. Optimising the use of these drugs within their licenced indications for type 2 diabetes and obesity is thus paramount for patients with MAFLD/MASLD. Several MASH-specific drugs are on the horizon and are likely to enrich our therapeutic armamentarium in the near future, particularly in non-cirrhotic MAFLD/MASLD. Much work still needs to be done to understand the specific features of MAFLD/MASLD-related cirrhosis and develop efficacious treatments for this disease stage. Future research should focus on optimising lifestyle intervention strategies, improving adherence and success rates, exploring the role of new weight-loss medications, and identifying effective weight loss surgical methods for MASH patients with obesity. Combination therapies targeting multiple pathways and the integration of digital health interventions hold potential for enhancing the efficacy and safety of MAFLD/MASLD treatments.

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Summary

MAFLD4 Clinical Management of MAFLD (Lifestyle Change Nutrition and Need of Medications)

MAFLD4 Clinical Management of MAFLD (Lifestyle Change Nutrition and Need of Medications)

MAFLD4-1

Dr. Diana Alcantara-Payawal

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Hepatology Committee, Cardinal Santos Medical Center

Philippines

Integrative Approach to MAFLD: Comprehensive Strategies for Care and Management

Integrating care for MAFLD involves a systematic approach encompassing various steps to ensure comprehensive management and optimal outcomes. MAFLD emphasizes a holistic approach, incorporating lifestyle modifications, pharmacological interventions, and the management of comorbidities. With a focus on holistic, comprehensive care and secondary prevention, primary care physicians should be able to identify patients and implement screening protocols to identify individuals at risk of NAFLD, including those with obesity, type 2 diabetes, dyslipidemia, and metabolic syndrome. These involve using clinical assessment tools, such as liver function tests, imaging studies (e.g., ultrasound), and non-invasive fibrosis markers, to diagnose and stage MAFLD.

MAFLD care in the community must be part of a comprehensive evaluation of patients with NAFLD, involving a multidisciplinary team of healthcare professionals, including hepatologists, endocrinologists, dietitians, and exercise physiologists. A comprehensive metabolic multimorbidity management approach is critical in the intervention framework, recognizing the crucial role of the primary care nursing team and allied professionals with expertise in preventive hepatology and providing long-term nutrition and lifestyle interventions. One should consider pharmacotherapy for patients with NAFLD who fail to achieve adequate improvement with lifestyle modifications alone. These involve evaluating medications such as vitamin E, pioglitazone, and specific antidiabetic agents (e.g., GLP-1 receptor agonists) for their potential benefits in improving liver histology and metabolic parameters.

Finally, the multidisciplinary team addresses concurrent medical conditions, such as obesity, type 2 diabetes, hypertension, and dyslipidemia. It optimizes the management of comorbidities through lifestyle interventions, pharmacotherapy, and regular monitoring to minimize their impact on liver health and disease progression. Emerging evidence indicates that GLP-1 receptor agonists can improve steatohepatitis, but it will remain to be determined. Whether through lifestyle, pharmaceuticals, surgery, or a combination, weight management strategies should involve multidisciplinary input and be tailored to each patient.

At the end of the spectrum of care, one should establish a structured follow-up schedule to monitor disease progression, treatment response, and adherence to therapeutic interventions. The multiciliary team should perform regular assessments of liver function tests, imaging studies, and metabolic parameters to track changes in liver health and identify complications early.

By systematically integrating these steps into clinical practice, healthcare providers can deliver comprehensive care to patients with MAFLD, addressing the multifaceted nature of the disease and promoting better overall health and quality of life.

MAFLD4 Clinical Management of MAFLD (Lifestyle Change Nutrition and Need of Medications)
MAFLD4-2

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Taiwan

Clinical Management of MAFLD

Metabolic Associated Fatty Liver Disease (MAFLD), has emerged as a global health threat with a rising prevalence worldwide. The pivotal role of lifestyle modifications, nutrition, and the potential need for medications in addressing this multifaceted condition are critical for the unmet clinical issues.

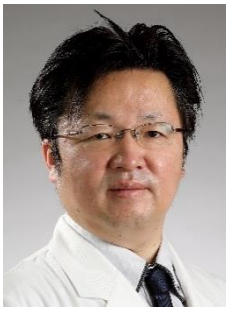
The cornerstone of MAFLD management is lifestyle interventions, including dietary modifications and increased physical activity, play a crucial role in mitigating the risk factors associated with MAFLD. Implementing a balanced and calorie-controlled diet, coupled with regular exercise, could contribute significantly to weight management, improvement in insulin sensitivity, and reduction of hepatic fat accumulation as well as liver inflammation.

Nutrition emerges as a key determinant in the clinical management of MAFLD. Specific dietary patterns, such as the Mediterranean or low-glycemic index diets, have shown promise in ameliorating hepatic steatosis and inflammation. Nutritional strategies include reducing intake of added sugars, saturated fats, and refined carbohydrates, while promoting the consumption of fiber-rich foods and omega-3 fatty acids.

While lifestyle modifications and nutritional interventions form the foundation of MAFLD management, there arises a need to explore pharmacological options. Medications targeting various aspects of MAFLD pathogenesis, including insulin resistance, inflammation, and liver fibrosis, are currently under investigation. The recent dramatic agents on weight reduction and thyroid hormone receptor-beta agonist have been remarkable potential agents for MAFLD

In conclusion, the clinical management of MAFLD necessitates a multifaceted approach, encompassing lifestyle modifications, dietary interventions, and, in certain cases, pharmacological interventions. The current evidences underscores the importance of personalized strategies tailored to the unique needs of individuals with MAFLD. As research continues to unravel the complexities of MAFLD.

MAFLD4 Clinical Management of MAFLD (Lifestyle Change Nutrition and Need of Medications)
MAFLD4-3



Dr. Masahito Shimizu
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Japan

NAFLD/NASH and sarcopenia - usefulness of nutritional and exercise therapy -

Sarcopenia is associated with poor prognosis and impaired quality of life in patients with chronic liver disease. Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) and its underlying obesity and diabetes are closely related to the development and progression of sarcopenia. Sarcopenia is also a risk factor for NAFLD/NASH and liver fibrosis. Thus, NAFLD/NASH and sarcopenia adversely affect each other and impair hepatic and skeletal muscle function. Particularly, increased ammonia and decreased branched-chain amino acids are closely associated with these pathologies. In the treatment of NAFLD/NASH complicated by sarcopenia, nutritional and exercise therapy that simultaneously improves liver and skeletal muscle function, i.e., “liver rehabilitation”, is important. Weight reduction with diet and exercise therapy improves liver function and liver histology in NAFLD/NASH. For NAFLD/NASH patients with obesity, a low-calorie diet that limits carbohydrates and fats should be taught to optimize energy intake. On the other hand, weight loss due to inappropriate nutritional therapy, such as excessive protein restriction, may contribute to increased skeletal muscle catabolism and sarcopenia. Combined diet and exercise can further improve hepatic function and liver steatosis, but these conditions in patients with NAFLD may be improved even when only exercise therapy is intervened without nutritional therapy. With regard to exercise intensity, moderate and higher levels are more useful, and when comparing aerobic and resistance exercise, resistance exercise similarly improves hepatic steatosis in NAFLD patients, even though energy expenditure is lower than that of aerobic exercise. Resistance exercise is also useful in the prevention of sarcopenia because it effectively improves muscle strength and muscle mass. BCAA supplementation improves the prognosis of cirrhotic patients with sarcopenia. In these patients, the combination of BCAA preparations and exercise therapy is also useful in the treatment of sarcopenia. On the other hand, abnormal BCAA metabolism and over-intake are associated with type 2 diabetes, insulin resistance, and obesity, and are thought to promote hepatic fat accumulation and the development and progression of NAFLD/NASH. In cirrhosis resulting from NASH, the progression of fibrosis and the dynamics of amino acids, including BCAA, should be evaluated and BCAA replacement therapy should be considered. In conclusion, it is critical to develop safe and appropriate liver rehabilitation to improve the prognosis and quality of life of NAFLD/NASH patients with sarcopenia.

MAFLD4 Clinical Management of MAFLD (Lifestyle Change Nutrition and Need of Medications)
MAFLD4-4

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Japan

Clinical Management of MASLD - Medications –

Pharmacological treatment for MASH is actively being developed, but so far no new drug has been approved for this disease. Resmetirom, which is currentlycompleteted in phase 3, is awaiting approval and is expected, but the pipeline under development is also showing promising results. At present, pharmacological treatment is selected according to MASH complications. In cases of diabetes mellitus, GLP-1 and SGLT2 inhibitors are used. In patients with high TG, the selective PPAR agonist Pemafibrate is promising, and we would like to present evidence for this. As a therapeutic MOA, it is also promising to improve the intestinal barrier function, and we would like to present our exploratory results.

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Summary

MAFLD5 Diagnosis of MAFLD

MAFLD5 Diagnosis of MAFLD

MAFLD5-1

Dr. Michiie Sakamoto

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Japan

Pathological Diagnosis of NASH, Fibrosis ad HCC

Pathological diagnosis and interpretation of NASH is made based on the histopathological features of steatohepatitis, i.e. 'steatosis', 'lobular inflammation', hepatocyte 'ballooning, 'Mallory-Denk bodies' and 'fibrosis'. However, there are many borderline cases that are difficult to evaluate. Pathologically, degeneration refers to a continuous and reversible change of morphology commonly seen in injured cells, mild, and moderate to severe pathological changes can be observed contemporaneously. This characteristic may also cause inconsistency in recognizing and evaluating the presence of ballooning degeneration and Mallory-Denk bodies. The Japan Society of Hepatology published a clinical guidebook illustrating the typical histology of definitive hepatocyte ballooning and Mallory-Denk bodies. This guidebook may help to improve and unify the histological interpretations in diagnosing NASH. Despite these efforts, however, limitations of inter-observer variability will most likely remain. Therefore, quantitative assessment of these reversible and continuous degenerative changes is required.

It is widely recognized that accurate staging of liver fibrosis is crucial to guide therapeutic decisions and to predict prognosis for patients with NASH. Digital image analysis (computational pathology) has emerged as a promising tool for quantitative assessment of fibrosis in chronic liver diseases. We measured area ratios of collagen and elastin fibers in Elastica van Gieson-stained biopsy tissues. The combined fiber area ratios correlated strongly with Brunt's stage, but this relationship was nonlinear with striking differences between stage 4 and stages 0–3. The highest tertile of the combined fiber area ratios was associated with fibrosis-4 index and serum type IV collagen 7s domain.

Steatosis, is also a characteristic morphology of HCC. We previously reported that scirrhous HCC with steatosis has different clinicopathological significance than scirrhous HCC without steatosis. Furthermore, steatohepatitic HCC, which is characterized by a steatohepatitic morphology, has been reported as a subtype of HCC. We elucidated the features of macrovesicular steatosis (MaS) and microvesicular steatosis (MiS) in HCC. HCCs were classified as MaS-HCC, MiS-HCC, or conventional HCC (cHCC) according to the cutoff value of 30% MaS or MiS in tumor cells. MaS-HCC had less portal vein invasion, a higher proportion of HCC with intratumoral fibrosis, and a lower risk of recurrence than MiS-HCC or cHCC. Both MaS-HCC and MiS-HCC had lower incidences of hepatitis virus infection and higher levels of HbA1c than cHCC. These indicated that MaS-HCC and MiS-HCC were associated with metabolic dysfunction but exhibited different biologic behaviors.

In my lecture, these features of NASH/HCC will be discussed from pathological point of view.

MAFLD5 Diagnosis of MAFLD

MAFLD5-2

Dr. Ian Homer Y. Cua
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Philippines

Identifying At-Risk Patients with MAFLD in Primary Care Settings

Detecting at-risk patients for Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) within the primary care setting is paramount for early intervention and prevention. As MAFLD, continues to rise in prevalence, a comprehensive approach is essential to identify individuals susceptible to this condition.

Understanding the nexus between MAFLD and metabolic dysfunction is pivotal. Patients grappling with obesity, type 2 diabetes, dyslipidemia, and insulin resistance stand at an elevated risk. Primary care practitioners should prioritize screening these high-risk populations, monitoring metabolic parameters to glean insights into potential MAFLD risks.

Delving into clinical history offers critical information in identifying at-risk patients. Thoroughly exploring a patient's lifestyle, dietary habits, and physical activity reveals vital clues. Routine inquiries about these aspects enable healthcare providers to tailor interventions based on specific risk factors during regular check-ups.

Non-invasive diagnostic tools play a pivotal role in primary care. Leveraging simple fibrosis scores, blood biomarkers, and imaging studies, such as ultrasound and VCTE, facilitates the assessment of liver health without resorting to invasive measures. Integrating these tools into routine health assessments empowers practitioners to identify potential MAFLD cases early, allowing for timely intervention and lifestyle modifications.

Interdisciplinary collaboration is fundamental in managing at-risk patients for MAFLD involving nutritionists, primary care physicians, internists, endocrinologists, gastroenterologist and hepatologists allows for comprehensive care. This collaborative effort enhances the management of metabolic dysfunction, contributing to superior patient outcomes.

Education emerges as a critical component for both healthcare providers and patients in MAFLD identification and prevention. Raising awareness about risk factors, symptoms, and preventive measures empowers individuals to make informed lifestyle choices. Continuous medical education for primary care practitioners ensures they stay abreast of the latest research and guidelines related to MAFLD identification and management.

In conclusion, the identification of at-risk patients for MAFLD in the primary care setting necessitates a holistic approach. Factors such as metabolic parameters, clinical history, diagnostic tools, collaborative efforts with specialists, and patient education collectively contribute to a proactive screening strategy. Early detection and intervention by primary care practitioners are integral to mitigating the impact of MAFLD on individual health, underscoring their pivotal role in fostering overall patient well-being.

MAFLD5 Diagnosis of MAFLD

MAFLD5-3

Dr. Mohammed Eslam
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Australia

Lean MAFLD

Excessive calorie consumption relative to expenditure, intake of unhealthy diets, and lack of physical activity are globally fuelling an increase in the prevalence of poor metabolic health, even in individuals of normal weight. Consequently, this trend entails increased risk of various metabolic disorders, including metabolic associated fatty liver disease (MAFLD), which affects up to a third of the global population.

MAFLD burden has grown in parallel with rising rates of type 2 diabetes and obesity and increases the risk of end-stage liver disease, hepatocellular carcinoma, death, and liver transplantation, and has extrahepatic consequences including cardiometabolic disease and cancers. Although classically is associated with obesity, there is accumulating evidence that not all overweight or obese develop fatty liver disease. On the other hand, a considerable proportion of patients with MAFLD are lean, indicating the importance of metabolic health in disease pathogenesis regardless of body mass index. A complex and dynamic interaction between a multitude of factors, including genetic, epigenetic, dietary, and lifestyle factors, enterohepatic circulation, and gut microbiota is likely to shape individual metabolic health status.

The clinical profile, natural history and pathophysiology of lean patients with MAFLD is not well characterised. In this talk, I am going to provide the recent epidemiological data on this group of patients. The talk will illustrate the novel concept considering the overall metabolic health and metabolic adaptation as a framework to best explain the pathogenesis of MAFLD and its heterogeneity, both in lean and non-lean individuals. This framework provides a conceptual schema for interrogating the MAFLD phenotype in lean individuals that can translate to novel approaches for diagnosis and patient care. I will also touch briefly on the current management of lean patients with MAFLD.

MAFLD5 Diagnosis of MAFLD

MAFLD5-5

Dr. Takuma Nakatsuka

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Japan

Risk Stratification and Prediction of Hepatocellular Carcinoma in MAFLD

Background: Metabolic dysfunction-associated fatty liver disease (MAFLD), which is strongly associated with systemic metabolic abnormalities, such as insulin resistance and glucose intolerance in the context of obesity, has become a leading cause of hepatocellular carcinoma (HCC) worldwide. Establishing an efficient surveillance strategy is urgently needed given the drastically increasing prevalence of MAFLD. However, optimal surveillance strategy remains unclear owing to the lack of evidence regarding risk stratification. Here we will show the utility of noninvasive tests for HCC risk stratification in patients with MAFLD.

Methods: Patients with MAFLD who underwent liver biopsy at our hospital were included. Liver stiffness measurement (LSM) using FibroScan was performed at the time of biopsy. FIB-4 index and Agile 3+ score (incorporating LSM, platelets, AST/ALT ratio, diabetes status, sex, age) were calculated. The performance of FIB-4 index, LSM, and Agile 3+ for diagnosing advanced fibrosis (AF: ≥F3) and predicting HCC was evaluated.

Results: Our cohort consisted of 300 patients with a median age of 55.0 years, median BMI of 27.8 kg/m2, median FIB-4 of 1.45, and median LSM of 8.7 kPa; 62.3% were male and 30.3% had diabetes mellitus. AF diagnostic performance (AUROC) was 0.82, 0.84, and 0.90 for FIB-4, LSM, and Agile 3+, respectively, with the Agile3+ being the best (DeLong test, P=0.001). During a mean observation period of 38.0 months after liver biopsy, 7 patients developed HCC. Compared to non-HCC cases, HCC-developed cases had significantly higher age at biopsy (54 vs 63 years, P=0.03), diabetes complication rate (29% vs 71%), FIB-4 (1.44 vs 2.49, P=0.03) LSM (8.7 vs 20.0 kPa, P<0.01), and Agile 3+ (0.79 vs 0.98, P=0.01). The c-index for predictive ability of HCC were 0.78, 0.80, and 0.85, for FIB-4, LSM, and Agile 3+, respectively. LSM ≥10 kPa, recommended cut off value of cACLD suspicion, could identify patients at high risk with an annual HCC incidence of 1.6%/PY, compared to 0.2%/PY in those with LSM <10 kPa (log-rank test, P=0.02). Furthermore, Agile 3+ >0.68, recommended cutoff value for AF rule-in, could identify patients with at high risk with an annual HCC incidence of 1.2%/PY, compared to 0.0%/PY in those with Agile3+ ≤0.68 (log-rank test, P=0.045).

Conclusion: LSM and Agile 3+ allow efficient risk stratification of HCC in patients with MAFLD. Their utilization would optimize personalized HCC surveillance strategy in MAFLD. Further studies are warranted to validate the utility of these tests in diverse MAFLD populations.

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Summary

HCV1 DAA Treatment for CH-C in Asia Pacific Region

HCV1. DAA Treatment for CH-C in Asia Pacific Region

HCV1-1

Dr. Tetsuya Hosaka

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Japan

Remaining issues in post-SVR era

Current direct-acting antiviral agents (DAAs) regimens can achieve sustained viral response (SVR) of over 97% in patients with chronic hepatitis C infection (CHC). Therefore, we are less likely to struggle with antiviral treatment for CHC. Several reports showed the eradication of HCV infection by DAAs therapy reduce the risk of HCC development. However, there are some patients who develop hepatocellular carcinoma (HCC) after SVR. Older age and advanced fibrosis are known risk factors of HCC after SVR. It is important to evaluate other risk factors of HCC. Then, we are going to focus on some metabolic factors and their association with HCC incidences after SVR among patients treated with DAAs or interferon (IFN)-based regimens in this lecture.

HCV1. DAA Treatment for CH-C in Asia Pacific Region

HCV1-2

Dr. Saeed Hamid

Department of Medicine Aga Khan University

Pakistan

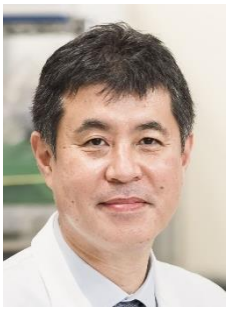
Achievements and prospects for eliminating viral hepatitis in Pakistan.

Pakistan is now home to the World's largest population of people living with Hepatitis C infection. As a result of high prevalence of Hepatitis C, Pakistan now also faces a liver cancer epidemic. Blood and Injection Safety have been the major drivers of infection.

Pakistan has made reasonable progress toward HCV elimination by so far diagnosing 30% of patients and treating 16%. availability of generic DAAs has been a major enabling factor in Pakistan. Based on this, a major program of screening, diagnosis and treatment has been developed and should be implemented soon.

HCV1. DAA Treatment for CH-C in Asia Pacific Region

HCV1-4



Dr. Taro Yamashita

Department of Gastroenterology Kanazawa University School of Medicine

Japan

Management of hepatitis C virus infection in Japan

Globally, about 58 million people are estimated to have chronic Hepatitis C virus (HCV) infection, and most affected areas are considered Eastern Mediterranean, Europe, Western Pacific, Africa, regions of Americas, and Southeast Asia. HCV infection has been the most common etiology of liver cirrhosis and hepatocellular carcinoma in Japan. Major genotype of HCV has been genotype1b, which is resistant to interferon-based therapies, following 2a and 2b in Japan. Accordingly, sustained virological response (SVR) rates were less than 50% before direct-acting antivirals (DAAs) developed and became available in 2014 in Japan. Currently, pan genotype DAAs glecaprevir/pibrentasvir and sofosbuvir/velpatasvir regimens are recommended for the treatment of HCV by the Japan Society of Hepatology, with attention to the status of renal function, presence of decompensated cirrhosis, and viral mutations including p32 deletion. SVR rates of these DAA regimens exceed 95%, and now almost all HCV infection can be successfully eradicated. However, because HCV infection is generally asymptomatic until the development of liver cirrhosis and hepatocellular carcinoma, most of patients are unaware of their HCV infection without screening tests. Furthermore, although most of HCV infected patients could relatively easily reach HCV testing and receive DAAs in urban areas, numbers of HCV infected patients are still considered undiagnosed and therefore remained untreated especially in rural areas in Japan. We are currently making an effort to provide the opportunity to receive the diagnosis and treatment of HCV infection in these people by utilizing information and communication technology.

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Summary

HCV2 Treatment with Direct Acting Antivirals (DAAs) for Cirrhotic Patients with or Without HCC

HCV2. Treatment with Direct Acting Antivirals (DAAs) for Cirrhotic Patients with or Without HCC

HCV2-1

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Kaohsiung Medical University

Taiwan

Treatment with Direct Acting Antivirals for Cirrhotic Patients with or without Hepatocellular Carcinoma

Hepatitis C virus (HCV) infection is a major health problem throughout the world. Patients with chronic hepatitis C (CHC) will lead to liver cirrhosis within 20 to 30 years. After the development of liver cirrhosis, the annual rates of hepatocellular carcinoma (HCC) occurrence are around 1 to 7%. The goal of antiviral treatment for HCV related cirrhosis is to suppress progression to liver failure and development of HCC and to prolong prognosis by reduction of liver inflammation and fibrosis, followed by HCV eradication. Simplified, treatment of chronic hepatitis C with pangenotypic drug regimens should be used in patients with compensated (Child-Pugh A) cirrhosis. However, protease inhibitor-containing regimens are contraindicated in patients with decompensated (Child-Pugh B or C) cirrhosis and patients with compensated cirrhosis with previous episodes of decompensation. Patients with decompensated cirrhosis not on the waiting list for liver transplantation and without severe concomitant comorbidities should be treated urgently. Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score <18–20 should be treated prior to liver transplantation. Nonetheless, patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score > 18–20 should be transplanted first. If waiting time is greater than 6 months for MELD scores >18–20, patients should be treated before transplantation. Patients with compensated cirrhosis and HCC who are eligible for curative therapy should defer DAA therapy until HCC treatment is completed. In HCV-related HCC patients awaiting liver transplantation with a long waiting times, HCV treatment should be initiated before liver transplantation. Cirrhotic patients with sustained virological response should undergo surveillance for HCC every 6 months by means of imaging and serum tumor markers.

HCV2. Treatment with Direct Acting Antivirals (DAAs) for Cirrhotic Patients with or Without HCC

HCV2-2

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Shinshu University School of Medicine

Japan

Risk factors of treatment failure of DAAs in chronic hepatitis C

In Japan, where the majority of patients are infected with Geno t ype 1 and 2, DAA treatment for chronic hepatitis C and compensated cirrhosis achieves SVR in nearly 100% of patients. In this study, we investigated the following two risk factors for the few cases of treatment failure among patients treated with DAA at Shinshu University Hospital and its affiliated hospitals in Japan: 1) DAA treatment for patients who had previously developed HCC and had been relapse-free for six months after radical treatment of HCC, and 2) serum chemokine levels measured before DAA treatment. 1) Of the 838 DAA-treated patients, 9.4% had prior HCC, and low pretreatment platelet counts and high AFP levels, advanced fibrosis (M2BPGi), and prior HCC were associated with treatment resistance, leaving prior HCC as the only risk factor in the multivariate analysis. 2) Nine chemokines were measured, and treatment resistance (56.3%; 9 of 16) was significantly observed in the group with low MIP-1β and high RANTES before treatment. Future issues are to improve the prognosis of patients with uncompensated cirrhosis by DAA treatment and the indication of DAA treatment in patients with HCC.

HCV2. Treatment with Direct Acting Antivirals (DAAs) for Cirrhotic Patients with or Without HCC

HCV2-3

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School of Clinical Medicine, Tsinghua University

China

Hepatocellular Carcinoma Occurrence and Recurrence in HCV Patients Treated with Direct Antiviral Agents

The big achievement of anti-hepatitis C virus (HCV) Direct Antiviral Agents (DAAs) is significant reduce incidence of Hepatocellular Carcinoma (HCC), however, there still is HCC occurrence and recurrence. When and how to use DAA for patients with HCC remains controversy. It is suggested that delaying DAA treatment in patients with prior history of hepatocellular carcinoma (HCC) maybe able to decrease the risk of HCC recurrence.

The multicenter cohort study already suggested that the patients with non-characterized nodules (no HCC) before DAA treatment have a higher risk to develop to HCC than patients without. Some study suggested that the risk of HCC recurrence in patients with DAA induced SVR ranges between 0.25 times less and 3.5 times higher than those with interferon induce SVR. But, there are also same meta-analysis and meta-regression supporting no difference in HCC recurrence between DAA and IFN induce SVR after adjusting for study follow-up and age. Meanwhile, the risk of death in patients with DAA induced SVR was between 0.26-fold lower and 7.14-fold higher. Therefore, it seems that DAA treatment and HCC recurrence risk play key impact on the endpoint in patients with HCC history.

Anyway, it is recommended to conduct post-SVR HCC surveillance if patients achieved SVR. SVR just mean reduction but not elimination the risk of HCC. The patients with advanced fibrosis (F3) and cirrhosis (F4) background have higher HCC occurrence and recurrence. Other factors, including diabetes, old age, obesity, male gender, would have additional risk for HCC occurrence and recurrence. Recently, new consensus for MASLD under steatotic liver disease umbrella should be taken into consideration for HCC development with and without achieving SVR.

HCV2. Treatment with Direct Acting Antivirals (DAAs) for Cirrhotic Patients with or Without HCC

HCV2-4

Dr. Masanori Atsukawa

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Japan

Morphological changes in esophageal varices in cirrhotic patients who achieved sustained virological response by direct-acting antivirals

Recently, DAAs have markedly improved treatment outcomes and have been approved for patients with liver cirrhosis including decompensated cirrhosis related with chronic HCV infection, which is frequently complicated by esophageal varices. Previously, some studies reported that achievement of SVR with DAAs decreased portal pressure to some extent. Recent studies reported post-SVR changes in the morphology of esophagogastric varices in patients with compensated cirrhosis. However, post-SVR esophageal variceal changes in patients with decompensated cirrhosis remain unclear. Therefore, this multicenter retrospective study aimed to clarify the morphological changes in esophageal varices after achieving SVR with DAAs treatment in patients with liver cirrhosis including decompensated cirrhosis. A total of 1,768 patients with chronic HCV infection achieved SVR with DAAs treatment at 26 participating institutions in Japan. Among them, 243 patients underwent esophagogastroduodenoscopy before DAAs treatment and after achieving SVR. Our study included 125 males and 118 females with compensated or decompensated cirrhosis with a median age of 68 (range, 44–91) years. Esophageal varices before DAAs treatment were classified into no varix in 155, F1 in 59, F2 in 25 and F3 in 4 patients. The improvement, unchanged, and aggravation rates of esophageal varices after SVR were 11.9%, 73.3%, and 14.8%, respectively. Low platelet count was extracted as an independent factor associated with esophageal varices aggravation. Of the 155 patients without esophageal varices before DAAs treatment, 17 developed de novo post-SVR esophageal varices. High ALBI score was extracted as an independent factor associated with de novo post-SVR esophageal varices. The cumulative incidences of de novo esophageal varices were 0%, 6.7%, and 17.7% at 1, 3, and 5 years, respectively. In conclusions, patients with cirrhosis can experience esophageal varices aggravation despite achieving SVR. In particular, patients with low platelet count and high ALBI score such as decompensated cirrhosis had a high likelihood of developing esophageal varices aggravation and de novo esophageal varices, respectively, even for long periods after achieving SVR.

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Summary

HCV3 Prognosis Portal Hypertension HCC in Post SVR CH-C/cirrhosis

HCV3 Prognosis Portal Hypertension HCC in Post SVR CH-C/cirrhosis

HCV3-1

Dr. Koichi Takaguchi

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Japan

Evaluation of the usefulness of liver stiffness in cancer development after DAA treatment for chronic liver disease type C

[Purpose] DAA treatment eliminated Hepatitis C Virus (HCV) in most cases of type C chronic liver disease. However, some cases of SVR are also found to develop cancer. Here we report on whether subsequent carcinogenesis can be predicted in cases in which liver stiffness was measured at the start of treatment.

[Method] Of the 751 patients who received DAA at our hospital by March 2023, 234 patients (115 men, 119 women, Average age: 64.6 years, Genotype 1: 144 cases, Genotype 2: 88 cases, Genotype 3: 1 case, Unknown: 1 case) with type C chronic liver disease were measured Liver stiffness(LS) before DAA treatment. [Results] The average observation period after completion of administration was 38.1 months. During this period, 7 cases developed cancer. The 5-year cancer incidence rates for all cases was 3.8%. The five-year cancer incidence rate for LS, platelets(PLT), Alb, AFP, ALBI score, hyaluronic acid, M2BPGi, FIB4index, and FAST before administration was 1.0% for LS less than 14.8, 16.8% for 14.8 or more, and 9.0% for PLT less than 134,000/μL. , 134,000/μL or more: 2.1%, AFP less than 7ng/mL: 2.5%, 7ng/mL or more: 7.4%, Hyaluronic acid less than 298ng/mL: 1.4%, 298ng/mL or more: 13.4%, M2BPGi less than 1.92: 1.9%, 1.92 or more: 6.2%, FIB4index less than 3.20: 1.2%, 3.20 or more: 8.8%, significant differences were observed in all of the above items.

[Conclusion] The liver stiffness measured before administration and the liver stiffness after administration were found to be predictive factors for subsequent carcinogenesis in patients with DAA treated chronic HCV infection.

HCV3. Prognosis Portal Hypertension HCC in Post SVR CH-C/cirrhosis

HCV3-2

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The Catholic University Liver Research Center

Korea

Prognosis, Portal Hypertension, HCC in Post SVR CH-C/Cirrhosis

Globally, an estimated 58 million people have chronic hepatitis C virus (HCV) infection, with about 1.5 million new infections occurring per year. In 2019, an estimated 290,000 deaths were attributed to hepatitis C-related complications. The primary treatment goal for hepatitis C is the eradication of the HCV to prevent complications such as fibrosis, cirrhosis, portal hypertension, hepatocellular carcinoma (HCC), and extrahepatic manifestations, ultimately leading to a reduction in mortality. The clinical endpoint of antiviral therapy is achieving a sustained virologic response (SVR) at 12 weeks post-treatment, where no detectable HCV RNA is found in the bloodstream.

Recent advancements in interferon (IFN)-free direct-acting agents (DAAs) have dramatically improved SVR rates. Achieving SVR leads to improvements in fibrosis and portal hypertension. It is known that reaching SVR is associated with the regression of liver stiffness, which is linked to a decrease in liver-related complications and mortality. According to Lens et al.'s research, HCV-related cirrhotic patients who achieved SVR showed progressive reductions in hepatic venous pressure gradient (HVPG), and those with high baseline HVPG were more likely to experience decompensation events.

Achieving SVR significantly reduces the risk of hepatic decompensation. Meta-analyses show that SVR lowers this risk by 84% and 89% in the interferon and DAA eras, respectively. A Korean multicenter study found no significant difference in decompensation events between IFN-SVR and DAA-SVR patients.

Achieving SVR also reduces the risk of developing HCC. SVR results in an approximately 70% reduction in the risk of HCC development, with this effect becoming evident within 3-6 months and increasing over time. Some studies suggest that there may be differences in HCC risk reduction between cirrhotic and non-cirrhotic patients after SVR. And various prediction models for post-SVR HCC risk have been reported.

In conclusion, achieving SVR in hepatitis C patients is closely associated with favorable outcomes in terms of fibrosis regression, portal hypertension improvement, reduced HCC risk, and enhanced survival. However, it is important to note that certain high-risk groups may still require vigilant monitoring even after achieving SVR.

HCV3. Prognosis Portal Hypertension HCC in Post SVR CH-C/cirrhosis

HCV3-3

Dr. Ankur Jindal

Additional Professor, Department of Hepatology, Institute of Liver and Biliary Sciences

India

Influence of HVPG in predicting outcomes in liver disease

Portal hypertension is a severe, almost unavoidable complication of chronic liver diseases and is responsible for the main clinical consequences of cirrhosis. Measurement of the hepatic venous pressure gradient (HVPG) is currently the best available method to evaluate the presence and severity of portal hypertension. Clinically significant portal hypertension is defined as an increase in HVPG to ≥10 mmHg; above this threshold, the complications of portal hypertension might begin to appear. Measurement of HVPG is increasingly used in clinical hepatology, and numerous studies have demonstrated that the parameter is a robust surrogate marker for hard clinical end points. The main clinical applications for HVPG include diagnosis, risk stratification, identification of patients with hepatocellular carcinoma who are candidates for liver resection, monitoring of the efficacy of medical treatment, and assessment of progression of portal hypertension. Patients who experience a reduction in HVPG of ≥20% or to <12 mmHg in response to drug therapy are defined as 'responders'. Responders have a markedly decreased risk of bleeding (or rebleeding), ascites, and spontaneous bacterial peritonitis, which results in improved survival.

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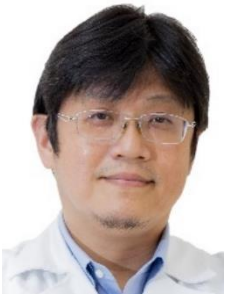
Summary

HCC1 Percutaneous Ablation for Liver Tumors

HCC1 Percutaneous Ablation for Liver Tumors

HCC1-1



Dr. Kai-Wen Huang

Centre of Mini-invasive Interventional Oncology, National Taiwan University Hospital

Taiwan

Percutaneous Ablation for Liver Tumors

Tumor ablation technology has evolved rapidly during the past several decades, with substantial technical and procedural improvements that can help improve clinical outcomes and safety profiles. With the significant evolution of imaging devices and ablation modalities during the last two decades, image-guided tumor ablation has become an ever more increasingly employed means for definitive treatment of focal malignancy, tumors in poor operative candidates, and for pain palliation in a minimally invasive manner. It has allowed larger ablation sizes with smaller instruments, and new technologies have enabled mini-invasive ablation with potential advantages in patient safety and treatment efficacy. As these technologies mature, the indications for percutaneous ablation continue to expand, and ablation promises to increasingly supplant surgery for local tumor therapy.

HCC1 Percutaneous Ablation for Liver Tumors

HCC1-2

Dr. Shinichiro Nakamura

Japanese Red Cross Society Himeji Hospital Department of Internal Medicine

Japan

Microwave Ablation for Hepatocellular Carcinoma

[Background and aim]

The next-generation microwave ablation (MWA) has been developed as a new percutaneous thermal ablation therapy for hepatocellular carcinoma (HCC). Compared to radio-frequency ablation (RFA), MWA has the advantage of faster heating and less susceptibility to heat sink effects due to the higher temperature generated and can make predictable spherical ablation zones.

We describe our MWA procedure and the clinical outcomes of patients with HCC.

[Methods]

We treat Child A or B patients with tumors less than 4 cm in diameter and three or fewer tumors without vascular invasion. MWA-antenna puncture was performed under ultrasound guidance. When the tumor was difficult to visualize using B-mode ultrasound, contrast-enhanced US (CEUS) or fusion imaging with CECT or Gd-EOB-DTPA enhanced MRI was used as a complementary method for MWA. If needed, artificial pleural effusion or ascites were prepared using a 5% glucose solution.

[Results]

Between September 2019 and September 2023, 564 consecutive patients with 802 HCCs (maximum tumor diameter ≤40 mm) were included.

The median maximum tumor diameter was 13.0 (interquartile range, 10.0–18.0) mm. We use CEUS, pleural effusion, and artificial ascites during MWA in 326 (40.7%), 73 (9.1%), and 439 (54.7%) HCCs, respectively. The cumulative local tumor recurrence rates at 1, 2, and 3 years were 4.6%, 8.6%, and 9.8%, respectively. The cumulative local tumor recurrence rate differed significantly by tumor size group: ≤20 mm group (n=651), 20–30 mm group (n=132), and ≥30 mm group (n=19) ($p<0.0001$). In the multivariable analysis, tumor size (per 1 mm) (hazard ratio [HR], 1.07; 95% confidence interval [CI], 1.03–1.11; $p=0.0002$) and ablative margin (per 1 mm) (HR, 0.83; 95% CI, 0.74–0.93; $p=0.0019$) were significantly associated with local tumor recurrence. Complications after MWA were observed in 40 cases (5.0%), and the major cases were biloma, 10; portal vein thrombosis, 9; bile duct dilatation, 6; pleural effusion, 5. Only tumor size (per 1 mm) (odds ratio, 1.08; 95% CI, 1.04–1.13; $p=0.0002$) was significantly associated with complications. Tumors located at difficult-to-MWA (n=135, 16.8%): caudate lobe and areas near the primary and secondary branches of the intrahepatic portal vein, inferior vena cava, gallbladder, heart, duodenum, abdominal esophagus, collateral veins around the liver, and spleen, were not associated with the local tumor recurrence and complications.

[Conclusions]

MWA is a safe and effective local ablation therapy for HCC.

HCC1 Percutaneous Ablation for Liver Tumors

HCC1-3

Dr. David C. Madoff

Department of Radiology & Biomedical Imaging Yale School of Medicine

USA

Tumor ablation combined with chemotherapy, targeted therapy and immunotherapy

Percutaneous ablation is used to eradicate all viable malignant cells & spare normal surrounding tissues. It is most often used in patients with “low volume disease” & for debulking. In the setting of hepatocellular carcinoma (HCC) in the setting of cirrhosis, ablation is now first-line therapy for tumors in very early or early stage. And, ablation can be used to treat tumors in patients with an unfavorable location or pattern of distribution for resection, or in patient with multiple co-morbidities. Lastly, ablation is often performed in the outpatient setting and can be repeatable.

In recent years, there has been considerable interest in combining systemic therapies with percutaneous ablation to improve response rates and overall survival in patients with liver tumors. This presentation will review the various percutaneous ablative modalities and discuss how adding systemic therapies such as chemotherapy, biologics, and immunotherapy, may impact patient care. Further, mechanisms of action of the various systemic therapies and current clinical trials that are currently underway will be discussed.

HCC1 Percutaneous Ablation for Liver Tumors

HCC1-4

Dr. Hyunchul Rhim

Department of Radiology Samsung Medical Center, Sungkyunkwan University

Korea

Strategic Optimization of Percutaneous Liver Ablation: A Comprehensive Approach

Percutaneous liver ablation is pivotal in modern liver cancer management, necessitating a tailored strategy for heightened effectiveness. This overview explores the imperative of strategic optimization, highlighting key components contributing to enhanced patient outcomes.

Strategic optimization involves a personalized methodology that extends beyond conventional practices. Incorporating advanced technologies and tailored patient care, practitioners can boost precision and procedural efficacy. Individualized treatment plans, guided by advanced imaging, enable accurate tumor delineation, minimizing collateral damage to healthy tissues.

Economic considerations are pivotal in the strategic optimization framework. Evaluating the cost-effectiveness of ablation techniques ensures judicious resource allocation without compromising patient care—a crucial aspect in the era of value-based healthcare.

Additionally, the overview emphasizes collaboration across medical disciplines. Integrating insights from radiology, oncology, and interventional medicine enriches research and facilitates the exchange of best practices.

In conclusion, strategic optimization in percutaneous liver ablation represents a paradigm shift. This overview outlines its key components, underlining its potential to redefine standards of care, improve outcomes, and shape the future of interventional oncology.

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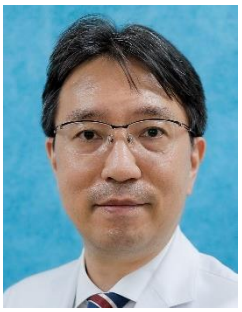
Summary

HCC2 Can Drug Therapy and Classical Local Treatment Coexist?

HCC2 Can Drug Therapy and Classical Local Treatment Coexist?

HCC2-1



Dr. Ryosuke Tateishi

Department of Gastroenterology The University of Tokyo Graduate School of Medicine

Japan

Role of Ablation for hepatocellular carcinoma in the era of systemic therapy

In solid tumors, the dogma is that cancer starts locally, invades surrounding tissues as it progresses, and eventually causes distant metastasis. Therefore, the common strategy was to aim for radical cure by local treatment for localized disease, and to prolong life by drug therapy for systemic disease. Recent advances in drug therapy for hepatocellular carcinoma (HCC) have influenced treatment strategies not only for advanced disease but also for patients with earlier stages. In populations where curative treatment is technically feasible but high recurrence rates are expected, phase III trials of adjuvant therapy after resection or ablation have been conducted and have reported improved recurrence-free survival rates. For more advanced patients, trials are underway to improve complete resection rates through preoperative neoadjuvant therapy. In addition, because necrotic cancer cells remain in the body after locoregional treatments such as ablation, TACE, and radiation therapy, many attempts have been reported to augment the effects of immunotherapy with these therapies. It has also been reported that after treating patients with systemic therapy, the addition of local therapy to some poorly responding nodules can improve overall tumor control, prolong the cancer-free period and ultimately achieve drug-free status. Therefore, it is now necessary to go beyond the conventional dogma of local therapy for local disease and systemic therapy for systemic disease, and freely use both local therapy and drug therapy in HCC treatment.

HCC2 Can Drug Therapy and Classical Local Treatment Coexist?

HCC2-3

Dr. Stephen Lam Chan

Department of Clinical Oncology, Faculty of Medicine, The Chinese University of Hong Kong

Hong Kong SAR, China

TACE plus systemic therapy: How and Who

Conventionally, TACE is reserved for patients with intermediate disease of HCC while systemic therapy is indicated following TACE treatment or in the presence of advanced disease. However, this concept is being challenged by recent randomized data showing that the addition immunotherapy-based systemic therapy to TACE could improve outcomes. The lecture will review the latest efficacy and safety data on the combination. Patient selection for this treatment combination will also be discussed.

HCC2 Can Drug Therapy and Classical Local Treatment Coexist?

HCC2-4

Dr. Hidetoshi Nakagawa

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Japan

Basis of combination therapy by radiofrequency thermal ablation and immune checkpoint blockade for unresectable hepatocellular carcinoma

Introduction: Despite significant advancements in cancer treatment since the establishment of immune checkpoint blockade, a considerable number of patients do not benefit from the latest immunotherapies, often due to insufficient tumor-infiltrating lymphocytes or limited antigen exposure. To address this, we propose leveraging the 'abscopal effect' through local ablation therapy before immunotherapy in patients with unresectable hepatocellular carcinoma.

Methods: We evaluated the antitumor effects of radiofrequency ablation (RFA) in BNL/MC38 tumor-bearing mice. RFA was applied to one of two bilateral tumors, with the untreated tumor monitored to assess antitumor responses. To explore the underlying mechanisms, we examined the roles of different immune cell subsets using nude mice, clodronate liposomes, and CD4/CD8 depletion antibodies. We also initiated a clinical study, "Randomized Phase II study of preceding radiofrequency ablation to atezolizumab plus bevacizumab combination therapy for patients with unresectable hepatocellular carcinoma (jRCT1041200075)." This study involves treating selected hepatic lesions with RFA before administering atezolizumab and bevacizumab to patients with unresectable hepatocellular carcinoma. The study includes a safety confirmation cohort (n=6) and a randomized cohort (n=60), focusing on progression-free survival as the primary endpoint and overall survival, objective responses, tumor control rates, and immunological responses as secondary endpoints.

Results: Animal studies demonstrated that RFA enhanced antitumor effects in residual tumors. Experiments in nude mice with BNL tumors confirmed that this enhancement was T-cell mediated. Macrophage ablation with clodronate liposome did not affect tumor growth in wild-type BNL mice. Tests using CD4 or CD8 depletion antibodies showed that T cells were responsible for the enhanced antitumor effects in MC38-bearing mice. Preliminary results from the clinical study's safety cohort indicate the combination therapy's safety and feasibility. Over a median observation period of 885 days, the best responses included one partial response and five stable diseases, with a median progression-free survival of 175 days.

Conclusions: The combination therapy involving RFA and cancer immunotherapy, with the aim of eliciting abscopal effects, presents a promising avenue in cancer immunotherapy. Preliminary results from the clinical trials support the safety and feasibility of this combination approach, encouraging further investigation.

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Summary

HCC3 Will Adjuvant Chemotherapy Post-Curative Treatment for Hepatocellular Carcinoma Be a Paradigm Shift

HCC3 Will Adjuvant Chemotherapy Post-Curative Treatment for Hepatocellular Carcinoma Be a Paradigm Shift

HCC3-1

Dr. Masafumi Ikeda

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Japan

Will Adjuvant Chemotherapy Post-Curative Treatment for Hepatocellular Carcinoma Be a Paradigm Shift?

According to the Barcelona Clinic Liver Cancer (BCLC) staging system, a single tumor or tumor size of ≤3 cm of hepatocellular carcinoma (HCC) are classified as early-stage, and liver resection, liver transplantation, or local ablative therap is recommended. These treatments aim for complete cure, and systemic therapy was firstly developed as post-curative adjuvant therapy. Although no standard post-curative treatments have been established yet, the effectiveness of adjuvant atezolizumab plus bevacizumab (Atezo+Bev) therapy as compared to active surveillance (IMbrave050) was demonstrated in 2023. The primary endpoint of recurrence-free survival (RFS) demonstrated to be significantly better in Atezo+Bev than in active surveillance [12-month RFS: Atezo+Bev 79% vs. active surveillance 68%, hazard ratio 0.70 (95% confidence interval: 0.54-0.91, p=0.007)]. In the subgroup analysis of RFS, the benefits of Atezo+Bev were consistent across all subgroups. However, there was no difference in overall survival [hazard ratio 1.42 (95% confidence interval: 0.80-2.54)], and the Kaplan-Meier curves for RFS became close after 2 years, suggesting the suppressive effect for early recurrence and no suppressive effect after 2 years. As the follow-up period (median) is still short at 17.4 months, long-term follow-up results are warranted.

Currently, in the early-stage HCC, post-curative treatment of systemic therapies are underway as comparator of placebo: EMERALD-2 (NCT03847428) compared with durvalumab plus bevacizumab, CheckMate9DX (NCT03383458) compared with nivolumab, and KEYNOTE-937 (NCT03867084) compared with pembrolizumab. These phase III trials are focusing on combined therapy or monotherapy of immune checkpoint inhibitors. From these results, whether a single immune checkpoint inhibitor or a combination of an immune checkpoint inhibitor and a VEGF inhibitor is necessary for adjuvant therapy will be determined.

HCC3 Will Adjuvant Chemotherapy Post-Curative Treatment for Hepatocellular Carcinoma Be a Paradigm Shift
HCC3-3

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Japan

The next step toward adjuvant therapy in patients with hepatocellular carcinoma

Adjuvant therapy for patients with hepatocellular carcinoma (HCC) after curative treatment, including resection and ablation, is still unestablished in clinical practice. There are some clinical studies that aim to prove prevention of HCC recurrence after curative treatment. The phase 3 clinical trial, atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk HCC (IMbave050), already showed positive results. The recurrence-free survival (RFS) was significantly longer in the patients treated with atezolizumab plus bevacizumab compared to the patients with active surveillance. In this study, the majority (88%) of patients received resection, and 90% of the patients treated with resection had solitary tumors. Moreover, 82% of patients were recruited from Asia, and 62% had HBV infection. In Western countries and Japan, the percentage of HCC patients with HBV infection is about 10%, and the number of non-viral HCCs, including MASLD, has been increasing globally. Even though this study met the primary endpoint, the median duration of follow-up was only 17.4 months in the treatment group and 17.6 months in the active surveillance group. IMbrave050 trial was the first successful clinical study and the first step toward adjuvant therapy in HCC. However, there are many concerns about adjuvant settings. First, we have to identify the patients with high-risk populations of recurrence. In the IMbrave050 trial, only 7 patients in the treatment group and 3 patients in the active surveillance group had ≥ 3 tumours. Second, we should mention the etiologies of patients. Third, it is important to consider the toxicity of adjuvant therapy. In the IMbrave050 trial, grade 5 adverse events occurred in 6 patients (2 of which were treatment-related) in the treatment group and 1 patient in the active surveillance group. In real-world practice, several studies were performed by using transarterial chemoembolization (TACE) + portal vein chemotherapy (PVC) or internal radiotherapy (IRT) as adjuvant therapy after curative resection in HCC and showed positive results. Although atezolizumab plus bevacizumab has been recommended as first-line systemic therapy in most HCC guidelines, it should be evaluated by comparing other therapies as adjuvant therapy. The next step toward adjuvant therapy in HCC is to solve such clinical questions and establish the appropriate adjuvant therapy for each patient.

HCC3 Will Adjuvant Chemotherapy Post-Curative Treatment for Hepatocellular Carcinoma Be a Paradigm Shift
HCC3-4

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Hong Kong SAR, China

Adjuvant Chemotherapy for HCC

Adjuvant treatment has been studied in HCC for long time with little success. At present, there remains no standard adjuvant therapy following patients with surgery or ablation. Immunosurveillance plays a key role in prevention of recurrence after treatment of curative intent. A number of adjuvant clinical trials on immune checkpoint inhibitors has been conducted. IMBRAVE050 showed that the use of atezolizumab and bevacizumab could improve the recurrence-free survival as compared to active surveillance amongst patients at high risk of recurrence following surgery or ablation. The readout of the IMBRAVE050 study has undoubtedly led to interest on immune based therapy in the adjuvant setting. The above will be covered by the lecture.

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Summary

HCC4 Current Status and Future Perspective of Hepatic Resection

HCC4 Current Status and Future Perspective of Hepatic Resection

HCC4-1

Dr. Osamu Itano

Department of Hepato-Biliary-Pancreatic & Gastrointestinal Surgery,

International University of Health and Welfare School of Medicine

Japan

ICG Fluorescence Imaging-Assisted Laparoscopic Anatomical Hepatectomy Using Inside-Out Transection

Background: Anatomical liver resection should not require the dissection of Glissonean branches during the intersectional liver transection. However, the conventional transection method is to set the transection plane connected from the demarcation line on the surface to the root of the corresponding Glissonean pedicle, therefore, the vessels that appear on the transection plane are dissected, creating unnecessary ischemic or congestion areas which can lead to complications. In this paper, we will show how to correctly implement the concept of anatomical resection, which is called “inside-out transection by central approach”, and the synergistic effect of using ICG fluorescence imaging further increases accuracy.

Methods: The root of the corresponding Glissonean pedicle is identified visually at the hilum and liver dissection started on the assumed transection plane from the root. The intersectional transection is proceeded inside-out, towards the peripheral, recognizing the flow of the glissonean branches. The “chicken claw” shape of Glissonean branches is the end of the branch, and the line connecting these signs is used for dissection. As a result, the dissection of the Glissonean branch will not occur. The corresponding Glissonean pedicle is dissected intrahepatically when enough surgical space inside the parenchyma is made for safe procedures. The ICG fluorescence method is used at this time.The direction of hepatic resection becomes even easier to recognize.Liver parenchyma near the surface is dissected in the end.

Results: hemihepatectomy (L:8, R:5), Sectorectomy (A:4, P:5, AM:1, M:2) Median operation time was 349 min, Median blood loss was 176ml. There was no postoperative complications equal or more than CD3.

Conclusion: ICG fluorescence imaging-assisted inside-out transection enables us to perform precise intersegmental transection in laparoscopic anatomical liver resection.

HCC4 Current Status and Future Perspective of Hepatic Resection

HCC4-3

Dr. Dong-Sik Kim

HBP Surgery & Liver Transplantation

Korea

Surgical Approach to Hepatocellular Carcinoma Located on Difficult Locations

Advance in surgical techniques and perioperative care have decreased operative morbidity and mortality much lower during last couple of decades. Among those advancements, incorporation of minimally invasive surgical techniques such as laparoscopic or robotic surgery into the field of liver surgery are considered as the most significant ones. It is well known that location of HCC is an important component in the process of treatment decision algorithm not only for liver resection but also for other locoregional treatments. In the perspectives of minimally invasive liver resection, posterosuperior segments such as segments 7 or 8 are considered as ‘difficult locations’ because it is often deep and very close to large veins such as right hepatic vein or inferior vena cava with potential of excessive intraoperative bleeding, often requiring extensive mobilization of full right lobe. Therefore, either open liver resection or full right lobectomy under laparoscopy may be preferred.

In this presentation, current surgical options for resection of HCC located in posterosuperior segments will be reviewed and advantage/disadvantage of each option will be discussed. The potential direction of future advancement will be discussed as well.

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Summary

HCC5 Current Status and Future Perspective of Transplantation

HCC5 Current Status and Future Perspective of Transplantation

HCC5-1

Dr. Susumu Eguchi

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Japan

Current status of machine perfusion for liver transplantation

[Background]

Machine perfusion (MP) for liver transplantation has been clinically applied, mainly in Europe and the USA to make the most of the limited number of donated organs. MP has also been performed in the liver for reconditioning extended criteria donors and functional evaluation before transplantation, and good transplant outcomes have been reported. On the other hand, when introducing MP in Japan, it is important to takes into account the differences in the current state of organ donation between Japan and Europe.

[Introduction of machine perfusion in Japan]

MP for preservation of a graft liver can be carried out depending on the temperature and the perfusate. In the Netherlands, the national protocol is to use different methods depending on the circumstances of the donor. Hypothemic oxiganated perfusion (HOPE) for cardiac arrest donor grafts (DCD), brain-dead donor grafts (DBD) with risk factors, and split liver transplant grafts; HOPE followed by Normothemic machine perfusion (NMP) for high-risk grafts that have not been accepted by each institution. In Japan, where liver transplantation is currently not performed for DCD grafts or marginal DBD grafts, we believe that HOPE should be introduced for marginal DBD grafts.

[Current state of device development]

The machine currently being developed for HOPE is a system that uses organ preservation solution (HTK solution) controlled at 8-10°C with a hydraulic difference pumpless perfusion system. The chamber that perfuses the graft is separate from the main body, allowing trimming of the graft during perfusion. Pig liver transplantation experiments were conducted, and the stability of the machine and the outcome after liver transplantation with HOPE were evaluated. Assuming clinical use, the liver was removed and transplanted after 3 hours of HOPE. Grafts treated with HOPE were implanted and survived for the 3 days expected in the protocol (n=2). In HOPE cases, lactate levels remained low after reperfusion, and post-operative transaminase and bilirubin levels were lower than in normally preserved cases.

[Conclusion]

Considering the current state of liver transplantation in Japan, we believe that HOPE for DBD livers, such as long-term ischemia and elderly donors, is a MP suitable for clinical implementation. Development of equipment for HOPE is progressing in large animal experiments, and preparations for clinical research are underway.

HCC5 Current Status and Future Perspective of Transplantation

HCC5-2

Dr. Masahiro Ohira

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Japan

Liver-Resident Natural Killer Cells as Adjuvant Treatment for Hepatocellular Carcinoma Post-Liver Transplantation

Effective prevention or treatment strategies for hepatocellular carcinoma (HCC) recurrence following liver transplantation (LT) are currently lacking. Standard immunosuppressive protocols post-LT tend to preserve innate immune components while suppressing adaptive cellular immunity. Central to the innate immune response, Natural Killer (NK) cells are pivotal in defending against neoplastic cells, making their enhancement a viable immunotherapeutic strategy against HCC post-LT. We suggest that the adoptive transfer of liver-resident NK cells, harvested from the donor liver graft perfusate, could induce an anti-tumor response without harming the recipient's healthy tissues.

In our study, 99 patients who preoperatively met the Japan criteria were examined. Of these, 42 patients who postoperatively exceeded the Milan criteria demonstrated significantly lower recurrence-free survival rates compared to the 57 within the criteria ($p=0.022$). Remarkably, among patients beyond the Milan criteria, those treated with NK cell therapy ($n=17$) showed a marked improvement in recurrence-free survival rates. Following NK cell infusion, we observed a significant increase in NK cell cytotoxicity and the percentage of TRAIL+ NK cells in the patients' peripheral blood ($p<0.05$). The administered donor NK cells were detectable in the peripheral blood up to one month post-infusion.

Our collaborative research with the University of Miami, initiated in 2009, has extended this approach to deceased donor LT (DDLT) recipients. This phase I trial encompassed 17 subjects with a median follow-up of 96 months, recording no adverse events related to the study. The high-dose NK cell group exhibited a significantly superior overall survival rate compared to the low-dose group ($p=0.0064$). Among the DDLT series for HCC, 53% of patients meeting the Milan criteria preoperatively had pathological findings exceeding the criteria postoperatively, yet none have experienced HCC recurrence to date.

In conclusion, IL-2 stimulated NK cells from both living and deceased donor liver transplants have been safely administered, suggesting a promising adjuvant immune therapy for HCC patients post-LT. A multicenter phase II trial is now underway in Japan and the USA.

HCC5 Current Status and Future Perspective of Transplantation

HCC5-3

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Liver Transplantation In Patients With Hepatitis B And Hepatocellular Carcinoma

The aetiology of most cases of hepatocellular carcinoma (HCC) is chronic hepatitis B virus (HBV) infection. More than 240 million people in the world are infected with HBV. Hepatitis B virus-associated carcinogenesis is a multifactorial process involving direct effects of viral proteins, indirect mechanisms through chronic inflammation and immune evasion, and the integration of HBV-DNA. The direct oncogenic effect of HBV may occur via multiple mechanisms. Integration of HBV-DNA into the host genome may result in genomic instability, which together with production of HBV proteins, especially the regulatory protein HBx, may result in uncontrolled cell proliferation. In Asia, except Japan, HBV-related HCC remains the most frequent indication for liver liver transplantation (LT). HBV reinfection and recurrence of HCC after LT are associated with increased graft failure and reduced patient survival. Patients with HBV recurrence are 3.6 times more likely to have HCC recurrence than patients without HBV. In one study, the HCC recurrence rate was significantly higher in patients with HBV recurrence than in those without HBV recurrence (40% vs 5.7% $p<0.001$). Current guidelines recommend the use of a combination of nucleos(t)ide analogues and Hepatitis B immunoglobulin after liver transplantation.

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Summary

HCC6 Current Status of TACE and HAIC

HCC6 Current Status of TACE and HAIC

HCC6-2

Dr. Hiroaki Nagamatsu

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Japan

New FP therapy for long-term prognosis in patients with advanced hepatocellular carcinoma

[Introduction] In Japan, hepatic arterial infusion chemotherapy(HAIC) is recommended as a optional treatment in the 2021 guidelines. In 2021, New FP therapy(NFP) was reported to have a longer prognostic effect than sorafenib in advanced hepatocellular carcinoma with intrahepatic lesions. [Objectives] I will show the performance of NFP in this study at our hospital. [Subjects] We perform 2 courses using the temporary indwelling catheter system via the left brachial artery, and then we remove the temporary reservoir during hospitalization. We repeat this treatment 3 to 5 times with an interval of about 2 months. We aim for cancer free by performing conversion therapy when PR or CR is obtained by NFP. We performed NFP on 290patients with advanced with vascular invasion. [Results]There is almost no deterioration liver function. A total of 200 patients (69%) responded to NFP therapy, of which 80 patients achieved cancer-free outcome. 32 patients became cancer-free outcom with only NFP. We were able to add hepatic resection to 33 patients. Median OS (MST) after HAIC in all patients was 18 months. MST in patients who responded was 29 months, and in patients who achieved cancer-free outcome, it was extended to 67 months. The 5-year survival rate of all patients was 22%, and 67% for patients who got cancer-free outcom. [Conclusions]NFP has a high response rate and contributes to improve or maintain liver function by controlling PVTT. In response cases, long-term survival can be obtained by adding conversion therapy.

HCC6 Current Status of TACE and HAIC

HCC6-3

Dr. Yasuteru Kondo

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Japan

DEB-TACE combined with HAIC and iCIs could be an affordable treatment option for advanced stage of HCC

The treatment efficacy for patients with advanced-stage HCC has been improved by molecular-targeted agents (MTA), immune check point inhibitors (iCIs), and radiation therapy, in addition to TACE and/or hepatic arterial infusion chemotherapy (HAIC). However, the treatment efficacy for patients with advanced-stage HCC treated by a single agent has not been adequate. iCIs and/or MTA including sorafenib, lenvatinib, regorafenib and cabozantinib etc. are standard treatments according to current international guidelines. However, alternative treatment modalities are required because of the low response rates and unsuitability of MTA and iCIs in the real world. Combinations and/or sequential treatments with various agents have been carried out to improve the treatment efficacy for patients with advanced-stage HCC. We modified the treatment regimens to improve the efficacy of DEB-TACE and HAIC for intermediate and advanced HCC. I will present about the role of Ultra-FP therapy (DEB-TACE and HAIC) and iCI treatment for the HCC patients.

HCC6 Current Status of TACE and HAIC

HCC6-4

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Japan

Current indication of TACE and combination therapy with systemic agents for HCC

Due to recent development of molecular targeted agents (MTA) and immune checkpoint inhibitors (ICI) for hepatocellular carcinoma (HCC), the role of transarterial chemoembolization (TACE) has been changing from palliative treatment to curative treatment. Previously it was reported that complete response (CR) obtained by TACE prolonged the overall survival. Therefore, the key is how to obtain CR in TACE. A randomized controlled trial (PRESIDENT study) conducted in Japan demonstrated the higher curability of selective conventional TACE (cTACE) compared with selective drug-eluting bead TACE (DEB-TACE). The CR rate at 3 months after TACE was 75.2 % in cTACE versus 27.6% in DEB-TACE. Recently, the result of primary analysis of TACTICS-L trial was reported. The combination of TACE with Lenvatinib (LEN-TACE) achieved high CR ratio of 53.2 % at 4 weeks after first TACE and 67.7 % in the best response. These seem to be higher when compared to TACTICS trial with the CR rate of 28% in the TACE plus sorafenib group. Furthermore, LEN-TACE achieved high CR ratio in patients beyond Up-to-7 criteria. Currently, several clinical trials of TACE combined with systemic therapies are ongoing. Molecular biological and immunological effects of MTA and ICA could be expected in combination with TACE.

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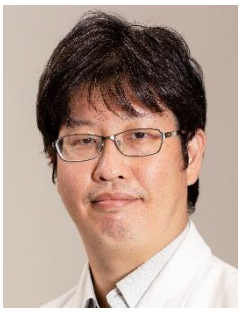
HCC7 Advancements in Radiation Therapy for Hepatocellular Carcinoma

HCC7 Advancements in Radiation Therapy for Hepatocellular Carcinoma

HCC7-1



Dr. Masaru Wakatsuki

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Japan

Carbon-ion radiotherapy for hepatocellular carcinoma

Radical treatment options for bulky unresectable locally advanced hepatocellular carcinoma (HCC) are limited. Stereotactic Body Radio Therapy (SBRT) is becoming popular in many countries as an effective treatment option for relatively small hepatocellular carcinomas, there are problems in terms of its effects on the normal liver and its efficacy against large hepatocellular carcinomas. Carbon-ion radiotherapy (C-ion RT) has improved dose distribution properties owing to Bragg peak and less lateral scattering and enable to perform higher prescribed dose for HCC than that of photons. Take advantage of this feature, C-ion RT is becoming popular in Japan as a new curative treatment option. National Institute for Quantum Science and Technology (former the National Institute of Radiological Sciences) began treating patients with C-ion RT in 1994 and has treated approximately 1,000 cases of hepatocellular carcinoma to the present. Since April 2022. Its effectiveness was recognized and C-ion RT for hepatocellular carcinoma larger than 4 cm was approved by the Japanese National Health Insurance since. The number of patients treated is increasing. It has been shown to be a safe and effective treatment, especially for hepatocellular carcinoma with vascular invasion, patients with low liver function, and patients with bulky hepatocellular carcinoma.

In this presentation, I would like to show the results of treatment to date and introduce the challenges and future directions of C-ion RT for hepatocellular carcinoma.

HCC7 Advancements in Radiation Therapy for Hepatocellular Carcinoma

HCC7-2

Dr. Yoshiko Doi

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Japan

The Role and Future of Stereotactic Body Radiotherapy for Hepatocellular Carcinoma

With advancements in imaging diagnostics and radiation therapy techniques, the application of stereotactic body radiotherapy (SBRT), delivering high doses of radiation in a short time, has become more feasible. Numerous studies have reported the high therapeutic efficacy and safety of SBRT for hepatocellular carcinoma (HCC). A prospective, phase II multicenter study of SBRT in previously untreated solitary primary HCC (STRSPH study) was conducted in Japan and reported a 90% local control rate and a 3-year overall survival (OS) rate of 78%. This study included many elderly patients and patients with comorbidities for whom standard treatments (radiofrequency ablation (RFA) and surgical resection) were not applicable, but the high local control rate and low toxicity of SBRT are thought to have led to the good results.

On the other hand, in the global treatment algorithm for HCC, decisions are guided by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. Consequently, treatment options rich in evidence, such as liver resection, RFA, transcatheter arterial chemoembolization, liver transplantation, and chemotherapy, are considered in the selection of HCC treatment. Unfortunately, among studies evaluating SBRT outcomes, none have presented high-quality clinical evidence assessable by the GRADE system. So, SBRT is absent from the treatment algorithm.

Nevertheless, studies have shown positive results not only in SBRT outcomes, but also in studies comparing outcomes with other treatment modalities in retrospective study. A meta-analysis of tumor outcomes for HCC treated with RFA or SBRT, utilizing meticulously selected studies, reported no significant difference in the OS rate between the two modalities (1- and 2-year OS rates were 91.8% and 77.7% after RFA, and 89.0% and 76.0% after SBRT, respectively).

SBRT exhibits notably high local treatment efficacy, particularly acting as a breakthrough in challenging scenarios where RFA is difficult (such as lesions just below the diaphragm, on the liver surface, peri-vascular lesions, and conditions with a bleeding tendency, as well as cases with tumors not visible by ultrasonography) or in instances of recurrence post-TACE. This underscores its potential as a promising therapeutic approach contributing to overall prognosis improvement for HCC patients. It is imperative for radiation oncologists to communicate the heightened therapeutic efficacy and safety of SBRT to hepatologists and surgeons, making sustained efforts to broaden the applicability of SBRT implementation.

HCC7 Advancements in Radiation Therapy for Hepatocellular Carcinoma

HCC7-3

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Korea

Experience in clinical trials combining immunotherapy and radiotherapy

While systemic therapy is recommended for HCC patients with MVI by many academic guidelines, various liver-directed therapies such as surgical resection, transarterial chemoembolization with or without radiotherapy, and radioembolization have demonstrated significant outcomes. There may be an unmet need for improved treatment strategies integrating systemic and liver-directed therapy in patients with HCC and MVI.

External beam radiation therapy (EBRT) can be applied to patients with HCC in various situations, including those with symptomatic primary liver or metastatic lesions. Recent advances in the EBRT techniques, such as with stereotactic body radiotherapy (SBRT), proton beam therapy (PBT), and carbon ion radiotherapy, have enabled the delivery of higher radiation doses to achieve excellent local control. Proton beam therapy (PBT), an EBRT, demonstrated non-inferiority for local progression-free survival to radiofrequency ablation for small residual or recurrent intrahepatic HCC as a curative option. The combination of EBRT and transarterial chemoembolization (TACE) showed tolerability and superior efficacy for HCC with MVI compared with sorafenib alone. Although little is known about the clinical outcomes of the concurrent use of radiotherapy and immunotherapy, it can be expected to exert a synergistic effect in cancer treatment. Radiation therapy can have immunostimulatory effects. Substantial preclinical studies have shown that radiotherapy may synergize with immunotherapy. Preliminary clinical studies have recently been reported. A phase 1 trial of SBRT combined with immunotherapy (nivolumab with or without ipilimumab) exhibited favorable outcomes, and the combination therapy of EBRT and atezolizumab/bevacizumab demonstrated acceptable safety.

Based on the CheckMate-040 trial, which showed promising clinical activity and a favorable safety profile, nivolumab, a PD-1 inhibitor, obtained accelerated approval from regulatory agencies worldwide, including South Korea, as a second-line treatment, and a global first-line nivolumab trial could be initiated. Nivolumab monotherapy demonstrated a durable response in some patients; however, the response rate still remained at 20%. EBRT has shown good local control in HCC and may potentiate immunotherapy through immunomodulatory effects; therefore, we conducted a phase 2 study evaluating the efficacy and safety of concurrent therapy with nivolumab and EBRT in patients with advanced HCC and MVI.

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Summary

HCC8 Bridging Clinical and Basic Research

HCC8 Bridging Clinical and Basic Research

HCC8-1

Dr. Young Nyun Park

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Korea

Molecular pathologic spectrum between HCC and cholangiocarcinoma and their relation to histopathologic subtypes

Two main primary liver carcinomas are hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA). HCC is heterogeneous in moleculopathological features and biologic behavior. 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. 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. 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.

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.

HCC8 Bridging Clinical and Basic Research

HCC8-2

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Japan

Establishment of Genome analysis center, From Genomic Analysis to Clinical Practice in Hepatocellular Carcinoma

In 2019, Comprehensive Genomic Profiling test became eligible for insurance coverage, marking the widespread adoption of cancer genomic medicine. Our institution established a Genomic Analysis Center in April 2013 and has been actively engaged in cancer genomic medicine.

Yamanashi Prefectural Central Hospital has accumulated cancer registration data since 2006, totaling 29,024 cases (including 1,163 with hepatocellular carcinoma, HCC), and has obtained genomic informed consent from 9,484 patients (including 313 with HCC). We developed an in-house panel targeting Significantly Mutated Genes for each cancer type. Using NGS platforms (Genexus, Proton, PGM), we performed sequencing on 15,213 samples (lung 2,758, biliary/pancreatic 1,839, gynecological 921, liver 906, stomach 572, urological 532, breast 304, and others), generating a total of 5.6 trillion bases. Additionally, we have published 112 peer-reviewed articles.

In HCC, registration using REDCap in the A-HOC (APASL Hepatology/Oncology Consortium) has reached 506 cases. Analysis using in-house HCC panels (72 SMGs: 59,016 amino acids) has been completed for 198 cases 355 nodules (solitary: 130 patients with 130 nodules, synchronous: 33 patients with 81 nodules, metachronous: 16 patients with 35 nodules, syn+meta: 19 patients with 75 nodules). Whole transcriptome data has been obtained for 300 of these samples. There are 689 cases of DAA (Direct-Acting Antiviral) treatment, and tumor marker data (AFP, AFP-L3, DCP) have also been collected for these cases. Considering these data, we aim to validate the clinical applications of HCC analysis from a multifaceted perspective, including ① post-DAA occurrence of HCC, ② dynamics of oncogenic driver in serially occurring HCC nodules ③ the correlation between tumor markers and clinical/genomic data.

HCC8 Bridging Clinical and Basic Research

HCC8-3

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Japan

NAFLD becomes a promoter of hepatocellular and cholangiocellular tumors in mice

Background: It is epidemiologically clear that NAFLD, which is an increasing trend in recent years, accelerates hepatic inflammation, fibrosis and liver cancer development. In contrast, it is unclear whether NAFLD affects the cholangitis or development of another liver cancer, cholangiocellular carcinoma (CCC). The aim of this study is to investigate whether high fat diet promotes cholangitis and development of cholngiocellular tumors in mice.

Methods: We use liver-specific E-cadherin gene (Cdh1) knockout mice, Cdh1ΔLi, which was generated by crossing Cdh1flox/flox mice with Albumin-Cre transgenic mice, with spontaneous inflammation in the portal areas and periductal onion skin-like fibrosis, which resembles primary sclerosing cholangitis (PSC). High fat diet or normal diet was fed into the Cdh1ΔLi mice for 7 months. In addition, Cdh1ΔLi mice was crossed with LSL-KrasG12D (active Kras) mice and also fed with high fat diet.

Results: Cdh1ΔLi mice that received a high-fat diet for 7 months increased in body weight similarly to control mice, and the degree of fat deposition in the liver was increased but not different from controls. On the other hand, the extent of cholangitis and fibrosis, and numbers of bile ductules significantly progressed as compared to normal diet-administered mice. CD44-positive stem cell-like cells were significantly increased and ALT and ALP levels were also increased in mice with high fat diet. Liver specific LSL-KrasG12D/ Cdh1ΔLi showed 2-10 macroscopically tumors with both hepatocellular and cholangiocellular components after 9 months of birth with normal diet, whereas high fat diet induced aggressive and numerous numbers of cholangiocellular tumors only after 3 months of high fat diet. Interestingly hepatocellular tumors were rarely found in these mice. In contrast, liver specific LSL-KrasG12D mice showed aggressive hepatocellular tumors by high fat diet.

Conclusion: NAFLD exacerbates cholangitis and becomes a strong promoter of not only hepatocellular tumors, but also cholangiocellular tumors. In addition, NAFLD may cause transdifferentiation from hepatocellular to cholangiocellular component.

HCC8 Bridging Clinical and Basic Research

HCC8-4

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Japan

Development and Prospects of AI-aided Ultrasonography System -New Possibilities in Diagnosis of Liver Tumor-

The integration of artificial intelligence (AI) has aimed to enhance operational efficiency and mitigate human errors in the medical field. Image diagnosis support, a pivotal area for AI development, has witnessed the initiation of large-scale database construction and the deployment of numerous models in society. Notably, liver malignancies stand as the fifth leading cause of cancer-related deaths in Japan, underscoring the urgency of early diagnosis through ultrasonography for improved prognosis and reduced medical costs. However, the variable quality of ultrasound (US) diagnosis, dependent on the skill of examiners, presents a challenge. Hence, achieving AI-assisted standardization in the quality of US examination becomes crucial for effective disease management of malignant liver tumor.

Within the framework of the Japan Agency for Medical Research and Development (AMED)-ICT Infrastructure Development and Artificial Intelligence Implementation Project, we established a system for collecting US images and ancillary information, and developed an AI capable of detecting and discriminating liver masses in abdominal US B-mode examinations utilizing a comprehensive database.

A 2-step method employing YOLOv5 as a mass detector, convolutional neural network (CNN-VGG19) as a tumor discriminator, and DeepSORT to prevent duplicate detection was implemented. The detector demonstrated exceptional performance in pre-clinical tests, surpassing 90% in recall, precision, and F1-score through a 10-fold cross-validation. The discriminator, designed for the differential diagnosis of hepatocellular carcinoma, metastatic hepatocellular carcinoma, hemangioma, and cysts, achieved high accuracy, sensitivity, and specificity in a four-class classification and benign-malignant discrimination in cross-validation.

In an exploratory clinical trial under the AMED-Practical Research for Innovative Cancer Control Project, the performance of prototype AI model integrating detectors and discriminators in series was evaluated to determine the impact of AI-assisted improvement in human US diagnostic performance. The results revealed significant enhancements in liver mass detection indices (recall, precision, F1-score) and differentiation indices (accuracy, sensitivity, specificity, and Matthews correlation coefficient) particularly for non-expert, demonstrating the practical potential of the developed AI model to support human US diagnosis. Research projects are underway to refine and market the AI as Software as a Medical Device (SaMD). In addition, concurrently, efforts are also directed towards developing a model capable of differentiating intrahepatic cholangiocarcinoma.

The effectiveness of our AI in supporting US diagnostics has been recognized, especially among non-experts, where AI assistance has significantly improved all detection and differentiation indices. It can be described as a practical AI model that aids in the diagnosis of liver tumors in human US examinations.

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Summary

HCC9 The Future of Hepatocellular Carcinoma Treatment in Asia Pacific Region

HCC9 The Future of Hepatocellular Carcinoma Treatment in Asia Pacific Region

HCC9-1

Dr. Saeed Hamid

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Promoting a Multi-disciplinary team approach to the management of HCC in Asia Pacific.

The Asia Pacific region is home to the largest population of HCV and HBV infected persons. As a result the burden of HCC will likely increase significantly in the future years, related not only to HCV and HBV infection but also to the epidemic of MAFLD that the region is witnessing. Even patients cured of HCV infection with underlying liver cirrhosis are at risk of developing HCC, perhaps at a faster rate according to some patient series, after successful treatment.

The region has low rates of systematic screening for HCC in patients susceptible to develop HCC so that most HCCs, in LMICs particularly, present at a late stage of the disease. In addition, both diagnostic and therapeutic modalities in many countries of the region are limited and resources must be used carefully. This calls for a multi-disciplinary team approach that would be able to best allocate treatment resources to the properly selected patients.

HCC9 The Future of Hepatocellular Carcinoma Treatment in Asia Pacific Region

HCC9-2

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Prevention of Hepatocellular Carcinoma in Asia Pacific Region

Liver related deaths contribute to variable proportion of overall deaths in Asia-Pacific. Liver cancer accounts for 40% of liver related death in Asia-Pacific. Asia-Pacific contributes to 2/3 rd of global liver disease related deaths, 3/4 th of liver cancer related deaths and 80% of HBV related liver cancer deaths. Worldwide Age standardized incidence and mortality rates of liver cancer arehighest in East Asia. There are various risk factors for liver cancer, HBV, HCV, alcohol, NAFLD being common ones. Age standardized incidence of liver cancer due to HBV, Alcohol and NAFLD are highest in East Asia (China, North Korea and Taiwan) and has been increasing across all regions of Asia-Pacific. Age standardized incidence of liver cancer due to HCV highest in the high-income Asia–Pacific countries (Brunei, Japan, Singapore and South Korea) and has been increasing across all regions of Asia-Pacific.Strategies to prevent HCC include: Primary prevention against new cases of viral hepatitis, and secondary prevention of HCC in susceptible individuals. Most important interventions of primary prevention include HBV immunization, reduce aflatoxin exposure,reduce alcohol use and reduce NAFLD/obesity. Most important secondary prevention measures include treating viral hepatitis. Universal hepatitis B vaccination has resulted in dramatic reduction in incident cases of chronic hepatitis B and HCC in children and adolescents, as found in Taiwan. There is a lower liver cancer risk with antiviral therapy in chronic hepatitis B (including patients with even normal to minimally elevated ALT and no cirrhosis. Similarly HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. The WHO's Global Health Sector Strategy on viral hepatitis (2016) aims for elimination of viral hepatitis as a major public health threat by 2030 (i.e, 90% reduction in incidence and 65% in mortality) compared with a 2015 baseline. The Political Declaration of the High-level Meeting of the United Nations General Assembly on the Prevention and Control of Non-Communicable Diseases (NCDs) mandated the development of a global monitoring framework, including indicators, and a set of voluntary global targets for the prevention and control of NCDs. Following the declaration, WHO developed a global monitoring framework to enable global tracking of progress in preventing and controlling major NCDs. Global alcohol action plan will also strengthen the implementation of the " Global Strategy to Reduce the Harmful Use of Alcohol".

HCC9 The Future of Hepatocellular Carcinoma Treatment in Asia Pacific Region

HCC9-3

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The future of hepatocellular carcinoma treatment in Asia-pacific region

-My perspective

Up till 2024, hepatocellular carcinoma (HCC) remains a major cause of cancer-related mortality in Asia-Pacific region, with an age-standardized rate in Eastern Asia (17.8 new cases, 16.1 deaths) and South-Eastern Asia (13.7 new cases, 13.2 deaths). Most of the hepatocellular carcinoma are related to chronic hepatitis B (CHB) infection and are diagnosed only at late stage when “curative” measures such as surgical resection, local ablation or transplantation are no longer applicable. Even in those patients treated with “curative” measures, recurrence remains a major clinical problem especially those with accompanying liver cirrhosis. As a hepatologist in Asia-Pacific region, it is a major dismay that up to half of the CHB patients diagnosed with HCC were not aware of their hepatitis B surface antigen status, and very few had received any anti-viral therapy or undergone regular interval HCC surveillance, as recommended by APASL hepatitis B management guideline. This clinical scenario has not changed significantly over the past two decades. To this end, APASL has set up a viral elimination task force to explore strategy to formulate cost-effective policy, utilizing existing diagnostic and therapeutic means to benefit CHB, so as to reduce the incidence of HCC. On the other hand, in order to deal with an increasing clinical burden of HCC, our major objectives are (1) early detection of HCC in patients with high risk factors such as chronic viral hepatitis B with or without delta or C, MAFLD and alcoholic liver diseases (2) application of local regional therapy or systemic therapy to prolong overall survival with quality life or even to down-staged HCC so as to enable “curative” therapy with affordable cost. In recent few years, several multi-targeted tyrosine kinase inhibitors (TKI), vascular endothelial growth factors and immune-checkpoint inhibitors have been found to be effective in prolonging overall survival and even complete remission in those patients with advanced HCC. In the coming decade, one is expected to see more individualized therapy with new drug (using software such as AlphaFold) and biomarkers for HCC with the aid of artificial intelligence algorithms and big data deep mining (clinical, molecular, genetic, histology and imaging). We envisage “control” and even “cure” for patients with unresectable HCC in the foreseeable future.

HCC9 The Future of Hepatocellular Carcinoma Treatment in Asia Pacific Region

HCC9-4

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Japan

EMERALD-1: a Phase 3, randomized, placebo-controlled study of transarterial chemoembolization (TACE) combined with durvalumab (D) with or without bevacizumab (B) in participants with unresectable hepatocellular carcinoma (uHCC) eligible for embolization.

Background

TACE has been a standard of care for embolization-eligible uHCC; however, most people with uHCC treated with TACE progress within 1 year. Embolization may create a proinflammatory tumor microenvironment and increase VEGF signals; clinical studies have established the role of immune checkpoint inhibitors (ICIs, e.g. D) and VEGF inhibitors (e.g. B) in advanced HCC.

Methods

Participants were randomized 1:1:1 to the D+B+TACE, D+TACE, or TACE (cTACE or DEB-TACE per investigator choice). Participants received D (1500 mg) or placebo-for-D (Q4W) plus TACE. After completion of last TACE, participants received D (1120 mg) or placebo-for-D plus B (15 mg/kg) or placebo-for-B (Q3W). Primary endpoint was progression-free survival (PFS) for D+B+TACE versus TACE (RECIST v1.1). Secondary endpoints included PFS for D+TACE versus TACE, overall survival (OS), objective response rate (ORR), time to progression (TTP), and safety for D+B+TACE or D+TACE versus TACE. PFS, ORR, and TTP were assessed by blinded independent central review (RECIST v1.1).

Results

Demographic and baseline characteristics were generally balanced across arms. PFS significantly improved for D+B+TACE versus TACE (p=0.032; Table). PFS for D+TACE versus TACE was not statistically significant (p=0.638; Table). ORR and TTP were improved with D+B+TACE versus TACE (Table). Participants continue to be followed for OS.

Conclusions

D+B+TACE is the first ICI-based regimen in a global Phase 3 trial to show statistically significant and clinically meaningful improvement in PFS, versus TACE, in participants with embolization-eligible uHCC. D+B+TACE has the potential to set a new standard of care in uHCC.

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Summary

HCC10 Optimal Treatment Selection in Hepatocellular Carcinoma

HCC10 Optimal Treatment Selection in Hepatocellular Carcinoma

HCC10-2

Dr. Yoon Jun Kim

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Korea

Optimal use of TARE in advanced HCC in the era of IO

Transarterial radioembolization (TARE) has emerged as a valuable locoregional therapy in the management of advanced hepatocellular carcinoma (HCC). In recent years, the landscape of HCC treatment has been revolutionized by the introduction of immune checkpoint inhibitors (IO), offering new avenues for therapeutic intervention. However, the optimal integration of TARE with IO remains an area of active investigation and debate. The role of TARE from early-stage to advanced HCC will be thoroughly discussed, including its potential synergistic effects with IO therapy, challenges, considerations in patient selection, timing of treatment, and management of adverse events. Additionally, ongoing clinical trials and future directions aimed at elucidating the role of TARE in the era of IO will be highlighted. A comprehensive understanding of the interplay between TARE and IO holds promise for optimizing treatment strategies and improving outcomes in patients with advanced HCC.

HCC10 Optimal Treatment Selection in Hepatocellular Carcinoma

HCC10-3

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Taiwan

A personalized approach for optimal treatment selection in HCC

The treatment of HCC is diverse depending on tumor stage and affordability of patients. A personalized approach remains an unmet medical need. Recently, the application of AI had introduced into the field of HCC management. In our recent study, the risk of recurrence after surgical resection of HCC could be predicted by an evolutionary learning-derived clinical-radiomic GARSL models. This model can further discriminate the risk of recurrence either in high or low risk patients defined by IMbrave 050 study, indicating that the requirement of adjuvant immunotherapy after surgical resection of HCC can be determined by this AI model in our daily practice in near future. TACE unsuitability is an emerging issue for intermediate stage HCC. We have recently proposed a novel 7-11 criteria to divide BCLC B HCC into low-, intermediate-, and high tumor burden; and define the outcomes of TACE through different radiologic patterns, both can assist decision making before TACE. More studies support the concept that the dissimilarities in gut microbiome composition are associated with immune status and susceptibility to immunotherapy. Recently, we identify the associated of gut microbiota and metabolites with outcome of HCC undergoing immune checkpoint inhibitors treatment, supporting the potential role of gut microbiota in selection patients with HCC for immunotherapy.

HCC10 Optimal Treatment Selection in Hepatocellular Carcinoma

HCC10-4

Dr. Masayuki Kurosaki

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Japan

Eliminating viral hepatitis C: Not to leave anyone behind from HCV cure

Hepatitis C remain important background for liver-related mortality. HCV cure improve liver function and may reduce mortality in decompensated cirrhosis if treated before the point of no return. Identification of high-risk cases for HCC after HCV cure is important to personalize surveillance. Situation of DAA treatment for HCV patients complicated with active HCC may differ between countries due to lack of evidence. These points will be discussed.

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Summary

HCC11 Tumor Microenvironment in Hepatocellular Carcinoma

HCC11 Tumor Microenvironment in Hepatocellular Carcinoma

HCC11-1

Dr. Kazuomi Ueshima

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Japan

The role of locoregional therapy aimed at improving the tumor microenvironment in systemic chemotherapy for hepatocellular carcinoma

With recent advances in systemic chemotherapy for hepatocellular carcinoma, two types of combined immunotherapy, atezolizumab plus bevacizumab and durvalumab plus tremelimumab, are now available. Although response rates and longer survival have been achieved, further efforts are needed to enhance efficacy. Locoregional therapies such as TACE have the effect of changing the tumor microenvironment, and it has been suggested that TACE may maximize the therapeutic effects of combined immunotherapy. To confirm the hypothesis, The Phase 3 IMPACT trial combining atezolizumab plus bevacizumab with TACE is now ongoing in Japan. It has already been reported that In the Phase 3 EMERALD-1 trial, combining TACE with durvalumab plus bevacizumab improved PFS. The result of the Phase 3 LEAP-012 trial, TACE in combination with lenvatinib and pembrolizumab, is expected. In addition, the results of the Phase 3 EMERALD-3 trial, TACE in combination with the triplet of durvalumab, tremelimumab, and lenvatinib, are also expected. In the future, multidisciplinary treatment of combined immunotherapy with locoregional therapy, such as TACE, will become the standard treatment for hepatocellular carcinoma.

HCC11 Tumor Microenvironment in Hepatocellular Carcinoma

HCC11-2

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Cancer Prevention in patients with chronic HCV Infections

Hepatitis C virus (HCV) infections are a significant global health concern, contributing substantially to hepatocellular carcinoma (HCC), the sixth most prevalent cancer and fourth-leading cause of cancer-related deaths worldwide. The progression from chronic HCV infection to HCC spans 20 to 40 years, influenced by factors such as age at infection, viral genotype and loads, alcohol consumption, comorbidities (diabetes and obesity), HIV coinfection, gender, liver fibrosis, and host genetics.

While primary prevention through vaccination is ideal, there is currently no HCV vaccine. Consequently, HCC prevention focuses on effective antiviral therapy as secondary prevention for de novo HCV-related HCC and tertiary prevention for HCC recurrence after curative therapy. Achieving sustained virological response (SVR) with interferon (IFN)-based or directly-acting antiviral (DAA) agents significantly reduces HCC incidence, liver-related mortality, and HCC recurrence post-curative therapy.

Despite SVR, the risk of HCC persists, with preexisting liver cirrhosis and age recognized as crucial risk factors. Understanding pathogenetic mechanisms and identifying risk surrogate biomarkers can enhance follow-up strategies post-HCV eradication. HCV infection induces epigenetic changes, including H3K27ac, associated with increased oncogene expression and decreased tumor suppression genes, persisting after SVR.

Several factors contribute to a higher post-SVR HCC risk, including advanced age, liver cirrhosis, diabetes, alcohol consumption, elevated baseline AFP (≥ 10 ng/mL), and specific genetic variations (MICA, PNPLA3, MBOAT7, TM6SF2, and GCKR). Notably, aspirin, metformin, and statin use have shown promising chemo-preventive effects, reducing HCC risk in large cohort studies among HCV-cured patients.

HCC11 Tumor Microenvironment in Hepatocellular Carcinoma

HCC11-3

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Understanding microenvironment of hepatocellular carcinoma for biomarkers and therapeutic discovery

Despite recent success in cancer immunotherapies, the complex dynamics within tumor-immune microenvironment (TIME) remain elusive. With the multidimensional analysis pipeline, we have successfully identified and described key immunological factors in hepatocellular carcinoma (HCC) that contribute to disease progression and clinical response to therapy. Our team has identified peripheral immunological biomarkers associated to therapeutic response in HCC patients treated with radiotherapy and anti-PD-1 immunotherapy, shedding light on potential mechanism for treatment response and guiding the design of novel therapeutic strategies. More recently, we have explored the immune landscape of steatotic-related HCC to uncover potential mechanisms driving immunosuppression and to identify novel immunotherapeutic targets.

HCC11 Tumor Microenvironment in Hepatocellular Carcinoma

HCC11-4

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Japan

Tumor microenvironment in hepatocellular carcinoma and its optimal treatment approach

Over the past decade, the treatment landscape for advanced hepatocellular carcinoma (HCC) has evolved significantly, shifting from multikinase inhibitors to a focus on immunotherapy, particularly anti-programmed cell death protein 1 (PD-1) and anti-PD-L1 antibodies. These monoclonal antibodies enhance the immune response against tumors by blocking the PD-1/PD-L1 pathway, thus preventing the downregulation of the immune system and activating T-cells. Despite the initial lack of statistical superiority in phase III trials of nivolumab and pembrolizumab, the combination of atezolizumab (anti-PD-L1 antibody) and bevacizumab (anti-VEGF antibody) emerged as a standard therapy, significantly improving overall survival in the IMbrave 150 trial. This approach addresses tumor-induced immunosuppression, facilitated by VEGF's role in inhibiting T-cell function and creating an immunosuppressive microenvironment.

Further advances include the combination of durvalumab (anti-PD-L1) with tremelimumab (anti-CTLA-4), enhancing T-cell activation and proliferation within tumors, as demonstrated in the HIMALAYA study. However, challenges remain in treating "cold tumors" with low immune cell infiltration, where T-cell activation is often inadequate. Emerging therapies, such as CAR-T therapy and bispecific antibodies targeting HCC-specific proteins, along with the potential synergy between immunotherapy and radiation therapy, offer hope for activating T-cells in these challenging cases. Future advancements in systemic therapy for advanced HCC are expected to focus on strategies that enhance T-cell activation, aiming to effectively treat the majority of HCC cases characterized as "cold tumors."

APASL 2024 Kyoto

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Summary

HCC12 Clinical Trials in Hepatocellular Carcinoma: Challenges of Multinational Multicenter Trials

HCC12 Clinical Trials in Hepatocellular Carcinoma: Challenges of Multinational Multicenter Trials

HCC12-1

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Clinical Trials in Hepatocellular Carcinoma: Challenges of Multinational, Multicenter Trials

Hepatocellular carcinoma (HCC), the most common type of primary liver cancer, presents significant therapeutic challenges, particularly in the context of multinational, multicenter clinical trials. There are many challenges and propose strategies for effective management. The complexity of HCC, influenced by underlying liver disease, comorbidities, and diverse etiologies, necessitates a multifaceted approach in clinical research. Multinational, multicenter trials for HCC are pivotal in advancing global understanding and treatment strategies. However, these trials face unique challenges, including variability in clinical practices, regulatory differences, and heterogeneous patient populations. There is disparity in HCC epidemiology, risk factors, and standard care protocols across different countries. Variations in disease presentation and progression, influenced by geographic and genetic factors, further complicate trial design and outcomes analysis. Moreover, there are problems on patient recruitment, adherence to protocols, data collection consistency, and the impact of cultural and linguistic barriers. We underscore the importance of harmonizing regulatory requirements and clinical guidelines to facilitate smoother conduct of these trials. Clinical studies delve into the methodological challenges of ensuring statistical power and validity in such diverse settings. Strategies to overcome these include adaptive trial designs, robust statistical methods to handle heterogeneity, and the use of centralized data monitoring systems.

In conclusion, the complexities inherent in multinational, multicenter clinical trials for HCC are challenging. It advocates for international collaboration, standardization of practices, and innovative trial designs to enhance the efficacy and generalizability of clinical research in the realm of hepatocellular carcinoma.

HCC12 Clinical Trials in Hepatocellular Carcinoma: Challenges of Multinational Multicenter Trials

HCC12-2

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Utilizing Real-world Data for Systemic therapy in Hepatocellular Carcinoma.

In the current landscape, the escalating costs of drug development not only pose challenges to the development process but also contribute to the rising prices of approved medications. Considering this situation, there is growing anticipation for new drug development utilizing real-world data (RWD). Developing a single novel drug using RWD is not necessarily straightforward. However, it seems possible to develop better treatment sequence by evaluating the effects of treatment sequencing, combination therapies, and their impact on therapeutic outcomes and adverse events.

Systemic therapy for advanced hepatocellular carcinoma (HCC) has made remarkable progress. In Japan, regimens including atezolizumab plus bevacizumab, sorafenib, and lenvatinib were available for first line treatment, and regorafenib, ramucirumab, and cabozantinib for second line until the approvement of tremelimumab plus duruvalumab in 2022. In real-world clinical practice, treatment is being delivered in a variety of sequences. We launched the Hepatoma Registry of Integrating and Aggregating EHRs (electric health record): HERITAGE study to establish a registry of RWD in Japan. In this study, among the HCC cases registered in the nationwide follow-up survey of primary liver cancer conducted by Japan Liver Cancer Association, cases treated with systemic therapy between 2015 and 2022 were included. We will show the RWD of systemic therapy for HCC in Japan, including changing patient characteristics, treatment sequences, and treatment efficacy.

HCC12 Clinical Trials in Hepatocellular Carcinoma: Challenges of Multinational Multicenter Trials

HCC12-3

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New Therapeutic Strategies against HBV, an Old Foe

Hepatitis B virus (HBV) infection continues to pose a significant public health concern, resulting in notable levels of illness and death worldwide and affecting approximately 292 million individuals. With advancements in antiviral therapy, the current treatment approach for chronic hepatitis B (CHB) involves the use of nucleos(t)ide analogs (NAs) to inhibit HBV DNA replication. This leads to a reduced risk of cirrhosis, hepatocellular carcinoma (HCC), and liver-related deaths, all while maintaining a favorable safety profile. However, a majority of patients require prolonged and continuous treatment for sustained suppression of HBV DNA, as NAs cannot achieve a functional cure for HBV infection. Additionally, concerns persist regarding the long-term development of HCC, considering risks from untreated patients in the "grey-zone" beyond the scope of current international treatment guidelines over the past decade and potential hazards from remaining viral factors like HBV DNA integration into host cells. Efforts are underway to overcome these limitations.

Evolving therapeutic strategies involve expanding and simplifying guidelines to include patients in the “grey-zone” within treatment criteria. Expert opinions in East Asia suggest simplifying treatment criteria by recommending antiviral therapy for patients meeting specific conditions. (a) HBV DNA ≥ 2000 IU/mL and ALT ≥ 1× ULN; (b) HBV DNA ≥ 2000 IU/mL, ALT < 1× ULN and ≥ F2 fibrosis and/or ≥ A2 necroinflammation occurs; (c) cirrhosis and detectable HBV DNA; or (d) HBV DNA ≥ 2000 IU/mL, ALT < 1× ULN and a family history of cirrhosis or HCC, extrahepatic manifestations or age > 40 years, regardless of HBeAg status.[1] Retrospective studies have shown that a notable proportion of patients not meeting treatment criteria had significant diseases, such as fibrosis with elevated HBV DNA despite being within the normal range of ALT.[2,3] Importantly, a considerable proportion of patients developing HCC did not conform to current international treatment criteria, emphasizing the need for expanding treatment criteria.[4-7] Results from a recent randomized controlled study suggest that the 3-year intervention with NAs for patients in the “grey-zone” achieved a significantly greater reduction in distinct viral-host DNA integration, indicating potential benefits in reducing HCC development.[8] Future prospective studies are warranted to investigate these simplified criteria.

Simultaneously, strategies involving newly developed drugs are raising optimism for achieving a functional cure for HBV infection, categorized into replication inhibitors, agents inducing antigen burden reduction, and immune modulators9. Studies propose a dual combination of these drugs with existing NAs to diminish HBsAg quantitation.[9,10] Ongoing clinical trials exploring triple combinations offer initial data on efficacy and insights into their feasibility and potential for reducing HBsAg quantitation.[9,10] Various therapeutic strategies and agents have shown functional cure outcomes, albeit largely in a limited subset of patients. While multiple pathways exist toward achieving this goal, identifying the most effective strategy remains elusive thus far.[9-11]

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HCC12 Clinical Trials in Hepatocellular Carcinoma: Challenges of Multinational Multicenter Trials

HCC12-4

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Follow Up Strategies in Patients with Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the fifth most common cancer among malignancies in men all over the world. It is the third most common leading cause of death and one of the leading causes of death among patients with cirrhosis. Hepatocellular carcinoma represents about 90% of primary liver cancers and constitutes a major global health problem. HCC accounts for more than 300,000 deaths in China and more than 650,000 deaths worldwide every year. The annual HCC incidence was highest in Asian Pacific Islanders (0.65%), followed by whites (0.57%) and then African Americans (0.40%).

Patients detected at an early stage can achieve 5-year survival rates of 70% with transplant or resection, whereas those with advanced HCC are only eligible for palliative treatments and have a median survival of less than one year.

The goal of surveillance is to detect HCC at an early stage when it is amenable to curative therapy and to reduce all-cause mortality. First, HCC risk must be high enough in the at-risk groups to justify surveillance. Second, surveillance tests must accurately detect HCC at an earlier stage than it would otherwise present because of symptoms, signs, or incidental imaging. Third, effective treatments, which improve outcomes in screen-detected HCC compared to treatments for non–screen-detected HCC, must be applied.

- Surveillance should be offered for patients with cirrhosis irrespective of etiologies when the risk of HCC is 1.5%/year or greater. HCC surveillance is associated with a smaller tumor size, with lower alpha–fetoprotein levels.
- Earlier BCLC tumor stage, with impact on therapeutic strategy resection/transplantation or radiofrequency ablation more often applied.
- It is an independent predictor of increased survival, with significantly higher 1-, 3-, and 5-year survival rates. Reduction in mortality.
- US and alpha fetoprotein (AFP) serum measurement in combination, are used as a triage test before CT and MRI. CT and MRI play a role of add-on tests to confirm the diagnosis and to stage the disease.
- Semi-annual surveillance intervals were associated with improved early HCC detection and overall survival compared to longer surveillance intervals.
- it is recommended to perform at least 3 follow-ups every year for high-recurrence-risk patients in the first 2 years after ablation, while in low-recurrence-risk patients, it is recommended to perform 2–3 follow-ups every year.
- Few studies characterized surveillance-related harms, although available data suggests surveillance harms are mild in severity.

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Summary

HCC13 Unraveling the Progression of Genomic Anomalies in Hepatocellular Carcinoma

HCC13 Unraveling the Progression of Genomic Anomalies in Hepatocellular Carcinoma

HCC13-1

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Unraveling the Progression of Genomic Abnormalities in Hepatocellular Carcinoma

Currently, about 900,000 people around the world are diagnosed with liver cancer every year, and it is estimated that deaths from liver cancer will increase by 55% by 2040. Most of these cases are due to infection with hepatitis viruses such as hepatitis B and C, or excessive alcohol abuse, but the recent increase in liver cancer caused by MAFLD/MASH in India, Europe, and the United States is also attracting attention. Most liver cancers occur against the background of cirrhosis associated with chronic liver disease. Dysplastic nodules occur in liver cirrhosis, and it is thought that in addition to TERT promoter mutations, gene mutations such as P53 and CTNNB1 accumulate, causing liver cells to become cancerous. From the perspective of the cancer microenvironment, why cancer occurs against the background of liver cirrhosis has been analyzed in detail. It is also interesting that liver cancer is classified histologically, molecularly, and immunologically. New information about the development of liver cancer from MASH, which is increasing in number of people, is increasing, including the elucidation of ACVR2A and mutagenesis signatures. In this lecture, I will provide a general discussion of the mechanisms involved in liver cancer development, especially from the perspective of genetic abnormalities.

HCC13 Unraveling the Progression of Genomic Anomalies in Hepatocellular Carcinoma

HCC13-2

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The Role of Hepatitis B Virus Integration in Hepatocarcinogenesis

Hepatitis B virus (HBV) is a major cause of hepatocellular carcinoma (HCC). HBV DNA can get integrated into the hepatocyte genome to promote carcinogenesis. However, the precise mechanism by which the integrated HBV genome promotes HCC has not been elucidated.

1) We identified the fusion HBx, the HBx-human fusion protein derived from HBV integrant, in Hep3B cells and investigated its role in hepatocarcinogenesis. The identified full-length fusion mRNA was 3,725 bp in length, and the fusion HBx, which consisted of 1-140 amino acids of HBx followed by 61 amino acids from the human genome, was translated from the fusion mRNA. The fusion HBx knockdown resulted in reduced cell proliferation and invasion, and loss of tumor development in nude mice. Moreover, the fusion HBx, but not wild HBx, provided anchorage-independent growth ability in soft agar although its transactivation ability was abrogated. Microarray analysis revealed that fusion HBx deregulated endoplasmic reticulum (ER) stress response by modifying ATF3, ATF4, and ATF6 transcription. Interestingly, the effects of fusion HBx on ER stress signaling pathway were similar to those of C-terminal truncated HBx, but significantly different from those of wild HBx. Our findings suggest that the fusion HBx plays a significant role in hepatocarcinogenesis by modifying ER stress response and could be an attractive target for the treatment of HBV-induced HCC.

2) Published data, consisting of 426 Liver tumor samples and 426 paired adjacent non-tumor samples, were re-analyzed to identify the integration sites. Genome Reference Consortium Human Build 38 (GRCh38) and Telomere-to-Telomere Consortium CHM13 (T2T-CHM13 (v2.0)) were used as the human reference genomes. In addition, GRIDSS VIRUSBreakend was used to detect HBV integration sites. A total of 5361 integration sites were detected using T2T-CHM13. In the tumor samples, integration hotspots in the cancer driver genes, such as TERT and KMT2B, were consistent with those in the previous study. Enrichment of integration was observed at chromosome 11q13.3, including the CCND1 promoter, in tumor samples. Recurrent integration sites were observed in mitochondrial genes. GRIDSS VIRUSBreakend using T2T-CHM13 is accurate and sensitive in detecting HBV integration. Re-analysis provides new insights into the regions of HBV integration and their potential roles in HCC development.

HCC13 Unraveling the Progression of Genomic Anomalies in Hepatocellular Carcinoma

HCC13-3

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Integrated Omics Analysis for the Progression of Hepatocellular Carcinoma

Recent advances in gene analysis technologies such as next-generation sequencing system have facilitated genome-wide investigation in various cancers including hepatocellular carcinoma (HCC). Comprehensive and un-supervised transcriptomic analysis has been conducted, revealing that HCC samples can be divided into several subtypes with distinct gene expression patterns. Additionally, genome and exome analysis through next-generation sequencing, as well as methylome, metabolome and proteome analysis using methylation array and mass spectrometry, have been conducted. During this period, the “two-class” model, categorizing HCC into proliferative and non-proliferative classes, was proposed. Publicly available data including mutation signatures and expression profiles of hundreds of HCC cases were generously provided by the Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium (ICGC) Research Network, advancing the understanding of the relationship between the subtypes, clinicopathological factors, and tumor microenvironment including vascular endothelial cells and immune cells. On the other hand, since the approval of antiangiogenic agent sorafenib, treatment options have been lacking due to a series of clinical trial failures for nearly 10 years. However, other antiangiogenic inhibitors including regorafenib, lenvatinib, cabozantinib and antiangiogenic antibodies have emerged, followed by combination of immune checkpoint inhibitors, which can ameliorate progression-free and overall survival in HCC patients. Nevertheless, starting with the clinical report that HCC with CTNNB1 active mutations conferred potential resistance to immune checkpoint blockade, investigations on the link between the subtypes and drug response are ongoing by further use of single-cell gene analysis. In the same period as such development in genome-based medicine, it has coincided with the acceleration of remarkable innovations in genome-editing technology using the CRISPR/Cas9 system. The integration of comprehensive genome editing technologies, such as multiplex genome editing, which introduces multiple genomic aberrations simultaneously, with barcode sequencing technology has led to the development of in vivo screening methods, allowing preclinical models that mimic each subtype to be individually reproduced. Immunocompetent subtype models reflect the molecular characteristics of the subtype and the tumor immune microenvironment and can help evaluate the efficacy of single and combination therapies and understand the molecular and immunological mechanisms underlying vulnerability and resistance to them. Thus, consensus classifications and associated preclinical models are extremely promising for establishing predictive biomarkers and escalating the clinical development of subtype-specific therapies.

HCC13 Unraveling the Progression of Genomic Anomalies in Hepatocellular Carcinoma

HCC13-4

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Unraveling the Progression of Genomic Abnormalities in Hepatocellular Carcinoma

The natural history of hepatocellular carcinoma presumably evolves from initial chronic hepatitis, subsequent cirrhosis and eventually HCC. In analogous to most human cancers, genomic mutations gradually appear and accumulate during the process, and finally lead to HCC. However, so far we still cannot chronicle the time-sequences of the incriminated mutations in details.

Most of known common genetic mutations of human HCC, irrespective of etiology, such as TERT promoter mutations, p53 or beta-catenin, or ARID gene mutations, occur in the late stage, from dysplastic nodules to early HCC. In the non-dysplatic cirrhotic nodules, WGS failed to identify recurrent genetic mutations. Therefore, we still do not know what mutations drive the clonal expansion in the cirrhosis stage.

One exception to this is noted in HBV-related HCC in which HBV DNA integration takes place in the very early stage of viral infection or hepatitis, probably 20-30 years before the development of HCC. Two HBV DNA integration hotspot genes have been identified in TERT promoters or Exon3-6 of MLL4 gene. HBV DNA integration into the two sites clearly grants advantages for subsequent evolution into HCC. This case may hint the early genomic abnormalities residing in these two pathways: TERT gene over-expression or truncated MLL4 mediated epigenetic mutations and warrant further investigation.

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Summary

ACLF1 Recent Changes of Incidence and Etiology of Acute Liver Failure in Asia Pacific Region

ACLF1 Recent Changes of Incidence and Etiology of Acute Liver Failure in Asia Pacific Region

ACLF1-1

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Development of Novel Hepatitis B Therapy with Antiviral Host Factors Induced by Acquired Immune Responses

Background: Nucleos(t)ide analogs, potent antiviral agents, effectively diminish hepatitis B virus (HBV) DNA but fall short of curing HBV infection due to the persistence of covalently closed circular DNA (cccDNA). Our previous work with a human hepatocyte HBV infection model revealed that IFN-γ regulates HBV cccDNA via the STAT1-related pathway (Hepatol Res. 2020, 2022). In this investigation, we delved into novel antiviral host factors governing cccDNA and elucidated their molecular mechanisms using in vitro HBV infection systems, employing gene knockdown techniques and functional gene expression analysis.

Methods: The 1.3-mer HBV genome plasmid (genotype C2) with core promoter A1762T/G1764A and precore G1896A mutation was transfected into HepG2 cells, establishing the "HepG2.D11 clone." The supernatant containing HBV was introduced to primary human hepatocytes (PXB cells). siRNA knockdown experiments and RNA microarray analyses were conducted. Gene expression was assessed using GeneSpring GX software and Gene Set Enrichment Analysis. Additionally, single-cell RNA sequencing (scRNAseq) data from the Human Protein Atlas (HPA) for 30 major tissues/organs were scrutinized.

Results: In the STAT1 knockdown experiment, HBsAg, intracellular HBV DNA, and cccDNA decreased in PXB cells, while HBsAg and HBV DNA increased in HepG2.D11 cells (HBV DNA PXB-siSTAT1/HepG2.D11-siSTAT1, 0.51/1.91 folds; $p < 0.05$). RNA microarray analysis revealed 65 genes with altered expression in PXB-siSTAT1 cells (> 2.0 folds, 42 genes; < 0.5 folds, 23 genes). Subsequent siRNA screening experiments identified two anti-HBV candidate genes, fumarylacetoacetate hydrolase (FAH) and Nicotinamide N-methyltransferase (NNMT), whose knockdown increased HBsAg and cccDNA (HBsAg PXB-siFAH/-siNNMT, 1.58/1.33 folds; $p < 0.05$). In HepG2.D11 cells, knockdown of FAH and NNMT also raised HBsAg and HBV DNA ($p < 0.05$). scRNAseq showed high expression of both FAH and NNMT in the liver, particularly in hepatocytes. Of the two genes, FAH is the enzyme catalyzing hydrolysis into fumaric acid. In HepG2.D11 cells, dimethyl fumarate reduced HBsAg and HBV DNA (HBV DNA, 0.72 folds; $p < 0.05$).

Conclusion: Our study identified novel antiviral host factors, FAH and NNMT, that reduce HBV cccDNA levels using in vitro HBV infection assay systems in primary human hepatocytes. Comprehensive functional screening unveiled a couple of undefined host factors contributing to the control of viral infection independently of STAT1.

ACLF1 Recent Changes of Incidence and Etiology of Acute Liver Failure in Asia Pacific Region

ACLF1-2

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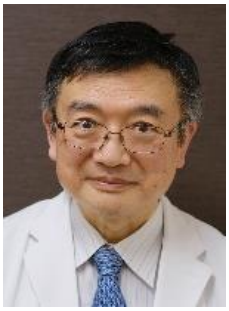
Recent changes of incidence and epidemiology of acute liver failure in Asia-Pacific region

There is no international registry of acute liver failure (ALF) in the Asia-Pacific region. Instead, data on the outcomes of ALF are available by referring to published studies on ALF evaluated in nationwide surveys and at individual centers. In Asia, viral hepatitis has been the main cause of ALF; however recent publications suggest that the incidence of ALF due to drugs and herbs is increasing in most countries (Jindal et al., 2022). Pan Zhao et al. reported in 2013 that traditional Chinese medicine was a major cause of ALF in China. In India, HEV was the etiology of ALF in 419 (28.7%) cases, whereas non-A non-E hepatitis, HBV, and antituberculosis therapy were the etiologies in 527 (36.0%), 128 (8.8%), and 103 (7.0%) cases, respectively (Shalimar et al., 2017). A large study by the Indian DILI Network disclosed that antituberculosis drugs (62.9%) were the most common types of drugs that had caused ALF (Devarbhavi et al., 2021). In South Korea, according to the prevalence of HAV infection, the number of HAV ALF cases requiring liver transplantation were increasing (Kim, 2010). In Australia, paracetamol was the most common etiology of ALF, accounting for 49.7% of cases (Hey et al., 2019).

The Intractable Hepato-Biliary Diseases Study Group of Japan conducted a nationwide survey on ALF and late-onset hepatic failure (LOHF) since 2011. Until 2011, they had performed such surveys on fulminant hepatitis and LOHF. A total of 2,368 patients with fulminant hepatitis and/or acute liver failure (acute and subacute) and 172 patients with LOHF were enrolled in nationwide surveys. In cases seen from 1998 to 2009, the viral etiology in the acute type of hepatitis accounted for 67.4%, whereas from 2010 to 2015, it decreased to 32.7% for overall cases of the acute type and 43.8% for hepatitis cases specifically. In the years 2016 to 2021, the respective percentages further declined to 26.9% and 39.1%, indicating a continued decrease in viral etiology rates. During that period, HBV was the etiology for 92 cases, representing 15.9% of the total cases of ALF (acute and subacute) and LOHF, and 20.2% of hepatitis cases. In cases of hepatitis, the ratios of autoimmune and drug-induced etiologies were 8.1% and 11.6%, respectively, for the period 1998 to 2009. However, in the years 2010 to 2015, these ratios increased to 14.4% and 11.0%, and further rose to 16.9% and 16.6% during the period from 2016 to 2021.

ACLF1 Recent Changes of Incidence and Etiology of Acute Liver Failure in Asia Pacific Region

ACLF1-4



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Japanese style artificial liver support system

Japan is a country where blood purification therapy is most advanced than any other countries in the world. The reason for this is the development of Japanese industrial technology and the harsh environment surrounding transplant medicine. In Japan, blood purification therapy that can keep a patient awake and in a stable condition is essential. In the Japanese medical environment, a requirement for blood purification therapy is the ability to reliably awaken patients and maintain them in a stable state. The method developed for this purpose is blood purification therapy that combines plasma exchange and hemodiafiltration. The characteristics of hemodiafiltration are that blood is purified using a large amount of replacement fluid and that blood purification takes a long time. Even though method of hemodiafiltration is the same, the conditions are very different from those used for renal replacement therapy. Since using this treatment, most patients have recovered from coma, and it is now possible to safely maintain them until their own livers regenerate or a suitable donor is found. Today, the number of elderly patients with comorbidities is increasing, and it is difficult to perform dialysis under strict dialysis conditions for such patients. Due to these circumstances, there are a certain number of patients with acute liver failure who do not undergo blood purification in recent years. In the future, it is necessary to improve vascular access and develop blood purification therapy that is easy to do.

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Summary

ACLF2 Treatments and Prognosis of ACLF in Asia Pacific Region

ACLF2 Treatments and Prognosis of ACLF in Asia Pacific Region

ACLF2-1

Dr. Chia-Yen Dai

Management of acute-on chronic liver failure (ACLF)

Liver failure is a common medical ailment and its incidence is increasing. It can present as acute-on chronic liver failure (ACLF): an acute deterioration of known or unknown chronic liver disease. ACLF is a clinical syndrome manifesting as acute and severe hepatic derangements resulting from varied insults. ACLF is a distinct entity where acute hepatic decompensation occurs in an established chronic liver disease or cirrhosis patient on exposure to acute insult in a defined time frame resulting in a high short-term mortality. Acute-on-chronic liver failure (ACLF) is a syndrome of hepatic decompensation (jaundice, coagulopathy, ascites, and/or HE), where the insult is only hepatic and leads to liver failure in a period of 4 weeks. Jaundice and coagulopathy precede the development of ascites. Non-hepatic organ failure, i.e., AKI, sepsis, AVB develops after the ACLF syndrome or less commonly, with the onset, depending on the severity of liver failure. The acute events in ACLF include infection, autoimmune liver disease, or acute variceal bleeding. Accurate and reliable assessment of underlying CLD in the setting of ACLF is important for the subsequent management and need for liver transplants in these patients. The disease severity assessment is needed for prognostication and to guide the therapy. Several prognostic models and disease severity scores for ACLF have been developed. From Taiwan's reports, the AARC score at day 14 is an independent risk factor for mortality in ACLF. For 28-day and overall mortality prediction of patients with ACLF admitted to the ICU, APACHEIII, and CLIF-C ACLF scores might outperform other models. Antiviral therapy should be started immediately in ACLF HBV reactivation and liver transplantation, for patients with advanced ACLF also having good outcomes, should be offered early in the course of ACLF. Excellent outcomes have been reported in living donor Liver transplantation for patients with ACLF with 90-day, 3-year, and 5-year survival rates of 97.3%, 95.5%, and 92.9% with is similar to those of non-ACLF groups: 96.9%, 94.2%, and 91.1%, respectively. Plasma exchange was superior to standard medical therapy for 30- and 90-day survival for ACLF in the systematic review and meta-analysis. Attempts to abrogate, ameliorate, or reverse the ongoing injury would allow the return of hepatic synthetic functions and the reversal of the liver damage. Early predictors of mortality and non-reversibility of the condition would pave the way to offer priority liver transplantation to such patients.

ACLF2 Treatments and Prognosis of ACLF in Asia Pacific Region

ACLF2-2

Dr. Akash Shukla

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Hepatology, Sir HN Reliance Foundation Hospital, Mumbai

India

Management of vascular disorders in patients with ACLF

Vascular liver diseases like portal vein thrombosis (PVT) or Budd Chiari syndrome (BCS) may present with acute on chronic liver failure (ACLF). The possible associations of PVT with ACLF (PVT-ACLF) have been recently described and the principles of management of these patients proposed. The treatment options for PVT in this setting would include observation, anticoagulation and/or radiological interventions like thrombolysis and thrombectomy. The choice of therapy would depend upon the extent of thrombosis and the clinical consequences of PVT. The other vascular disease is BCS, where association with ACLF (BCS-ACLF) and its management is described. While we know that acute on chronic BCS is associated with poor outcomes, there is recent data on clinical features and management of BCS-ACLF. In patients with ACLF where the acute event is vascular thrombosis like PVT or hepatic vein thrombosis (HVT), there is a potential for reversibility of liver failure, especially in the 'golden window', similar to other ACLF, and all attempts need to be made towards urgent recanalization of these vein(s), while in patients with pre-existing BCS or cirrhosis with PVT who present with ACLF, liver transplant may be the best option.

ACLF2 Treatments and Prognosis of ACLF in Asia Pacific Region

ACLF2-3

Dr. Madhumita Premkumar

Department of Hepatology

Postgraduate Institute of Medical Education and Research

Chandigarh

Treatments and Prognosis of ACLF in Asia Pacific Region

Acute on chronic liver failure is associated with a state of persistent inflammation and immune dysregulation in patients with underlying liver disease, collectively driving a systemic inflammatory response syndrome which results in an increase propensity to sepsis and secondary organ failures. Prevention of ACLF, recognition of sepsis, and treatment of organ failures are key in improving the prognosis of such patients. Although liver transplantation is the definitive modality of treatment, given the organ shortage and limited resources, the need for new therapies to improve ACLF outcomes in Asia is crucial. We need to identify mechanistic drivers to improve the prognosis of patients with ACLF. If patients are selected carefully during the permissive window of clinical presentation even non transplant modalities such as plasmaexchange, antivirals, steroid therapy, etc can have encouraging outcomes once the underlying etiology of ACLF and the acute precipitant are controlled. Despite advances, ACLF remains a challenge in the field of hepatology with considerable research needed to improve upon the prevention, prognostication, and treatment modalities.

APASL 2024 Kyoto

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Summary

ACLF3 Liver Regeneration up to date

ACLF3 Liver Regeneration up to date

ACLF3-1

Dr. Kuo-Chao Yew

Gastroenterology and Hepatology Department Tan Tock Seng Hospital

Singapore

Revolutionising Liver Health: The Science and Potential of Liver Regeneration

The liver's extraordinary regenerative capability, coordinated by the intricate "Hepatostat" system, maintaining a consistent liver-to-body-weight ratio, sets it apart from other organs. Prominently demonstrated in partial hepatectomy, this regenerative capability offers profound insights into harnessing natural regenerative potential and serves as a tissue engineering model. However, chronic liver diseases disrupt this equilibrium, causing hepatocyte depletion, hepatic stellate cell activation, and collagen buildup, while genotoxic environments can trigger liver oncogenesis through cellular diploidy induction.

In contemporary times, significant strides have been taken in comprehending cellular kinetics, histological transformations, and signalling pathways pivotal in liver regeneration. Moreover, understanding zone-specific initiation unravels the precise orchestration of diverse soluble factors governing liver zonation. The identification of progenitor cells opens doors to innovative therapies involving cellular, drug, and gene manipulation. Excitingly, the past decade has witnessed breakthroughs such as bioengineered livers for disease modelling, 3D printing in liver transplantation, and integration of artificial intelligence, signifying newfound enthusiasm in the field.

This lecture delves into the potential of liver regeneration, providing a glimpse into the promising future of Hepatology.

ACLF3 Liver Regeneration up to date

ACLF3-2

Dr. Taro Takami

Department of Gastroenterology and Hepatology, Yamaguchi University Graduate School of Medicine

Japan

Development of self-contained liver cirrhosis regeneration therapy for decompensated liver cirrhosis

Hepatitis C has been the most common cause of cirrhosis in the past, but now alcohol consumption is the most common cause and fatty liver disease is steadily increasing. In 2023, the concept of steatotic liver disease (SLD) was proposed, which includes the replacement of the word "fatty" with "steatotic. Thus, cirrhosis caused by SLD is expected to increase from hepatitis viruses in the future, and the development of hepatocellular carcinoma surveillance methods and antifibrotic therapy are needed. So far, we have developed a less invasive liver regeneration therapy using autologous bone marrow mesenchymal stem cells (MSCs) based on "autologous bone marrow cell infusion (ABMi) therapy (non-cultured, bone marrow mononuclear cell fractionation, peripheral intravenous infusion)" as a liver regeneration therapy for decompensated liver cirrhosis, and from September 2020, " self-contained liver cirrhosis regeneration therapy (robot culture with new culture medium, Bone marrow MSCs, hepatic artery administration)" is being conducted as a clinical trial (jRCT2063200014). Through research to elucidate the mechanism of action of bone marrow MSCs, he has reported (1) enhanced MMP activity by changing the polarity of intrahepatic inflammatory macrophages, (2) decreased fat deposition by increasing β-oxidation, and (3) downregulated liver fibrosis-related genes of hepatic stellate cells by MSC-extracellular vesicle (EV) derived micro RNAs. We have also confirmed that MSC-EVs improved liver fibrosis and fat deposition in SLD-related cirrhotic murine livers by a Gubra-Amylin-NASH (GAN) diet and a single injection of carbon tetrachloride. Thus, liver regeneration therapy using MSCs might be able to be effective treatment for decompensated liver cirrhosis including SLD-related liver cirrhosis.

ACLF3 Liver Regeneration up to date

ACLF3-3

Dr. Shuji Terai

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Niigata University

Japan

Development of Regenerative Therapy for Liver Cirrhosis -Mesenchymal stem cells, HMGB1 peptide, extracellular vesicles-

We have been developing regenerative therapies for liver cirrhosis. The liver is a regenerative organ, but fibrosis reduces its regenerative capacity, and a clinical study in 2003 and a subsequent multicenter clinical study (Autologous bone marrow cell infusion therapy) showed that improvement of fibrosis induces regeneration in patients with non-compensated liver cirrhosis. Subsequently, since 2015, conducted a clinical trial for cirrhosis using allogeneic mesenchymal stem cells. From a series of basic studies. The mechanism was clarified that mesenchymal stem cells administered from peripheral blood vessels repopulated mainly to the lungs, where they emit extracellular vesicles, making macrophages anti-inflammatory, improving fibrosis, and inducing regeneration. Furthermore, extracellular vesicles obtained by induction of mesenchymal stem cells with IFNγ were found to be useful for improving fibrosis and inducing regeneration. On the other hand, the optimization of the liver fibrosis evaluation method in clinical trials for liver cirrhosis has also been clarified by conducting clinical trials of mesenchymal stem cells and HMGB1 peptide as a corporate clinical trial and an investigator-initiated clinical trial. In the future, we are preparing to establish an international standard for how extracellular vesicles can be used as a treatment that maintains clear quality in terms of Mode of Action.

In this presentation, we will present the future perspective of a new regenerative therapy for liver cirrhosis.

ACLF3 Liver Regeneration up to date

ACLF3-4

Dr. Si Hyun Bae

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The Catholic University Liver Research Center

Korea

Next-Generation Stem Cell Therapeutics for the Treatment of Liver Cirrhosis: from bench to bedside based on Functional Enhancement System

Liver cirrhosis are common clinical manifestations of advanced liver diseases. Currently, liver allograft transplantation is the gold standard for the treatment of end-stage liver disease. A shortage of suitable organs, high costs and surgical complications limit the application of liver transplantation. Nowadays, stem cell therapy gained more and more attention due to its attractive efficacy in treating liver disease especially in cirrhosis during the clinical trials. Due to the regenerative properties of the liver, various kinds of cell therapies using hepatocytes, hematopoietic stem cells, bone marrow mononuclear cells, and mesenchymal stem cells (MSCs) are being investigated as alternative treatments to liver transplantation.

Among them, Mesenchymal stem cell therapy has been considered as a promising alternative approach for end-stage liver disease, because they show potential to regenerate injured tissues or organs, such as homing, transdifferentiation, immunosuppression, and cellular protective capacity.

Some clinical trials have confirmed the effectiveness of MSC therapy for liver disease, but currently, there is no approved MSC therapy for the treatment of liver disease, because the types of liver disease that are most suitable for MSC application should be determined, and the preparation and engraftment of MSCs should be standardized. These may be bottlenecks that limit the use of MSCs.

More robust preclinical and clinical studies will be needed for the key strategies to enhance the functionality of MSC which include priming factors such as cytokines, genetic modification, and tissue engineering treatments for liver diseases. In the future, each method has its advantages and challenges, and researchers continue to explore the most effective and safe approaches for liver regeneration using MSCs.

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Summary

ACLF4 Drug Induced Liver Injury in Asia Pacific Region (Including Herbs)

ACLF4 Drug Induced Liver Injury in Asia Pacific Region (Including Herbs)

ACLF4-2

Dr. Hayato Nakagawa

Department of Gastroenterology and Hepatology, Mie University

Japan

Unraveling the Pathophysiology of ICI-Induced Immune-Mediated Hepatotoxicity through a Comparison with Autoimmune Hepatitis

Autoimmune hepatitis (AIH), although a well-known disease, still lacks sufficient understanding of its pathogenesis. Additionally, there is a need for the development of biomarkers, especially for cases resistant to steroids or experiencing relapse. On the other hand, advancements in cancer immunotherapy have brought forth a new concern—immune-mediated hepatotoxicity induced by immune checkpoint inhibitors (ICI), known as ICI-induced immune-mediated hepatotoxicity (IMH). Given its recent emergence, the pathophysiology of IMH remains unclear, and established treatment methods are yet to be defined. While steroids are the primary choice for IMH treatment, resistance cases are frequent compared to AIH. In such instances, empirical recommendations include agents like mycophenolate mofetil, but definitive evidence is lacking.

The anticipation of the growing importance of immunotherapy in the future underscores the urgency for understanding the pathophysiology of these conditions. As part of our efforts in what we term "next-generation precision medicine," we have conducted multi-omics analyses using liver tissues from AIH patients for pathophysiological insights and biomarker development. Currently, we are integrating multi-omics data, including liver biopsy samples from IMH, which shares commonalities with immune-related liver disorders. Through this comprehensive analysis, incorporating the transcriptome data from AIH alongside IMH samples, we aim to elucidate the pathophysiology of both conditions and identify biomarkers. In this session, I will present a portion of this data.

ACLF4 Drug Induced Liver Injury in Asia Pacific Region (Including Herbs)

ACLF4-3

Dr. Yock Young Dan

Dept of Medicine. National University of Singapore

Singapore

Drug Induced Liver injury in Asia-Pacific Region

Drug-induced liver injury (DILI) is a heterogeneous group of liver diseases where the aetiology is ascribed to the administration of a drug or herbal medication resulting in liver injury. The manifestation is protean and ranges from non-specific raised aminotransferase to acute liver or chronic liver disease. It is believed that the incidence and prevalence are higher in Asian countries due to the higher use of tuberculosis drugs and traditional herbal medication. The high prevalence of Hepatitis B and C, genetic variability in multiethnic heterogeneous population in Asia, suspected underreporting of DILI and lack of unified database all contribute to lack of coherent strategy to DILI in Asia. The common drugs and herbs reported to cause DILI in Asia will be discussed with regards to their underlying pathogenesis and common manifestations.

ACLF4 Drug Induced Liver Injury in Asia Pacific Region (Including Herbs)
ACLF4-4

Dr. Hiroteru Kamimura
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Japan

Analysis of International Comparisons of Drug-induced Liver-related Adverse Event Reports in FDA and PMDA Databases

Aim: This study aimed to analyze the current trends of drug-induced liver-related adverse events in the Food and Drug Administration Adverse Event Reporting System (FAERS) and Japanese Adverse Drug Event Report (JADER) databases.

Methods: The characteristics of implicated drugs were investigated by analyzing big data on drug-induced liver-related adverse events over the past 20 years in FAERS, comparing drug rankings between the JADER and FAERS databases, and calculating rankings of drugs inducing liver-related adverse events using the Medical Dictionary for Regulatory Activities Terminology.

Results: In the 452 272 cases registered in FAERS from 1997 to 2019, warfarin, paracetamol, and adalimumab were the drugs most related to drug-induced liver injury (DILI). In the 38 919 cases registered in JADER from 2004 to 2019, sorafenib, nivolumab, and herbal extracts were the drugs most related to DILI. No associations were found between the top 30 drugs in either of the two databases. Notably, the number of drug-induced liver-related adverse event reports and total adverse events has sharply increased in recent years.
Post-marketing surveillance reporting may contribute to rankings in JADER, even when considering severity at the time of reporting and outcomes after reporting.

Conclusions: Although liver-related adverse events are largely caused by host immunity and other constitutional factors, differences in primary diseases, countries, and historical backgrounds lead to differences in the number of reports. An international comparison suggested that the rapidity of the reporter and reporting form using mobile devices may have contributed to this.

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Summary

Portal Hypertension1 Elastography: Current Strategy for Practical Care

Portal Hypertension1 Elastography: Current Strategy for Practical Care

PH1-1

Dr. Grace Lai-Hung Wong
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Role of Elastography in Hepatitis Elimination

Elastography is one the most popular noninvasive assessments of liver fibrosis in patients with chronic viral hepatitis. Specifically, Vibration controlled transient elastography (VCTE) is now an integral part of the clinical care pathway of chronic viral hepatitis in order to determine the prognosis, the need of treatment, as well as monitor disease progression and response to treatment. As alanine aminotransferase (ALT) is one of the major confounding factors of liver stiffness in chronic hepatitis B, an ALT-based algorithm has been developed and higher liver stiffness measurements (LSM) cutoff values for different stages of liver fibrosis should be used in patients with elevated ALT levels up to 5 times of the upper limit of normal. Otherwise falsely-high LSM results up to cirrhotic range may occur during ALT flare. VCTE is also useful in predicting patient prognosis such as development of hepatocellular carcinoma (HCC), portal hypertension, post-operative complications in HCC patients, and also survival. Failed acquisition of VCTE may happen up to 25% in obese patients. Furthermore, obese patients may have higher LSM results even in the same stage of liver fibrosis. The XL probe, a larger probe with lower ultrasound frequency and deeper penetration, increases the success rate of VCTE in obese patients. The median LSM value with XL probe was found to be lower than that by the conventional M probe, hence cutoff values approximately 1.2 to 1.3 kPa lower than those of M probe should be adopted. Recent studies revealed a novel ultrasonic controlled attenuation parameter (CAP) of the machine is a useful parameter to detect even low-grade steatosis noninvasively. CAP may also be used to quantify liver steatosis by applying different cutoff values. As both LSM and CAP results are instantly available at same measurement, this makes VCTE a very convenient tool to assess any patients who are at risk or confirmed to suffer from chronic liver diseases.

Portal Hypertension1 Elastography: Current Strategy for Practical Care

PH1-2

Dr. Hidekatsu Kuroda

Department of Gastroenterology, Division of Internal Medicine, Iwate Medical University School of Medicine

Japam

Advances in ultrasound diagnosis in chronic liver diseases using LOGIQ E10x

In the field of chronic liver disease (CLD) diagnosis, the evolution of ultrasound technology has been remarkable. Not only has there been an improvement in image quality, but also many features have been incorporated to assist in addressing the challenges of objectivity and reproducibility that were inherent in ultrasound. These features include quantification and standardization of numerical values. This article provides an overview of how hepatologists leverage these functions from the perspective of liver specialists and how they are applied in routine clinical practice.

Portal Hypertension1 Elastography: Current Strategy for Practical Care

PH1-3

Dr. Masashi Hirooka

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Japan

Clinical utility of the liver and spleen stiffness measurement in the patients with portal hypertension

Portal hypertension is a critical condition often associated with complications such as varices and ascites, making measurement of the hepatic venous pressure gradient (HVPG) a well-established surrogate marker. HVPG measurement allows prediction of complications associated with cirrhosis, including varices and ascites. According to the Baveno VII criteria, liver stiffness measurement (LSM) plays a crucial role in the diagnosis of clinically significant portal hypertension (CSPH). LSM values below 10 kPa effectively rule out compensated advanced chronic liver disease (cACLD), while LSM values between 15 kPa and a platelet count of 150,000 or greater may rule out CSPH. LSM values above 25 kPa suggest the presence of CSPH. However, the challenge lies in the "gray zone" cases that cannot be definitively categorized using these criteria.

To overcome this limitation and reduce the gray area, markers that correlate better with HVPG than LSM are needed. The spleen, which is emerging as a potential marker, shows a promising role in the assessment of HVPG. Spleen stiffness measurement (SSM) has been reported to correlate better with HVPG than liver stiffness and various fibrosis markers, with a high predictive ability for high-risk esophageal varices.

Our research group, the Spleen Stiffness-IPD-MA Study Group, conducted a systematic review and meta-analysis of individual patient data and reported the favorable diagnostic performance of the Baveno VII SSM criteria. Despite the promising results, accurate measurement of SSM poses challenges compared to LSM. Proper measurement techniques, including the use of new devices and accurate assessment of low controlled attenuation parameter (CAP) values, can improve the reliability of SSM measurements.

In conclusion, our findings suggest the potential of SSM as a valuable marker in the prediction of portal hypertension complications when added to LSM.

Portal Hypertension1 Elastography: Current Strategy for Practical Care

PH1-4

Dr. Xiaolong Qi

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China

Emerging non-invasive methods for evaluation of cirrhotic portal hypertension

Clinically significant portal hypertension (CSPH) is associated with symptomatic gastro-oesophageal varices (GOV), the development of hyperdynamic circulation, and patients with compensated advanced chronic liver disease at risk of clinical decompensation. Hepatic venous pressure gradient (HVPG) measurement and esophagogastroduodenoscopy are the gold standard methods for assessing CSPH (HVPG ≥10 mm Hg) and GOV, respectively. However, they are limited by their invasiveness in clinical practice. In recently years, there are a lot of new technologies focuses on the development of non-invasive approaches to the diagnosis and serial monitoring of portal hypertension.

Imaging techniques used for portal hypertension include ultrasound, computed tomography (CT) and magnetic resonance (MR). Elastography techniques measure liver and spleen stiffness by quantifying the velocity of an induced shear wave, including transient elastography, point-shear wave elastography, and two-dimension shear wave elastography; and MR elastography. Liver stiffness measurement has been proved to be sufficiently accurate to identify CSPH and safe to screen high-risk varices combined with platelet count in clinical practice. Laboratory tests and serum markers need to be interpreted critically because some of their individual components can be affected by a variety of comorbidities. Artificial intelligence (AI) has made great strides in the field of medicine. Information of CT and MR imaging can be integrated and applied to detection of cirrhosis and portal hypertension by AI.

In summary, a wide spectrum of novel non-invasive tests have emerged and represent a major advantage in the assessment of portal hypertension. However, there are still many challenges to integrating non-invasive screening methods into clinical practice, and more data are needed to establish consensus on standard practice and implementation.

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Summary

Portal Hypertension2 Management of Portal Hypertension: Standard and Beyond

Portal Hypertension2 Management of Portal Hypertension: Standard and Beyond

PH2-1

Dr. Cosmas Rinaldi Adithya Lesmana

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Innovation Management in Portal Hypertension: Standard and Beyond

Portal hypertension (PH) is still a challenging condition in daily practice as it carries a lot of complications, such as the presence of vascular complication (esophageal varices/EV, gastric varices/GV, gastric antral vascular ectasia/GAVE, gastropathy, colopathy, rectal varices), ascites, hepatic encephalopathy, hepatorenal syndrome, and hepatopulmonary syndrome. The diagnosis of PH is confirmed when the portal pressure reaches 5 mmHg and above. Clinically significant portal hypertension (CSPH) is the most important condition in liver cirrhosis (LC) patients, as it can predict the possible complications arise, and to decide further management including porto-systemic shunting procedure and liver transplantation. However, the gold standard for PH is the indirect measurement, hepatic vein pressure gradient (HVPG) measurement. Even though this procedure is considered as a safe and minimally invasive, but possible adverse events, such as bleeding, pain, infection, and perforation could still happen. It is not always accurate in the setting of non-cirrhotic portal hypertension condition. This procedure is also cannot be performed concomitantly with esophagogastroduodenoscopy (EGD) procedure.

Recently, endoscopic ultrasound (EUS) has been developed for managing liver disease condition. There have been innovations in measuring portal pressure using a novel manometer as well as standard manometer. EUS can be used for portal pressure gradient measurement, where it is a direct measurement, and it can be done with other innovation procedures, such as EUS-guided liver biopsy, EUS-guided vascular injection, and EUS-guided radiofrequency ablation (RFA) for liver tumor. It would need a special training and further validation before it can be recommended as the first-line approach in the future.

Portal Hypertension2 Management of Portal Hypertension: Standard and Beyond

PH2-3

Dr. Akira Yamamoto

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Department of Diagnostic and Interventional Radiology

Japan

Interventional Radiology for Portosystemic Shunt Related Disease

Interventional radiology for portosystemic shunt related diseases addresses embolization of portosystemic shunts (PSS) causing varices and hepatic encephalopathy. Balloon occluded retrograde transvenous venography (BRTO) for a treatment for gastric varices, a form of PSS, has been reported to improve liver function. In recent years, studies have suggested that the more liver function is preserved prior to treatment, the better liver function improves. This presentation will discuss embolization of large PSS and its results, as well as our approach in cases of encephalopathy with PSS with poor liver function.

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Summary

Portal Hypertension 3 Cross Talk with Multiple Organs in Cirrhosis

Portal Hypertension 3 Cross Talk with Multiple Organs in Cirrhosis

PH3-1

Dr. Masanori Atsukawa

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Japan

Impact of 2022 ESC/ERS diagnostic criteria for pulmonary hypertension in cirrhotic patients with portal hypertension in Japan

Portopulmonary hypertension (PoPH) is defined as PAH associated with portal hypertension. So far, conventional PoPH was defined as a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg, pulmonary vascular resistance (PVR) > 3 Wood units (WU), and pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg according the previous diagnostic criteria, whereas in 2022, the European guideline for pulmonary hypertension revised the hemodynamic definition of pulmonary hypertension in pre-capillary PH by lowering the mPAP to > 20 mmHg and the PVR to > 2 WU. From now on, prevalence of patients with PoPH according to the new guideline may change among cirrhotic patients with portal hypertension. At Nippon Medical School, 186 patients with liver cirrhosis and portal hypertension were subjected and underwent right heart catheterization in this analysis. The median mPAP, PVR and PAWP were 12.9 mmHg (range, 6.6–40.8), 0.8 WU (range, 0.1–4.5) and 7.5 mmHg (range, 2.2–15.4) respectively. For both diagnostic criteria, many of the 186 patients were below the cut-off values for both mPAP and PVR, respectively (conventional, n = 184; new, n = 182). Two (1.1%) patients had conventional PoPH. In addition, two patients that were not diagnosed as PoPH by the conventional diagnostic criteria were included in the PoPH range by the new diagnostic criteria. For each diagnostic criteria, there were no patients that met only one criterion of mPAP and PVR, and were divided into two groups. mPAP and PVR were significantly but weakly correlated ($p = 7.44 \times 10\text{-}5$, $r = 0.286$). With the new diagnostic criteria of PoPH, there were patients that were not diagnosed with PoPH by conventional diagnostic criteria, resulting in an increase in the number of patients diagnosed with PoPH from 1.1% to 2.2% in this cohort. In particular, it is possible that the change in the cut-off value of PVR was particularly important, since patients with a PVR of 2 to 3 WU were newly diagnosed. As new diagnostic criteria are likely to be adopted in Japan in the future, the number of patients diagnosed with PoPH is expected to increase.

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Portal Hypertension4 Noncirrhotic Portal Hypertension: Current Status and Problem

Portal Hypertension4 Noncirrhotic Portal Hypertension: Current Status and Problem

PH4-1

Dr. KC Sudhamshu

Department of Hepatology, National Academy of Medical Sciences

Nepal

Non cirrhotic portal hypertension: Current status and problem

First described by Banti in 1889, non-cirrhotic portal hypertension (NCPH) refers to a heterogeneous group of liver disorders characterized by portal hypertension, splenomegaly, hypersplenism, and cytopenia in absence of liver cirrhosis. It has been referred to by different names over time such as non-cirrhotic portal fibrosis (Indian subcontinent), hepatoportal sclerosis (West), and idiopathic portal hypertension (Japan). NCPH is diagnosed after excluding other causes of portal vein or hepatic venous outflow tract obstruction. The disease progresses through different phases with symptoms ranging from splenomegaly and anemia to complications of portal hypertension such as gastrointestinal bleeding, ascites.

Later, the term idiopathic non-cirrhotic portal hypertension (INCPH) was proposed by a consensus of experts who introduced a common nomenclature and diagnostic criteria: essentially, the presence of an unexplained portal hypertension and the absence of cirrhosis in liver histology.

Recently, in order to overcome those difficulties and to reach a uniformity in the nomenclature, the term Porto-Sinusoidal Vascular Disease (PSVD) has been proposed by the European Association for the Vascular Liver Disease. Now it is not limited to the exclusion criteria but provides positive diagnostic criteria. The new diagnostic criteria define the diagnosis of PSVD in presence of one of the three following features:

1. At least one specific sign of portal hypertension (gastroesophageal or ectopic varices, porto-systemic collaterals, bleeding due to portal hypertension) in the absence of cirrhosis at an liver biopsy
2. At least one specific histological sign of PSVD (obliterative portal venopathy, nodular regenerative hyperplasia, incomplete septal fibrosis or cirrhosis) and absence of cirrhosis at liver biopsy. As per this criteria there may be absence of signs of portal hypertension);
3. At least one non-specific sign of portal hypertension (ascites, low platelets, splenomegaly) at an adequate liver biopsy and in addition to at least one non-specific histological sign of PSVD (portal tract abnormalities: multiplication, dilation of arteries, periportal vascular channels, and aberrant vessels; architectural disturbance: irregular distribution of the portal tracts and central veins; non-zonal sinusoidal dilation; mild perisinusoidal fibrosis) and to the absence of cirrhosis

The exact cause of INCPH or PSVD remains a mystery, prompting ongoing research. There are no specific tests. Instead, accurate diagnosis relies on a high-quality liver biopsy, and the skilled interpretation of a pathologist. Notably, no treatments specifically aimed at controlling the disease progression have been explored. Currently, the treatment relies on the prevention of complications related to portal hypertension, following current guidelines of cirrhotic portal hypertension.

Dr. Ashish Kumar
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India

Non-cirrhotic Portal Hypertension: Problem and Current Status

Non-cirrhotic portal hypertension (NCPH) is a significant medical condition characterized by increased pressure in the portal vein system, which is not caused by cirrhosis of the liver. This condition is relatively rare compared to cirrhotic portal hypertension but carries substantial clinical implications. My presentation will explore the etiology, pathophysiology, clinical manifestations, diagnosis, and management strategies for NCPH.

Etiology and Pathophysiology

NCPH can arise from a variety of causes, including vascular disorders like portal vein thrombosis, splenic vein thrombosis, or Budd-Chiari syndrome; structural abnormalities like schistosomiasis; and systemic diseases such as sarcoidosis and autoimmune hepatitis. Unlike cirrhotic portal hypertension, where the primary issue is increased resistance to blood flow within the liver, in NCPH, the resistance may occur pre-hepatically (before the liver), intrahepatically (within the liver but not due to cirrhosis), or post-hepatically (after the liver).

The pathophysiology of NCPH involves the disruption of normal portal venous flow due to these varied causes, leading to increased portal pressure. This increase in pressure can lead to the development of collateral vessels and splenomegaly, among other complications.

Clinical Manifestations

Patients with NCPH may present with a range of symptoms. The most common manifestation is gastrointestinal bleeding, typically from esophageal or gastric varices, similar to what is seen in cirrhotic patients. However, patients with NCPH often have preserved liver function. Other presentations can include splenomegaly, ascites (less common than in cirrhosis), and features of hypersplenism like pancytopenia.

Diagnosis

Diagnosis of NCPH requires a combination of clinical, laboratory, and imaging findings. Liver function tests are typically normal or show only mild abnormalities. Imaging studies, such as Doppler ultrasound, CT scan, or MRI, are critical for identifying the site and cause of the increased portal pressure. In some cases, a liver biopsy may be necessary to exclude cirrhosis and to identify intrahepatic causes of NCPH.

Management

Management of NCPH focuses on treating the underlying cause, if identified, and managing complications. Primary prevention of variceal bleeding is essential and can be achieved through pharmacotherapy (e.g., beta-blockers) or endoscopic interventions. In cases of variceal bleeding, endoscopic therapy is the mainstay of treatment. Additionally, management of hypersplenism and its hematologic complications may be necessary.

In cases where medical management is inadequate, surgical options such as shunt surgeries or even liver transplantation may be considered, depending on the underlying pathology and patient's overall condition.

Conclusion

Non-cirrhotic portal hypertension is a complex condition with diverse etiologies and manifestations. Its management requires a thorough understanding of its pathophysiology and a multidisciplinary approach. Early recognition and appropriate intervention are key to improving outcomes in patients with NCPH. Further research is needed to better understand this condition and to develop more effective management strategies.

Portal Hypertension4 Noncirrhotic Portal Hypertension: Current Status and Problem

PH4-3

Dr. Manoj Kumar Sharma

Department of Hepatology and Liver Transplantation Institute of Liver and Biliary Sciences

India

Porto-sinusoidal vascular disease: Histological spectrum and hemodynamic correlation

The diagnosis of porto-sinusoidal vascular disease (PSVD) is based on liver biopsy (without cirrhosis), with or without portal hypertension, with normal or mildly elevated liver stiffness values and no complete portal vein thrombosis. Three defined histological entities [—ie, obliterative portal venopathy, nodular regenerative hyperplasia, and incomplete septal cirrhosis] entities are specific enough to be regarded as diagnostic for porto-sinusoidal vascular disease even in the absence of any clinical, imaging, or laboratory features of portal hypertension. Other pathological features are often associated with these three entities and are important to recognise, because they can provide essential information to support diagnosis of porto-sinusoidal vascular disease. A clinical scenario of autoimmune, haematological, or prothrombotic disease support the diagnosis. Hepatic venous pressure gradient (HVPG) and transient elastography (TE-LSM; FibroScan) are usually normal or mildly elevated in PSVD. There are subset of cases that can have elevated HVPG and TE. In our recent study we found that cases of obliterative portal venopathy with bridging and incomplete septal cirrhosis can have high HVPG. Crowding of reticulin fibres, scattered collagen bundles, and hyperplasia of hepatocytes with the higher fibrosis contents can cause intrahepatic flow resistance and elevation of HVPG in these conditions. This is linked to a higher fibrosis content in these groups. While patients with mega sinusoids and fibrosis (MSF) and nodular regenerative hyperplasia may have higher TE values, the fibrosis content was not found to be higher in these patients. It suggests that TE in these categories is spuriously elevated. The increased fibroscan value could be due to an architectural remodel in nodular regenerative hyperplasia. Wide spaces with plasma content in the lumen and a thin rim of fibrosis along the sinusoids in MSF cases can altogether cause a falsely raised TE.

Portal Hypertension4 Noncirrhotic Portal Hypertension: Current Status and Problem

PH4-4

Dr. Hisashi Hidaka

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Japan

Noncirrhotic Portal Hypertension: Current Status and Problem

Non cirrhotic portal hypertension (NCPH) is a clinicopathologic disease characterized by the presence of clinical signs and symptoms of portal hypertension (PH) in the absence of liver cirrhosis (LC). NCPH has been referred to as PSVD (porto-sinusoidal vascular disease). Three histologic features have been identified: obstructive portal vein, nodular regenerative hyperplasia, and incomplete septal fibrosis. Furthermore, it is submitted that the presence or absence of complications of PH is not required. On the other hand, the cause of PSVD remains unknown in most cases. However, future studies may reveal genetic alterations and molecular mechanisms associated with this disease. Treatments of complications of PH in PSVD and LC are similar. For esophageal varices, EVL treatments and nonselective beta blockers are used. For isolated gastric varices, BRTO is almost always the first choice. Thrombocytopenia is often treated with splenectomy, partial splenic embolization. Although thrombopoietin receptor agonists is used for thrombocytopenia in LC, it is not used for PSVD. Furthermore, development of HCC is extremely rare. It is known that hyperplastic nodules sometimes develop in PSVD. This phenomenon is thought to involve the following mechanisms. Marked narrowing of peripheral portal veins induces atrophy of hepatocytes. Blood flow of patent portal veins and aberrant vessels increases compensatory, causing hyperplasia of hepatic lobules adjacent to atrophic lobules. In my lecture, I would like to focus on the pathogenesis, diagnosis of PSVD, and the treatments of its complications including the differences from LC.

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The 33rd Annual Meeting the Asian Pacific Association for the Study of the Liver

Summary

Portal Hypertension5 Cirrhosis Care Emerging Changes

Portal Hypertension5 Cirrhosis Care Emerging Changes

PH5-1

Dr. Takumi Kawaguchi

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Japan

Effects of Exercise on Physical Function and Prognosis of Patients with Liver Cirrhosis and HCC

Sarcopenia and frailty are highly prevalent in patients with liver cirrhosis and hepatocellular carcinoma (HCC). Generally, the beneficial effects of exercise on sarcopenia and frailty have been established. However, opposing results have been reported regarding the effects of exercise on serious events in patients with liver cirrhosis. Due to the lack of scientific evidence, exercise therapy remains weakly recommended in the Japanese clinical practice guidelines for liver cirrhosis.

First, we performed a meta-analysis of randomized controlled trials (RCTs) to examine the effects of exercise on physical function and serious events in patients with liver cirrhosis. A literature search was conducted in 2022. Eleven RCTs were selected for the meta-analysis (exercise group, n=232; control group, n=193). A meta-analysis was performed using a random-effects model. In the eleven RCTs, a meta-analysis demonstrated the 6-minute walking distance significantly improved in the exercise group compared with the control group. Moreover, in a stratification analysis based on a combination of aerobic and resistance exercise, the incidence of serious events was 6.25% and 24.7% in the combination exercise and control groups, respectively. A meta-analysis demonstrated a significant reduction in the incidence of serious events in the combination exercise group compared with the control group.

Next, we investigate the effects of exercise on the prognosis of patients with HCC. We performed a prospective observational study, which analyzed 152 patients with HCC who underwent transcatheter arterial chemoembolization (TACE). Patients were classified into the exercise (n=85) and control (n=67) groups. Independent factors associated with survival were evaluated by Cox regression analysis. There were no exercise-related severe adverse events throughout the study periods. Along with Child-Pugh class A, “exercise” was identified as an independent factor associated with survival in Cox regression analysis. The survival rate was significantly higher in the exercise group than in the control group.

In conclusion, we demonstrated that exercise improved physical function in patients with liver cirrhosis. We further demonstrated that resistance exercise in combination with aerobic exercise reduces serious events in patients with liver cirrhosis by a meta-analysis of RCTs. Moreover, in patients with HCC, exercise had beneficial effects on the prognosis with no worsening of liver function. These findings suggest that exercise therapy should be considered a fundamental therapy for patients with both liver cirrhosis and HCC.

Portal Hypertension5 Cirrhosis Care Emerging Changes

PH5-2

Dr. Necati Örmeci
İstanbul Health and Technology University
Turkey

Cirrhosis Care: Emerging Changes

Cirrhosis is characterized by degeneration, regeneration and fibrosis because of the common end stage in a number of chronic progressive liver diseases. It is an important health and economic problem in the world. Five and a half million patients are affected at a cost of more than $1.5 billion annually in the United States. There is a significant difference in terms of prognosis between compensated and decompensated stages. Acute decompensation- of liver cirrhosis should be prevented. Etiologic factor(s)such as viral, autoimmune, metabolic, alcoholic and toxic should be treated according to guidelines. Smoking, toxic drugs for liver and alcohol should be stopped. Infections should be treated adequately. Vaccinations for HAV, HBV, Influenza, Pneumococcus, Herpes zoster are strictly recommended. Mortal complications like bleeding, ascites, encephalopathy, spontaneous bacterial peritonitis (SBP), acute on chronic liver disease may occur after decompensation of the cirrhosis.

The patients with cirrhosis who have no documented history of previous GI bleeding, and have medium/large varices on endoscopy, should receive either non- selective beta blocker or endoscopic variceal ligation (EVL) within one month of varices diagnosis. If the patients are found to have bleeding esophageal varices, they should receive EVL at the time of index endoscopy. They should receive EVL every 1-2 weeks until obliteration, non-selective beta blockers, or a combination of EVL and non-selective beta blockers to prevent recurrence of variceal hemorrhage.

Ascites is treated with both sodium restriction and diuretics with furosemide (40-160 mg /day) and spironolactone (100-400 mg/day). Patients undergoing large volume paracentesis (>5 liters removed) should receive intravenous albumin, 6-8 grams per liter removed. TİPS can be applied as a vital salvage therapy. SBP, hepatorenal syndrome and hepatic encephalopathy should be managed according to guidelines. Screening for HCC should be performed by ultrasound examinations and AFP in every 6 months. Sarcopenia and nutritional screening should be performed, and nutritional support focusing on late-night snacks, avoiding fasting, high (1 g/kg/day) protein and calorie.

(~30 kcal/kg/day) consumption, increasing physical activity should be recommended. Bone diseases should be screened and managed accordingly. The management of common non-pain symptoms such as pruritus, muscle cramps, sleep disturbances, sexual dysfunction and fatigue should be managed adequately. The patients with cirrhosis and MELD score ≥ 15 should be evaluated for liver transplantation.

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Summary

Portal Hypertension6 Liver fibrosis: from Bench to Bedside

Portal Hypertension6 Liver fibrosis: from Bench to Bedside

PH6-1

Dr. Jordi Gracia-Sancho

Hepatology, IDIBAPS - Hospital Clínic de Barcelona - CIBEREHD

Spain

Liver Fibrosis & Portal Hypertension: Molecular Mechanisms and Therapeutic Opportunities

Portal hypertension represents one of the major clinical consequences of chronic liver disease, having a deep impact in patients' prognosis and survival. Its pathophysiology defines a pathological increase in the intrahepatic vascular resistance as the primary factor in its development, being subsequently aggravated by a paradoxical increase in portal blood inflow. Elevation in vascular resistance derives from de-regulations in hepatic cells function, which leads to the development of intrahepatic vascular dysfunction and fibrosis. Additionally, now we know that hepatic mechanobiological cues actively contribute to aggravate and perpetuate portal hypertension.

Hepatic microvascular dysfunction occurs early in the course of chronic liver disease as a consequence of inflammation and oxidative stress and determines loss of the normal phenotype of liver sinusoidal endothelial cells (LSEC) that become proliferative, pro-thrombotic, pro-inflammatory and vasoconstrictor. The cross-talk between LSEC and hepatic stellate cells (HSC) induces activation of the later, which in turn proliferate, migrate and increase collagen deposition around the sinusoids, contributing to fibrogenesis, architectural disruption and angiogenesis, which further increase the hepatic vascular resistance and worsen liver failure by interfering with the blood perfusion of the liver parenchyma. Moreover, recent data suggest that the phenotype of liver cells could be further impaired due to the altered mechanical properties of the cirrhotic liver itself, therefore creating a deleterious vicious cycle that would further worsen portal hypertension in advanced stages of the disease.

This lecture will critically summarize the current knowledge in portal hypertension pathophysiology, focusing on the intrahepatic mechanisms leading to fibrosis and vascular dysfunction development.

Portal Hypertension6 Liver fibrosis: from Bench to Bedside

PH6-2

Dr. Seung Up Kim

Internal Medicine, Yonsei University

Korea

Association between liver fibrosis and cardiometabolic/liver-related outcomes in steatotic liver disease

My talk includes the association between liver fibrosis and various outcomes related to cardiometabolic health and liver-related complications in individuals with steatotic liver disease, shedding light on the complex interplay between these factors.

Nonalcoholic fatty liver disease (NAFLD) has become a global health concern, driven by sedentary lifestyles and poor dietary habits. My talk focuses on individuals spanning the spectrum of steatotic liver disease, from simple hepatic steatosis to advanced fibrosis. To assess the severity of liver fibrosis, advanced imaging techniques such as elastography and magnetic resonance imaging were employed.

Individuals with advanced fibrosis demonstrated a higher prevalence of hypertension and dyslipidemia, suggesting a potential link between the progression of hepatic fibrosis and systemic cardiovascular health. Further investigations are underway to uncover the underlying mechanisms of this association, offering valuable insights into the intricate relationships between liver health and cardiovascular well-being.

Beyond cardiometabolic outcomes, the research also explores the impact of liver fibrosis on liver-specific complications. Individuals with advanced fibrosis exhibited a substantially elevated risk of hepatic decompensation, including conditions like ascites, hepatic encephalopathy, and variceal bleeding. Moreover, the study delves into the correlation between fibrosis severity and the risk of developing hepatocellular carcinoma, with preliminary data indicating a progressive increase in cancer incidence with advancing fibrosis stages.

The implications of these findings are far-reaching for both clinical practice and public health strategies. Identifying individuals with steatotic liver disease at risk of advanced fibrosis enables targeted interventions to mitigate cardiovascular and liver-related complications. This may involve lifestyle modifications, pharmacological interventions, and emerging anti-fibrotic treatments, all aimed at altering the disease trajectory and improving overall outcomes.

In summary, the comprehensive assessments of cardiometabolic and liver-related outcomes provide a holistic understanding of the condition, enabling effective risk stratification and personalized patient care.

Portal Hypertension6 Liver fibrosis: from Bench to Bedside
PH6-3

Dr. Nobuhiro Nakamoto
Division of Gastroenterology and Hepatology, Department of Internal Medicine,
Keio University School of Medicine
Japan

Immunological mechanisms of MASH resolution

The excessive accumulation of extracellular matrix proteins results in fibrosis—a condition implicated in several diseased conditions, such as metabolic dysfunction-associated steatohepatitis (MASH), viral hepatitis, and autoimmune hepatitis. Despite its prevalence, direct and effective treatments for fibrosis are lacking, warranting the development of better therapeutic strategies. Accumulating evidence has shown that liver fibrosis—a condition previously considered irreversible—is reversible in specific conditions such as hepatitis virus elimination. I On the other hand, the mechanism of fibrosis resolution in MASH, a multifactorial disease, remains unclear. In recent years, it has become clear that not only cell-cell interactions in the liver, including hepatic stellate cells (HSCs), hepatocytes, and macrophages, but also inter-organ interactions with extrahepatic organs, including the small and large intestines, that originate from intestinal bacteria and their metabolites are involved in the pathogenesis of liver fibrosis. Using a murine diet-induced MASH and the subsequent resolution model, we demonstrate direct roles of CD8+ tissue-resident memory CD8+ T (CD8+ Trm) cells in resolving liver fibrosis. Single-cell transcriptome analysis and FACS analysis revealed CD69+CD103−CD8+ Trm cell enrichment in MASH resolution livers. The reduction of liver CD8+ Trm cells, maintained by tissue IL-15, significantly delayed fibrosis resolution, while adoptive transfer of these cells protected mice from fibrosis progression. During resolution, CD8+ Trm cells attracted hepatic stellate cells (HSCs) in a CCR5-dependent manner, and predisposed activated HSCs to FasL-Fas-mediated apoptosis. Histological assessment of patients with MASH revealed CD69+CD8+ Trm abundance in fibrotic areas, further supporting their roles in humans. In this symposium, we will review the recent advances in the development of drugs for MASH and mention the potential for improving liver fibrosis treatment through immune regulation.

Portal Hypertension6 Liver fibrosis: from Bench to Bedside

PH6-4

Dr. Dong Joon Kim

Division of Gastroenterology and Hepatology Department of Internal Medicine

Hallym University College of Medicine

Korea

Liver Fibrosis: Pathophysiology, Clinical Implications, and Therapeutic Perspectives

The progression of chronic liver diseases (CLD), irrespective of etiology, involves persistent inflammation and sustained progression of liver fibrosis. Liver fibrosis is a key determinant for liver disease outcome and risk of hepatocellular carcinoma (HCC).

Although the process of liver fibrosis is influenced by the specific etiology, it is recognized as a common and etiology-independent events despite different mechanism of primary liver injury and disease-specific cell responses. The progression of liver fibrosis follows shared pathophysiology across the main liver disease etiologies.

Scientific discoveries during the last decades have transformed the understanding of the pathophysiology of liver fibrosis. Liver fibrogenesis and fibrinolysis is a dynamic, highly integrated process. It can start with hepatocyte injury and inflammation, which recruits and activates additional liver immune cells, leading to the activation of the hepatic stellate cells (HSCs). HSC is the primary source of myofibroblasts (MFs), which result in collagen synthesis and excessive accumulation of extracellular matrix (ECM) protein.

Removal or elimination of the causative agent such as control or cure of viral infection has shown that liver fibrosis is reversible. However, reversal often occurs too slowly or too infrequent to avoid life-threatening complications particularly in advanced fibrosis. Thus, there is an unmet medical need for anti-fibrotic therapies to prevent liver disease progression and HCC development.

In this presentation the relevant established and/or emerging pathophysiological issues underlying CLD progression will be addressed and their impact for the development of urgently needed anti-fibrotic therapies will be discussed.

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Portal Hypertension7 Portal Hypertension in Unusual Condition

Portal Hypertension7 Portal Hypertension in Unusual Condition

PH7-1

Dr. Hong Soo Kim

Soon Chun Hyang University Hospital, Internal medicine

Korea

How to follow up of patient with act Metabolic dysfunction –associated fatty liver disease (MAFLD)

Metabolic dysfunction–associated fatty liver disease (MAFLD) is the most common cause of chronic liver disease worldwide. MAFLD includes a wide spectrum of liver injury including simple steatosis and non-alcoholic steatohepatitis (NASH) that may lead to serious complications such as liver cirrhosis and liver cancer

The identification of Nonalcoholic steatohepatitis (NASH) or NAFLD is clinically important because NASH indicates an increased risk for fibrosis progression and the need for aggressive treatment and closer follow-up. Population based study suggests that NAFLD is becoming an important cause of HCC, and these rates are increasing by approximately 10% per year. So we needs follow up guideline of patients with NAFLD but there is no accepted consensus on the optimal strategy for monitoring patients with NAFLD and their response to treatment.

According to The Asian Pacifc Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease, patients with NAFLD may need a FibroScan yearly or once every three years. The frequency is dependent on your previous FibroScan results. It is important to distinguish mild (F1-F2) from advanced or severe (F3-F4) fibrosis, as patients with severe fibrosis have a greater risk of complications and need to undergo screening for hepatocellular carcinoma with NAFLD.

Portal Hypertension7 Portal Hypertension in Unusual Condition

PH7-2

Dr. Takuto Hikichi

Department of Endoscopy, Fukushima Medical University Hospital

Japan

Endoscopic Treatment for Esophageal and Gastric Varices in Japan

Esophageal varices (EVs) and gastric varices (GVs) are treated with drug therapy, interventional radiology, and surgical operation, but endoscopic treatment is the mainstay of treatment for patients with bleeding or high risk of bleeding.

Endoscopic treatment for EVs is widespread worldwide, and endoscopic variceal ligation (EVL) is widely used not only for bleeding cases but also for prophylactic cases. In Japan, endoscopic injection sclerotherapy (EIS) using intravariceal injection with ethanolamine oleate (EO) as a sclerosant agent has long been used for prevention of EV rupture. EIS is a treatment to embolize the inflow from portal vein that forms EVs, and theoretically has a low recurrence rate. However, due to the complexity and difficulty of the procedure, an increasing number of centers in Japan are using EVL as the main EV treatment, and EIS is now limited to high-volume centers. To reduce the EV recurrence rate by intravariceal EIS alone, extravariceal EIS with polidocanol has been used after intravariceal EIS. In addition, argon plasma coagulation (APC) after intravariceal EIS or extravariceal EIS is also used in Japan. At our institution, we are trying ablation using high-frequency hemostats as an alternative to APC. As a device for endoscopic treatment of EVs, EIS with ligation, in which the variceal puncture site is ligated during EIS, and EIS with ligation of the perforating vein that causes an extraesophageal shunt have also been performed. Recently, Furuichi et al. reported a technique for reliable intravariceal EIS using red dichromatic imaging, a kind of image enhanced endoscopy (IEE), to estimate the wall thickness and depth of EVs. Moreover, we have been using a technique to improve the success rate of variceal puncture by injecting gel into the esophageal lumen and using texture and color enhancement imaging, which is a kind of IEE.

The Sarin classification is a well-known endoscopic classification of gastric varices (GVs), based on the continuity with EVs and the location of GVs, and is divided into four categories: GOV (gastroesophageal varices)-1, GOV-2, IGV (isolated gastric varices)-1, IGV-2. Among them, GOV-1 is a varix flowing from the gastric cardia to the esophagus, and is defined as EVs in Japan. On the other hand, the Japan Society for Portal Hypertension classifies GVs into Lg-c, Lg-cf, Lg-f, Lg-a, and Lg-b. Lg-c is a varix localized at the gastric cardia, Lg-cf is a varix extending from the cardia to the fornix, and Lg-f is a varix localized at the gastric fornix. Lg-c, Lg-cf, and Lg-f correspond to IGV-1, and Lg-a and Lg-b correspond to IGV-2. In the following, EVs are defined as those corresponding to IGV-1. Endoscopic treatment for GVs is mainly endoscopic cyanoacrylate injection with N-butyl-2-cyanoacrylate (NBCA). In cases of GV hemorrhage, endoscopic cyanoacrylate injection with NBCA is preferred over EVL because of the rapid blood flow. In addition, we have been using endoscopic cyanoacrylate injection combined with intravariceal EIS with EO for prevention of GV rupture. The GV is occluded by NBCA and the inflow is embolized by EO. Furthermore, Irisawa et al. reported the combination of endoscopic-guided coil deployment and intravariceal EIS for prevention of GV rupture.

I will give a presentation on the current status of endoscopic treatment of EVs and GVs in Japan.

Portal Hypertension7 Portal Hypertension in Unusual Condition

PH7-3

Dr. Hiroshi Yoshida

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Japan

Management of portal hypertension based on portal hemodynamics

Portal hypertension is most commonly caused by chronic liver disease. As liver damage progresses, portal pressure gradually elevates and hemodynamics of the portal system gradually change. In normal liver, venous returns from visceral organs join the portal trunk and flow into the liver (hepatopetal blood flow). As portal pressure increases due to liver damage, congestion of some veins of the visceral organ occurs (blood flow to and from). Finally, the direction of some veins (the left gastric vein in particular) of the visceral organ change (hepatofugal blood flow) and develop as collateral veins (portosystemic shunt) to reduce portal pressure. Therefore, esophagogastric varices serve as drainage veins for the portal venous system to reduce the portal pressure.

In chronic liver disease, as intrahepatic vascular resistance is increased (backward flow theory) and collateral veins develop, adequate portal hypertension is required to maintain portal flow into the liver through an increase of blood flow into the portal venous system (forward flow theory). Splanchnic and systemic arterial vasodilatations increase the blood flow into the portal venous system (hyperdynamic state) and lead to portal hypertension and collateral formation. Hyperdynamic state, especially around the spleen, is detected in patients with portal hypertension. The spleen is a regulatory organ that maintains portal flow into the liver.

In this session, surgical treatment, interventional radiology, and endoscopic treatment for portal hypertension (esophagogastric varices in particular) are described based on the portal hemodynamics using schema.

Dr. KC Sudhamshu
Department of Hepatology, National Academy of Medical Sciences
Nepal

Portal Hypertension in unusual condition

Portal hypertension (PH) is defined as increased blood pressure in the portal venous system above 5 mg. Portal hypertension is classified as prehepatic, intrahepatic, and posthepatic. While cirrhosis dominates as the leading cause of PH in routine practice, NCPH and even rarer conditions can also appear in clinical settings. This presentation delves into PH seen in these less common scenarios. Following are the conditions where we can encounter PH

1. Arteriovenous malformations (AVMs)
2. Nodular regenerative hyperplasia (NRH)
3. Pseudocirrhosis
4. Hepatic fibrosis
5. Hepatic amyloidosis

First described in 1886 by Weigert, AVMs are generally uncommon, certain types can indeed contribute to PH. AVMs can be intrahepatic or extrahepaic. Extrahepatic can be of two main types namely mesenteric AVMs and splenic AVMs. Hepatic arterioportal fistulas (HAPFs) are intrahepatic causes of AVMs. It is usually categorized into three classes, as follows: Type 1: small peripheral intrahepatic; Type 2: large central HAPF; and Type 3: diffuse congenital intrahepatic.

NRH is a rare liver disease characterized by the abnormal growth of small, regenerative nodules throughout the liver. Unlike cirrhosis, which features scarring and fibrosis, NRH lacks fibrous septa between the nodules, making it a form of non-cirrhotic portal hypertension. NRH can be seen in autoimmune disorders like systemic lupus erythematosus, vascular diseases such as cystic fibrosis, viral infections and medications like azathioprine or methotrexate.

Pseudocirrhosis is a radiologic term to describe the development of diffuse hepatic nodularity caused by chemotherapy for hepatic metastasis, especially from breast cancer, pancreatic neuroendocrine, colorectal cancer. Portal hypertension can be observed in about 80% of patients with pseudocirrhosis. It is characterized by morphologic changes mimicking liver cirrhosis following chronic liver diseases. Increase in portal flow resistance at any site within the portal venous system due to mechanical obstruction is the plausible mechanism of PH.

Congenital hepatic fibrosis is a rare condition that manifests as intrahepatic bands of fibrous tissue originating in the portal tracts and surrounding multiple bile ductules and this can lead to the development of PH. This pathological finding often co-occurs with a spectrum of inherited renal disorders.

Lastly PH is a rare complication of hepatic amyloidosis and seems to be related to reduced sinusoidal lumen and increased resistance to blood flow due to massive perisinusoidal amyloid deposits.

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Summary

Biliary1 Current Surgical Management of Hilar Cholangiocarcinoma

Biliary1 Current Surgical Management of Hilar Cholangiocarcinoma

Biliary1-1

Dr. Yu Takahashi

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Japanese Foundation for Cancer Research

Japan

Aggressive surgery for advanced perihilar cholangiocarcinoma under careful preoperative preparation ~ a Japanese single-center experience in the past 15 years ~

Perihilar cholangiocarcinoma (PHCC) is a devastating disease, and the required operative resection is technically demanding and remains to be the most difficult challenge for HPB surgeons. Major hepatectomy and extrahepatic bile duct resection has been accepted as the standard procedure. A recent systematic review showed that the mortality rate was approximately 10% and liver failure was the most common reported cause of death. In some Japanese high-volume centers, trisectionectomy of the liver, combined pancreatoduodenectomy or combined vascular resection have been aggressively performed to achieve curative resection. Various preoperative preparations have been made to reduce postoperative mortality. We report here on the preoperative management and surgical outcomes of PHCC over the past 15 years, focusing on the following points:

- Preoperative Management: Biliary drainage (inside-stent) and portal vein embolization
- Hapatopancreatoduodecetomy
- Combined vascular resection
- Left trisectionectomy of the liver

Biliary1 Current Surgical Management of Hilar Cholangiocarcinoma

Biliary1-2

Dr. TanTo Cheung

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Hong Kong SAR, China

Oncological outcomes of patients with intrahepatic cholangiocarcinoma after curative resection – An Experience From Hong Kong

Background/objective: Hepatectomy is the mainstay of curative treatment for intrahepatic cholangiocarcinoma (ICC). The relationship between postoperative complication and oncological outcome has not been defined. We aimed to elucidate the effect of postoperative complication on long-term survival of ICC patients after curative resection.

Methods: Data of consecutive patients who had curative resection for ICC at our hospital from 1991 to 2013 were reviewed. Patients with cholangiohepatocellular carcinoma, metastatic adenocarcinoma or Klaskin tumor were excluded. Clinicopathological data and postoperative events were extracted from database for survival analysis.

Results: There were 107 patients in our series. Their median age was 61 years. The median follow-up time was 24 months. The median tumor size was 6 cm. Major hepatectomy was required in 52.3% of them. The median operation time and blood loss was 439 minutes and 0.9L respectively. R0 resection was achieved in 88.8% of them. The median length of stay was 11 days. The 30-day and 90-day mortality was 2.5% and 6.8% respectively. Major complications were found in 20.6% of them. Patients with postoperative complications had significantly inferior survival than patients without (3-yr DFS 38% vs. 27%, $P = 0.001$; 3-yr overall: 51% vs. 27%, $P < 0.001$). Multivariable analysis showed that postoperative complication was an independent factor associated with disease-free survival (OR 1.9 95% C.I. 1.10-3.24, $P = 0.021$) and overall survival (OR 2.1, 95% C.I. 1.13-3.93, $P = 0.018$).

Conclusion: Postoperative complication has a significant impact on ICC patients' long-term survival. Extra measures such as adjuvant chemotherapy should be considered for patients who develop major complications after surgery.

Biliary1 Current Surgical Management of Hilar Cholangiocarcinoma

Biliary1-3

Dr. Kei Nakagawa

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Japan

Pre- & Post Operative Management of Perihilar Cholangiocarcinoma

Treatment of biliary tract cancer (BTC) begins with a determination of whether the cancer is resectable or not. In resectable cases, radical surgery followed by adjuvant therapy is the standard treatment. Perihilar Cholangiocarcinoma (PHC) is the most invasive surgery among BTC. The results of basic-level resection of PHC at 24 high-volume centers in three countries are reported. Serious complications occurred in more than half of the cases, and a median mortality rate of 7% at 3 months postoperatively was reported.
Safety considerations must be taken into account for surgical indications for PHC.

In preparation for surgical treatment, it is necessary to determine the side to be resected and the surgical procedure to be used. It is important to determine where to resect the bile duct, artery, and portal vein respectively. It is also necessary to properly set the predicted liver dissection plane. MDCT before biliary drainage is permissive for these decisions. This process determines the postoperative course. Identifying the number of bile ducts to be transected is also useful information during anastomosis.

After this decision is made, biliary drainage are often required. In cases requiring massive hepatectomy, preoperative portal vein embolization (PE) is attempted to increase the residual liver volume. PE is expected to increase the volume of the remaining liver by about 20%. (ex. L234, 280 ml → 340 ml) The residual liver volume and the results of the ICG study are combined to avoid postoperative liver failure.

Postoperatively, Ultrasonographic confirmation of hepatic arterial, portal, and venous blood flow is useful. Obstruction of hepatic arteries and impaired hepatic venous return cause rapid liver failure. Increased ascites and coagulation disorder are signs of portal vein thrombosis or infection. Continued surveillance cultures from drain effluent and bile should be performed. When bile leaks occur during hepatic resection with choledocho-jejunostomy, infection and abscesses occur very efficiently. Recovery is difficult if postoperative liver failure or DIC develops. Adequate drainage position is important to maintain leakage of choledocho-jejunostomy and bile leakage from the plane of liver dissection. Endoscopic anastomotic dilation and drainage may be beneficial.

The most important aspect of radical surgery of PHC is the process leading up to resection. Compared to hepatic resection without biliary reconstruction, careful postoperative management is required due to bile leakage and liver positional instability.
Prompt judgment and treatment of any abnormalities is necessary until 2-3 weeks postoperatively, when the liver regenerates and liver function is restored.

Dr. Ko Tomishima
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Japan

Endoscopic Drainage and Diagnosis for Resectable Hilar Cholangiocarcinoma

As endoscopists, it is our responsibility to diagnose indeterminate biliary strictures and evaluate the progression of biliary tract cancer (BTC). The treatment strategy for BTC depends on the tumor site, institution, and patient background. Especially, perihilar cholangiocarcinoma (PHCC) has many variations in the morphology of bile duct branches, and the decision on whether to operate depends on the invasive bile ducts and the skill of the surgeon. Therefore, BTC treatment is difficult to standardize, and factors related to surgical decision making (tumor extension, surgical anatomy, liver reserve, and patients' general condition) are evaluated, but these factors are not always equally distributed. Postoperative bile duct jejunal anastomosis stenosis and bile leakage are problems, and it is the mission of the endoscopist to make an accurate diagnosis and avoid unnecessary surgery. When we diagnose bile duct stricture, we make use of CT, MRCP, EUS, IDUS, and ERCP, appropriately. In the preoperative evaluation of PHCC, the diagnostic accuracy by these image or biopsies varies and difficult to evaluate in cases of wall thickening after biliary drainage or cholangitis. Despite advances in imaging diagnosis, the differential diagnosis of benign and malignant biliary strictures can still be challenging. In recent years, the usefulness of preoperative chemotherapy has also been reported, and a proper preoperative diagnosis and careful decision regarding the timing of surgery are required. To diagnose precise extension of tumor, a pathological diagnosis is necessary along with image diagnosis. Many studies reported diagnostic ability using transpapillary devices. But these methods demonstrated poor sensitivity. The location in the bile duct for mapping biopsy and the number of biopsy samples should be determined depending on resectability, the morphological type, and future surgical planning. Recently, per-oral cholangioscopy (POCS) has become an important tool to diagnose and evaluate the tumor extension by direct visualization and targeted biopsy by POCS. POCS showed an additive effect in the evaluation of the preoperative PHCC, but further improvement is required with more adequate biopsy specimens. As for preoperative biliary drainage, the trend has changed from external drainage (PTBD) to internal drainage (plastic stent) due to the potential risks of seeding metastasis associated with PTBD. ENBD was also recommended, but has the disadvantages of requiring bile replacement, pharyngeal discomfort, and forced hospitalization, which causes physical and mental distress for the patient. In this session, we review preoperative diagnosis and drainage of the PHCC and present the POCS results and problems.

Dr. Taizo Hibi
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Japan

Living donor liver transplantation for unresectable perihilar cholangiocarcinoma: A multicenter, prospective study

Background and aim: Perihilar cholangiocarcinoma (phCCA) is an intractable cancer that often becomes unresectable in patients with either poor hepatic reserve/inadequate future liver remnant, extensive local vascular/biliary invasion, or in the presence of underlying primary sclerosing cholangitis. This study was aimed to evaluate the safety and efficacy of living donor liver transplantation (LDLT) in a multidisciplinary perspective to provide cure for unresectable phCCA under the concept of transplant oncology.

Patients and Methods: A phase I/II multicenter, prospective, single-arm interventional study was approved by the Ministry of Health, Labour and Welfare, Japan. We plan to recruit a total of 20 patients who were confirmed to meet the inclusion criteria by a central review committee. LDLT will be performed in ten high-volume centers selected by the Japanese Liver Transplantation Society. The primary endpoint is 3-year overall survival. Pretransplant drop-out rate is estimated around 30%-40% based on the results of the Mayo Clinic series; therefore, we presume at least 12 patients with unresectable pCCA would undergo LDLT. Of these, if 5 patients or more survive for 3 years, the rate will exceed 42% (95% confidence interval: 0.16-0.73), which is equivalent to that after LDLT at Mayo Clinic (3-year survival, 40%-50% range). The 3-year survival rate of non-LDLT (drop-out) patients is expected to be around 10%. If the primary endpoint is met, we conclude that LDLT provides prolonged survival for unresectable phCCA (significance level, 5%; statistical power, 81%).

APASL 2024 Kyoto

The 33rd Annual Meeting the Asian Pacific Association for the Study of the Liver

Summary

Biliary2 Liver Transplantation of Biliary Diseases

Biliary2 Liver Transplantation of Biliary Diseases

Biliary2-1

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Taiwan

Liver Transplantation for Biliary Atresia

Biliary atresia (BA) is the most common indication for liver transplantation in children. BA in the backdrop of pathological portal vein (PV) hypoplasia and sclerosis heightens the complexity of PV reconstruction and causes significant morbidity and mortality in pediatric LDLT.

The authors developed a novel approach for intra-operative PV stenting via the graft segment 4 PV stump (P4 stump) to address the challenge of suboptimal PV flow after reconstruction. The use of vascular stents is less invasive and provides advantages over the more technically demanding surgical revisions. Stenting avoids extended warm ischemia, and with self-expandable property, has the additional benefit of correcting size disparity and acute angulation between the graft PV and the recipient's hypoplastic and sclerotic PV. The P4 stump stenting approach affords procedural convenience, ease of manipulation, and consistent results with excellent long-term patency in children despite continued growth. This technique obviates the need for more demanding post-transplant stenting, and may preempt complicated revision surgery, portosystemic shunting or re-transplantation. (Ann Surg 2018)

The introduction of the meso-Rex bypass for symptomatic post-transplant PV thrombosis has caused a paradigm shift in the therapeutic approach for extrahepatic PV obstruction (EHPVO). However, in patients with a Rex recess that is not safely accessible due to extensive post-operative adhesions, perihilar collaterals, cavernous transformation and those who have exhausted all endoscopic, radiologic and surgical interventions, the authors developed a novel hybrid mesenteric-to-intrahepatic portal vein bypass using GORE® VIABAHN® for late-onset EHPVO after LDLT. This new approach although technically challenging, can be applied both in the pediatric and adult population, within or outside the context of liver transplantation, and is potentially useful for right liver grafts as well. (Hepatobiliary Surg Nutr 2024)

LDLT as definitive treatment for BA has yielded excellent recipient outcome and minimal donor morbidity. Innovative techniques evolve to improve recipient survival.

Biliary2 Liver Transplantation of Biliary Diseases
Biliary2-2

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Japan

Living-donor liver transplantation for PBC and PSC in Japan

Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are two major indications for liver transplantation. Despite the advance of medical treatments for these diseases, not a few patients develop cirrhosis and finally require liver transplantation. With the accumulation of experiences of liver transplantation for PBC and PSC and the improvement in the long-term survival after liver transplantation, the disease recurrence has become a matter of debate. While recurrent PBC is usually slow growing and has minimal impact on patient's prognosis, recurrent PSC impairs graft and patient survival significantly. In addition, in Japan where living donor liver transplantation (LDLT) is a mainstay for liver transplantation, LDLT-specific factors related with the development and the progression of the recurrent disease have been identified by the nation-wide studies. As for PBC, the disease recurrence in the long-term is not uncommon and the genetic factors and the sensitization for the donor have been attributed to the recurrent disease. In contrast, the recurrent PSC after liver transplantation is frequent, as high as 50%, with the worse graft and patent survival, which makes the poor recipient survival compared to that among PBC (62% vs 74% at 10y based on Japanese registry). In the recent nation-wide survey of LDLT for PSC, we found that the outcome of LDLT for PSC in Japan is improving along with the era and that the immunosuppressive modulation after LDLT will be of help in decreasing the recurrence rate. In this presentation, we review the outcomes of LDLT for PBC and PSC in Japan, and present some new insights for the recurrent disease of PBC and PSC after liver transplantation.

Biliary2 Liver Transplantation of Biliary Diseases

Biliary2-3

Dr. Naminatsu Takahara

Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo

Japan

Endoscopic Management of Biliary Complications after Living doner Liver Transplantation

Living donor liver transplantation (LDLT) has emerged as a crucial option for patients with end-stage liver disease. The key advantage of LDLT lies in its ability to ensure timely transplantation, resulting in a significant reduction in waiting list mortality, especially in the situation where the number of deceased donors is limited. Notable advances in surgical techniques and perioperative management have contributed to improved outcomes in LDLT, however, biliary complications remain a major unresolved issue to be addressed.

Currently, endoscopic management is a mainstay for post-LDLT biliary complications. Specifically, in cases complicated by bile leakage, endoscopic nasobiliary drainage is the preferred intervention. As for cases with anastomotic stricture, the standard strategy is balloon dilation followed by plastic stent placement, with repeat stent exchange until stricture resolution. The use of inside stents may prevent duodenobiliary reflux, and thus extending stent patency and minimizing the need for multiple stent exchange. Alternatively, recently developed covered self-expandable metallic stents with a lasso, enabling removal even after placed into the bile duct, provide an option to the multiple plastic stents placement. Furthermore, with the advent of balloon-assisted enteroscopy, it is now possible to endoscopically manage biliary complications in LDLT patients with Roux-en-Y hepaticojejunostomy.

However, these procedures are highly challenging due to the intricate nature of the biliary system in LDLT. Therefore, a comprehensive approach that integrates percutaneous and surgical interventions may be required as a salvage option when endoscopic management fails.

In this study, we comprehensively investigated clinical outcomes of endoscopic management for post-LDLT biliary complications. Additionally, we discuss recent advances as well as future perspectives in this field.

Biliary2 Liver Transplantation of Biliary Diseases

Biliary2-4

Dr. Shintaro Yagi

Intractable hepatobiliary disease study group in Japan

Japan

Proposal of Diagnostic Criteria of PSC Recurrence After Liver Transplantation

Recurrence after liver transplantation for primary sclerosing cholangitis (PSC) occurs at a relatively high incidence. The prognosis after recurrence is poor with incident of graft loss around 50%, because the treatment after recurrence have not yet been established. Although there are many reports of recurrent PSC, there is still debate over whether the diagnosis of PSC recurrence should be based on pathological diagnosis or imaging findings (ERCP/ MRCP). In addition, it is necessary to differentiate PSC recurrence from T-cell mediated rejection, antibody-mediated rejection, chronic cholangitis, chronic rejection, and stenosis of the bile duct anastomosis. Therefore, new diagnostic criteria for post-transplant recurrence have been awaited. Accordingly, we proposed new diagnostic criteria of PSC recurrence following transplantation from Intractable Hepatobiliary Disease Study Group in Japan.

Diagnostic criteria for PSC Recurrence Following Liver Transplantation

Ⅰ：Confirmed diagnosis of PSC prior to liver transplantation

Ⅱ：Histology

Onion-skin lesion/ fibrous obliterative cholangitis in liver biopsy

Ⅲ：Imaging >90 days posttransplantation

Ⅲa：Characteristic biliary findings (one of the followings)

1)Multifocal band-like strictures

2)Beaded appearance

3)Pruned-tree appearance

4)Diverticulum-like outpouching

Ⅲb：Equivocal biliary findings

Diagnosis of PSC recurrence following liver transplantation

Definitive ：Ⅰ ＋Ⅱ＋Ⅲ

Probable ：Ⅰ ＋Ⅱ/Ⅲa

Possible ：Ⅰ ＋Ⅲb

A diagnosis of PSC recurrence following liver transplantation can be made after the differentiation of followings. Caution should be paid for recurrent PSC in cases developing non-anastomotic biliary stricture within 90-day after transplantation without bellow mentioned factors.

A) Non-anastomotic biliary stricture following hepatic arterial thrombosis.
B) Ductopenia or non-anastomotic biliary stricture due to acute/chronic rejection proven by liver biopsy.
C) Secondary non-anastomotic biliary stricture following biliary anastomotic complications (biliary leakage and stricture) *
D) Non-anastomotic biliary stricture due to antibody mediated rejection (especially in cases of ABO blood type incompatible transplantation)

* It is well-recognized that recurrent PSC often develops after anastomotic biliary stricture.

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Summary

Biliary3 Management of Post Operative Biliary Complications

Biliary3 Management of Post Operative Biliary Complications

Biliary3-1

Dr. Hsiu Po Wang

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Taiwan

State of art of endoscopic management in surgically altered anatomy

Traditionally, biliary intervention can be achieved with radiological, endoscopic or surgical approaches. Endoscopic retrograde cholangiopancreatography (ERCP) has been the preferred modality for approaching biliary tree with success rate in excess of 95% in patients with normal anatomy. In contrast, ERCP with conventional equipment in patients with surgical altered anatomy has limited success, peaking at only 51%. For the surgically altered anatomy (SAA), non-surgical approach includes percutaneous route and luminal endoscopic route. Luminal endoscopic route includes enteroscopy with trans-anastomosis intervention and transmural endoscopic ultrasound (EUS) – guided intervention. The indications for biliary intervention include leakage / biloma in the early stage and stricture/stones/recurrent cholangitis in late stage. The percutaneous transhepatic biliary route (PTBR) has been considered as the choice for SSA. Additional endoscopic intervention can conduct with established PTBR. It includes cholangioscoy through PTBR for biopsy and lithotripsy, and PTB rendezvous technique for enteroscopy. Success rate of enteroscopy ERCP has reported various. Recent years, balloon-assistant enteroscopy (BAE) ERCP increased the success rate to more than 90%. One study showed the independent risk factor for failure is peritoneal dissemination with the success rate only 38.5%. The intervention procedures with BAE included dilation and stenting of the anastomotic stricture and lithotrisy; and recently cholangioscopy through the BAE. Transmural EUS-guided intervention has been developed and SAA is one of the indications when BAE-ERCP failed. The EUS procedures include EUS-guided antegrade intervention (EUS-AI) and EUS-guided hepatogastrostomy (EUS-HGS). EUS-AI provides the intervention including dilation and stenting of the anastomotic stricture and lithotrisy with efficacy and safety. EUS-HGS provides the transmural drainage from biliary to stomach. And after mature of the biliary-gastric filstula, additional transmural cholangioscopy can be performed for lithotripsy/biopsy. One multi-center study of EUS-BD for malignant biliary obstruction showed technical success rates : 100%, clinical success rates : 95%, short mean procedure time: 36.5 min, early AEs :15% and stent patency rate after 3 months of survival : 95.7%. Comparison between different approach has been studied. Comparing PTBD with EUS-BD in a meta-analysis, it showed no difference in technical success, but EUS-BD was associated with better clinical success, fewer post-procedure adverse events and lower rate of reintervention. Comparing BAE-ERCP and EUS-BD in a multi-center retrospective study, it showed higher technique (65% vs 98%) and clinical success rate (59% vs 88%) but higher adverse events (4% vs 20%).

In conclusion, among the different biliary approaches in SAA, EUS-guided intervention seems promising and with efficacy.

Biliary3 Management of Post Operative Biliary Complications

Biliary3-2

Dr. Yusuke Takasaki

Department of gastroenterology, Juntendo University

Japan

EUS Management of Bilio-Enteric Anastomotic Stricture

Benign biliary stricture may be a problem as a postoperative complication in surgically alter anatomy cases. In many cases, it is treated with ballon enterocopy assisted ERCP (BE-ERCP), but the endoscope may not be able to reach the anastomosis or find the bilo-enteric anastomosis. The long scopes may also limit the devices and may not provide adequate treatment. The longer treatment time of BE-ERCP is also a problem, which raises health issues not only for the patient but also for the doctor due to prolonged exposure to radiation. If stent exchange is performed frequently, radiation exposure becomes an unacceptable health problem. Percutaneous transhepatic bile duct drainage is also useful, but cosmetic problems and reduced quality of life are major problems. In addition, the long period of drainage tube placement can cause a variety of problems such as skin trouble, infection, and migration of drainage tube. In recent years, endoscopic ultrasound biliary drainage has come to be used not only for malignant biliary stricture but also for benign biliary stricture. However, the evidence for interventional EUS in benign disease is still insufficient, and there are many issues such as its indications, strategies for stenosis dilatation and treatment of concomitant bile duct stones. In this session, I will discuss bilio-enteric anastomotic stricture using endoscopic ultrasound biliary drainage, including our own approach.

Biliary3 Management of Post Operative Biliary Complications

Biliary3-3

Dr. Naminatsu Takahara

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Japan

Endoscopic treatment of hepaticojejunostomy anastomotic strictures with a double-balloon endoscope

Hepaticojejunostomy anastomotic stricture (HJAS) is a major complication of surgical biliary reconstruction, leading to a deterioration of quality of life as well as high morbidity and mortality. The surgically altered anatomy complicates the endoscopic approach to the hepaticojejunostomy anastomosis, making percutaneous transhepatic biliary drainage or surgical re-anastomosis the standard of care. However, with the emergence of the double-balloon endoscope (DBE), HJASs are increasingly managed endoscopically.

Several clinical studies have suggested that endoscopic treatment of HJAS is technically feasible, providing a reasonably high stricture resolution rate ranging 70–100%. However, there is a paucity of data on long-term outcomes in a large-scale cohort, and predictive factors for successful endoscopic management remain unclear. Furthermore, an optimal treatment strategy for refractory cases has not yet been determined.

In this study, we aimed to evaluate clinical outcomes of DBE-assisted ERCP for HJASs and identify predictive factors for long-term treatment success.

Biliary3 Management of Post Operative Biliary Complications

Biliary3-4

Dr. Yutaka Suzuki

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Japan

Short- and Long-term Outcomes for Secondary hepatolithiasis: Analysis from a Nationwide Cohort Study

Background: Hepatolithiasis is characterized by its intractable nature and frequent recurrence. Furthermore, cholangitis, sepsis, liver abscess, and cholangiocarcinoma frequently occur. The secondary hepatolithiasis following biliary reconstruction has been increased. In the eighth nationwide multicenter survey, 48% was secondary hepatolithiasis. Additionally, there is a noticeable rise in non-surgical treatments, particularly endoscopic interventions. The outcomes of secondary intrahepatic stone treatment, especially long-term results, remain unclear. This study evaluates secondary hepatolithiasis treatment modalities' short- and long-term outcomes to consider appropriate management strategies.

Methods: The study included 128 cases of secondary hepatolithiasis registered in a nationwide cross-sectional survey conducted by the Ministry of Health, Labour and Welfare in 2017. Based on medical records, this retrospective cohort study analyzed disease backgrounds, short-term outcomes of each treatment modality, and complications, including stone recurrences, cholangitis, and cholangiocarcinoma.

Results: The cause of choledocho-enterostomy was congenital biliary dilatation in 34 cases (27%), followed by anomalies of the pancreaticobiliary junction in 29 cases (23%). Treatment was administered in 110 cases (86%), with 94 cases undergoing non-surgical treatment, 13 cases undergoing exclusive surgical treatment, and 3 cases receiving both non-surgical and surgical treatments. Endoscopic retrograde cholangiography by balloon endoscopy (ERC) was the most frequently performed in 77 cases. In surgical treatment, systematic hepatectomy was the most common surgical treatment in 12 cases. The residual stone rate between hepatectomy and balloon ERC showed no significant difference in residual stones (0% vs. 16%, $p=0.344$). There was no significant difference in stone recurrence between the two groups (5-year incidence: liver resection 28.6% vs. balloon ERC 42.3%, $p=0.400$). During post-treatment follow-up, bile duct strictures were observed in 47 cases (37%), and bile duct dilation was observed in 72 cases (56%). Stricture was a significant risk factor for stone recurrence (5-year incidence: 67.3% vs. 17.8%, $p<0.001$) and cholangitis (5-year incidence: 56.1% vs. 10.1%, $p<0.001$). The bile duct dilation was a risk factor for stone recurrence (4-year incidence: 55.7% vs. 33.3%, $p=0.006$) but not for cholangitis.

Conclusion: Minimally invasive treatment, such as endoscopy, is recommended as a first choice treatment, but a combination with other treatment modalities, including surgery, should be considered in cases where its effectiveness is insufficient. Treatment for hepatolithiasis should address complete stone removal and the management of bile duct strictures and dilation.

Biliary3 Management of Post Operative Biliary Complications

Biliary3-5

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Japan

Novel choledochojejunostomy technique “T-shaped anastomosis” for preventing the development of postoperative cholangitis in pancreatoduodenectomy: A propensity score matching analysis

Background:

Cholangitis after pancreaticoduodenectomy (PD) is a serious complication that impairs quality of life including from repeated rehospitalization. However, there have been few studies of countermeasures to prevent this.

Objective:

We developed a novel method of choledochojejunostomy with a larger anastomotic diameter, the "T-shaped anastomosis," whose effectiveness we examine in this study.

Methods:

The study included 261 cases of PD. The T-shaped choledochojejunostomy was performed with an additional incision for a distance greater than half the diameter of the bile duct at the anterior wall of the bile duct and the anterior wall of the elevated jejunum. To compensate for potential confounding biases between the standard anastomosis group (n=206) and the T-shaped anastomosis group (n=55), we performed propensity score (PS) matching. The primary endpoint was the incidence of medium-term postoperative cholangitis (within 18 months after surgery) adjusted for PS.

Results:

1) In the PS matching analysis, 54 patients in each group were matched, and the median bile duct diameter measured by preoperative CT was 8.8 mm vs. 9.3 mm, the rate of preoperative biliary drainage was 31% vs. 37%, the incidence of cholangitis within 1 month before surgery was 9% vs. 13%, and the incidence of postoperative bile leakage was 2% vs. 2%, with no significant differences.

2) The incidence of medium-term postoperative cholangitis was 14.8% vs. 3.7%, and logistic regression with PSs showed that the incidence of postoperative cholangitis was significantly lower in the T-shaped anastomosis group (odds ratio, 0.221, 95% CI 0.032-0.937; P =0.039). Multivariate analysis revealed that the T-shaped choledochojejunostomy was an independent predictor of reduced incidence of cholangitis (odds ratio, 0.17, 95% CI 0.02-0.81; P =0.024).

3) In addition to 1:1 matching, a 2:1-matching, inverse-probability-of-treatment-weighting analytical method was performed as a sensitivity analysis. All analyses showed that the incidence of medium-term postoperative cholangitis was significantly lower in the T-shaped anastomosis group.

Conclusions:

The T-shaped choledochojejunostomy was shown to be effective with a significant reduction in the incidence of medium-term postoperative cholangitis.

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Summary

Biliary4 Tips and Tricks in Endo-Hepatology with EUS

Biliary4 Tips and Tricks in Endo-Hepatology with EUS

Biliary4-1

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Current Status of Endo-hepatology

Traditionally, the role of gastrointestinal endoscopy was limited to management of esophageal/gastric varices and portal hypertensive gastropathy. However, since the introduction of the concept of endo-hepatology in 2012, several procedures have been developed for endoscopic management of liver diseases. These include endoscopic ultrasound (EUS)-guided liver biopsy, liver stiffness measurement, portal pressure gradient measurement, ablation of liver tumors, and vascular interventions for conditions like gastric varices. In this presentation, the current status and a future direction of “Endo-hepatology” for liver diseases and their complications will be discussed.

Biliary4 Tips and Tricks in Endo-Hepatology with EUS

Biliary4-2

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Japan

Current Status of EUS-BD

EUS-BD (Endoscopic Ultrasound-Guided Biliary Drainage) is rapidly becoming popular worldwide due to its usefulness. Especially notable is the advancement in endoscopic instruments, where the development and improvement of these instruments have led to increased success rates and enhanced safety of the procedure.

The indications for EUS-BD have also evolved over time. Previously, EUS-BD was indicated only for cases where ERCP (Endoscopic Retrograde Cholangiopancreatography) was unsuccessful or not feasible. However, recently, in cases where ERCP is anticipated to be challenging, Primary EUS-BD is performed without attempting ERCP. Moreover, the indications have expanded from malignant to benign conditions. In this presentation, I would like to explain, using video, the changes in indications for EUS-BD, the development of instruments, and the advancements in techniques.

Biliary4 Tips and Tricks in Endo-Hepatology with EUS
Biliary4-3

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Tips & Tricks in Endo-hepatology with EUS

Endohepatology is an emerging subspeciality dealing with endoscopic diagnosis and management of liver diseases. It includes both - diagnostic endoscopic ultrasound (EUS) guided elastography, and interventional EUS guided therapy for gastric varices, EUS-guided liver biopsy and direct portal pressure measurement.

EUS guided Elastography is an exploratory diagnostic technique that evaluates tissue stiffness. Liver fibrosis alters the liver's stiffness, making it an ideal target for elastography. EUS 'shear wave elastography' plays a significant role in evaluating liver fibrosis. By quantifying the stiffness, EUS elastography can help in staging the degree of fibrosis. Its comparison with transcutaneous liver stiffness measurement (VCTE) using liver biopsy as gold standard showed good correlation and thus a safe and reliable alternative to VCTE. It offers advantage in obese patients, where 'percutaneous transient elastography' might be less effective due to the increased distance between the probe and the liver.

EUS guided Liver Biopsy (EUS-LB) has emerged as viable alternative for acquiring liver tissue compared to traditional percutaneous and trans-jugular routes. EUS-LB is particularly useful in cases where other methods are contraindicated, such as in patients with ascites, coagulopathy, or obesity. EUS-LB offers several advantages, including decreased patient anxiety, increased satisfaction due to sedation, shorter post-procedural monitoring time, less post-procedure pain, and lower complication rates.

EUS guided Portal Pressure gradient (EUS-PPG) measurement a newer technique, is gaining attention as a potential alternative to conventional HVPG. Direct EUS-PPG involves sequential trans-gastric puncture of hepatic vein and portal vein under EUS guidance using a fine-needle aspiration (FNA) needle which is connected to a digital pressure transducer. By subtracting hepatic venous pressure from portal pressure, the EUS-PPG measurement is determined.

EUS guided management of Gastric Varices using coil and/or glue injection is an evolving technique in managing gastric varices. This method utilizes the advanced imaging resolution of EUS to precisely identify and target gastric varices. The standard protocol involves placing coils within the varices, followed by the injection of cyanoacrylate glue under direct visualization. These coils act as a scaffold, enhancing the glue's efficacy in variceal obliteration, promoting thrombosis, and thus reducing the bleeding risk. This targeted approach reduces the required volume of glue, diminishing the likelihood of systemic embolic events, a notable concern in glue-based therapies. The combination of coil and glue results in superior variceal obliteration, reduced rebleeding rate.

Biliary4 Tips and Tricks in Endo-Hepatology with EUS
Biliary4-4

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EUS-guided liver and liver tumor biopsy

Endoscopic Ultrasound-Guided Liver Biopsy (EUS-LB) is an important development in the study of liver diseases, providing a way to diagnose and understand liver conditions with accuracy and safety for the patient. While tests that do not require a biopsy are becoming more common, getting tissue samples from the liver is still necessary for diagnosing diseases, understanding their severity, and deciding on treatment. Traditionally, liver biopsies have been done through the skin or a vein in the neck, but EUS-LB offers a new method that combines the best aspects of these traditional approaches with the added benefits of using ultrasound to guide the biopsy needle.

The use of a special needle called the 19G Fine Needle Aspiration (FNA) needle since 2012 has significantly improved the success of EUS-LB by ensuring that enough tissue can be collected for examination. Research and studies have shown that EUS-LB can collect enough tissue for diagnosis just as well as the traditional methods, and it is considered safe and standardized for use.

In this lecture, we will explore how EUS-LB has changed the way we diagnose liver diseases. We will look at how this technique compares to older methods in terms of effectiveness, safety, and cost. Special attention will be given to how the biopsy is done, including the type of needle used and the steps taken during the biopsy, which are key to getting good tissue samples and avoiding complications. This discussion will also cover how EUS-LB is more comfortable for patients, potentially less costly, and how it fits into the overall care of individuals with liver diseases.

In summary, EUS-guided liver biopsy is a significant step forward in diagnosing liver conditions, offering a less invasive option with many benefits. Adopting this method can lead to better diagnosis and treatment for patients, making it an important tool for doctors, especially in a global context where sharing knowledge and practices can improve patient care everywhere.

Biliary4 Tips and Tricks in Endo-Hepatology with EUS

Biliary4-5

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Tips and Tricks in Endo-Hepatology with EUS: Challenge and Limitations

Esophageal varices (EV) is one of the most common complications in patients with liver cirrhosis (LC). Bleeding esophageal varices (BEV) is one of the challenging conditions in clinical practice due to its high mortality rate. Esophagogastroduodenoscopy (EGD) is the standard tool for screening the presence of EV as well as managing the high-risk stigmata EV. However, the portal pressure itself, and the possible of extra-luminal EV (deep EV) has become a new challenge in patients with recurrent bleeding. Recently, endoscopic ultrasound (EUS) has been investigated to be the most promising tool not only for portal pressure evaluation, but also for a better prevention of variceal bleeding. In the need of liver disease progression evaluation, EUS has been showed to be an important tool to get liver biopsy specimen. EUS is a one stop comprehensive modality for diagnosis, treatment, and make a prognosis especially in LC patients. In patients with liver mass or small nodules which might be difficult to be detected through imaging evaluation, EUS would become a better alternative as the need of liver biopsy as well as possible local treatment, such as radiofrequency ablation (RFA) for malignant liver tumor can be performed in the same session. The limitations are to get adequate tissue sample due to its hard liver parenchyma in advance LC patients, narrowed and irregular hepatic vein for hepatic vein pressure measurement, and the tumor mass location at the right lobe of the liver which is more difficult to approach for EUS-guided RFA. Pre-procedural comprehensive evaluation is still the most important thing to do, such as coagulation issue, the presence of massive ascites, and the target location of the liver mass. Other factors such as the needle type, additional liver elastogram software, and the scope position would give a better result.

In the biliary cases, EUS has been showed to have high sensitivity for gallstones, and possible malignant condition, especially for distal malignant biliary obstruction. The only limitation is to evaluate the possible hilar malignancy (intraductal cholangiocarcinoma). In this situation, intraductal ultrasound (IDUS) might be a better option for hilar or mid common bile duct lesions assessment.

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Summary

Biliary5 Immune and Target Therapy for Cholangiocarcinoma

Biliary5 Immune and Target Therapy for Cholangiocarcinoma

Biliary5-1

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Recent Advancement in Immune and Targeted Therapy for Cholangiocarcinoma

Cholangiocarcinoma is an entity defined by both anatomic and molecular heterogeneity. Combination immunotherapy and chemotherapy defines the first line systemic therapy naïve advanced cholangiocarcinoma. Identification of a number of oncogenic alterations has allowed for therapeutic targets in the latter line settings.

Biliary5 Immune and Target Therapy for Cholangiocarcinoma

Biliary5-2

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Japan

Real world data of gemcitabine, cisplatin, and durvalumab combination therapy for advanced biliary tract cancer.

Background: Drug therapy for advanced biliary tract cancer has made steady progress. In recent years, in addition to conventional chemotherapy using cytotoxic agents, molecular targeted drugs and immunotherapy have been introduced into treatment. In particular, first-line treatment with immune checkpoint inhibitors is expected to be a promising approach. Currently, the combination of gemcitabine (GEM) + cisplatin (CDDP) with durvalumab or pembrolizumab have been reported to be effective for advanced biliary tract cancer. In Japan, GEM + CDDP + durvalumab combination therapy has been in clinical use for more than a year.

Patients and methods: We retrospectively analyzed consecutive patients with advanced biliary tract cancer who were treated with GEM + CDDP + durvalumab combination therapy as 1st line therapy between March 2023 and October 2023 at our institution.

Results: A total of 42 patients were included. Median age was 67 and 25 patients (60%) were performance status 0. The primary sites were: intrahepatic cholangiocarcinoma 15, extrahepatic cholangiocarcinoma 15, gallbladder cancer 11, and ampullary carcinoma 1). Seventeen patients (40%) were recurrent case. Response rate and disease control rate were 19.0% and 81.0%, respectively. The median progression-free survival was 5.6 months. The median overall survival was not reached. Two patients were converted to surgical resection. Major grade 3/4 adverse events were neutropenia. Skin rash occurred in 8 patients (19%) and one patient experienced immune-related adverse event of adrenal insufficiency.

Conclusions: GEM + CDDP + durvalumab combination therapy has shown the efficacy and safety for the treatment of advanced biliary tract cancer in clinical practice.

Biliary5 Immune and Target Therapy for Cholangiocarcinoma

Biliary5-3

Dr. Hayato Nakagawa

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Japan

Unveiling the Cellular Origins and Therapeutic Targets in Extrahepatic Cholangiocarcinoma: Insights from Mouse Models and Genetic Markers

The cellular origin of cholangiocarcinoma is a fascinating subject. Regarding extrahepatic cholangiocarcinoma (ECC), there has been a focus on peribiliary glands (PBGs) as a potential stem cell niche for biliary epithelial cells (BECs), raising interest in PBGs as the cellular origin of ECC. We recently developed a new mouse model of ECC by activating Kras specifically in CK19-positive duct cells and deleting TGFβR2 and E-cadherin. In this model, BECs undergo detachment and apoptosis due to the loss of E-cadherin, leading to chronic inflammation in the bile duct. Detailed histological analysis revealed the gradual dysplasia of PBGs during inflammation, eventually progressing to cholangiocarcinoma.

To definitively establish PBG as the cellular origin of biliary tract cancer, we needed animal experiments utilizing a PBG-specific gene recombination system. Consequently, we aimed to identify PBG-specific markers and discovered that Axin2, a target gene of the Wnt/β-catenin pathway, is specifically expressed in PBGs of the periampullary region. Genetic lineage-tracing demonstrated that Axin2+ periampullary PBG cells function as biliary epithelial stem cells. Notably, the deletion of PTEN in periampullary PBG cells resulted in ampullary carcinoma, which was suppressed by a Wnt inhibitor. Therefore, Wnt signaling emerges as a potential therapeutic target for ampullary carcinoma.

Moreover, we have established additional mouse models of extrahepatic cholangiocarcinoma by combining different genetic abnormalities and have identified lipid metabolic reprogramming as a potential therapeutic target. In this session, I will present a portion of this data.

Biliary5 Immune and Target Therapy for Cholangiocarcinoma

Biliary5-5

Dr. Hiroshi Ohyama

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Japan

Liquid biopsy of tumor-derived DNA in pancreaticobiliary malignancies in bile and plasma

BACKGROUND: Pancreaticobiliary cancer (PBCA) is a highly progressive disease with a poor prognosis. Obtaining sufficient pancreaticobiliary tumor tissue for genomic profiling has limitations because many PBCAs are unresectable, and only a small amount of tissue is obtained via biopsy. Liquid biopsies using plasma do not provide sufficient sensitivity. Thus, this study aimed to determine the effectiveness of liquid biopsy between bile and plasma for identifying oncogenic and drug-matched mutations.

METHODS: A panel of 60 significantly mutated genes specific to PBCA was generated in-house and it was used for genomic analysis of 212 deoxyribonucleic acid (DNA) samples (87 bile supernatant, 87 bile precipitate, and 38 plasma) from 87 patients with PBCA. Of the 87 patients with PBCA, 33 (38%) were in early (stages I or II), and 54 (62%) were in advanced stages (stages III or IV). A total of 87 bile cytological specimens were collected from 87 patients, of which 32 (36%) were Class V, and 4 (5%) were Class IV. The quantity of extracted DNA from bile and plasma was compared, as were genomic profiles of 38 pairs of bile and plasma from 38 patients with PBCA. Finally, we investigated 87 bile and 38 plasma for the ability to detect druggable mutations.

RESULTS: The amount of DNA was significantly lower in plasma than in bile ($P < 0.001$). Oncogenic mutations were identified in 21 of 38 (55%) patients in bile and 9 (24%) in plasma samples ($P = 0.005$). Bile was significantly more sensitive than plasma in identifying druggable mutations ($P = 0.032$). Oncogenic mutations were detected in 0/3 (0%), 5/11 (45%), 7/17 (41%), 9/20 (45%), 4/4 (100%), and 24/32 (75%) in unsuitable and classes I to V, respectively, with differences between classes ($P = 0.012$). We detected 23 drug-matched mutations in combined bile and plasma, including 5 ERBB2, 4 ATM, 3 BRAF, 3 BRCA2, 3 NF1, 2 PIK3CA, 1 BRCA1, 1 IDH1, and 1 PALB2.

CONCLUSIONS: Bile is an ideal clinical specimen in PBCA because it contains a large amount of tumor-derived DNA. Liquid biopsy using bile may be useful in searching for therapeutic agents, and the utilization of the obtained genomic information may improve the prognosis of patients with PBCA.

APASL 2024 Kyoto

The 33rd Annual Meeting the Asian Pacific Association for the Study of the Liver

Summary

Biliary6 Interventional EUS for Biliary Diseases

Biliary6 Interventional EUS for Biliary Diseases

Biliary6-1

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Japan

Terminology and Classification in Interventional-EUS

Development of Interventional EUS (I-EUS) is rapidly, and new procedure, indications and devices are reported day by day. There are no standard rules in the words which used in published numerous reports, and confusions are arising. The authors had published “Clinical practice guidelines for safe performance of endoscopic ultrasound/ultrasonography-guided biliary drainage: 2018” in 2019, and confused in terminology of I-EUS. Then, Japan Gastroenterological Endoscopy Society (JGES) decided to make “Subcommittees for Terminology of Interventional EUS” (Chair: Isayama H). In this lecture, the progress of this activity and decided terminology and classifications of I-EUS will be told. From our discussion, I-EUS are classified into 5 categories; 1) EUS-sampling, 2) EUS-guided through-the-needle examination (EUS-TTNE), 3) EUS-guided drainage/anastomosis (EUS-D/A), 4) Trans-endosonographically/guided created route (Tran-ESCR) procedure, 5) EUS-guided delivery. 1) EUS-sampling is including tissue acquisition (EUS-TA) and fluid sampling, and can use EUS-FNA as well. 2) EUS-TTNE is the diagnostic procedures through the punctured needle; imaging, measurement and biopsy (TTNB) using miniature devices can through the needle cavity. 3) EUS-D/A is drainage procedures for organs and fluid collections. EUS-D/A for the organs (bile duct, pancreatic duct, gallbladder, digestive tract, etc.) is drainage procedure but anastomosis simultaneously, then use “-stomy” (EUS-guided hepaticogastroenterology, EUS-guided pancreatogastrostomy). However, fluid collection is disappeared after drainage, then only words of drainage is available (transgastric EUS-PFD for WON). 4) ESCR is proposed new word represents a general term of EUS-guided/endosonographically created route. Endoscopic necrosectomy is performed through the matured route after EUS-guided drainage of walled off necrosis. Other trans ESCR procedures are antegrade stenting or stone management through the anastomosis. 5) EUS-guided delivery is the procedure to deliver the liquid, drug, equipment, energy, etc. after the puncture. Tumor ablation therapy, neurolysis implantation of fiducial markers are included. In this proposal, there were some newly created words. T-DAS is “transluminal drainage/anastomosis stent” including plastic and metallic stent, and lumen apposing metal stent is representative. The aim of T-DAS is keeping the ESCR differ from the conventional stent which keep the luminal patency at the stricture. Many doctors are using “fistula” for created route in EUS-D/A, however, “Fistula” is originally means accidentally created unusual route which are harmful, inconvenient and should be closed. Then, we proposed “anastomosis” and “route” in EUS-D/A and “ESCR” as a general term. We believed newly proposed terminology and classifications are useful to categorize various and brad-new procedures.

Biliary6 Interventional EUS for Biliary Diseases

Biliary6-3

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Tips and Tricks of Interventional EUS for Liver

The intervention for the liver using Liner EUS includes liver biopsy, liver tumor biopsy, and liver abscess drainage. Recently, EUS-FNB (Fine Needle Biopsy) from liver tumors has been increasingly performed to collect tumor specimens for cancer genomic medicine. In particular, tumors in the liver S1 region, located deep in the body, are difficult to access percutaneously, making EUS-FNB useful. The use of EUS enables simultaneous liver tumor biopsy, biopsy of enlarged lymph nodes, and ascites collection, offering greater utility than percutaneous biopsy. Understanding the EUS anatomy of the liver is necessary to visualize the targeted liver area. The trick to visualize the liver area is to focus on the vessel. In my presentation, a video will be used to explain the visualization of the liver segment, EUS-FNA, and liver abscess drainage.

Biliary6 Interventional EUS for Biliary Diseases

Biliary6-4

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Interventional EUS for Biliary Diseases

The integration of interventional Endoscopic Ultrasound (iEUS) into routine clinical practice has significantly bridged a critical gap in managing biliary diseases, notably aiding patients with complex anatomical challenges or those at high risk from conventional surgical or endoscopic procedures. Its minimally invasive nature, coupled with the capability for direct visualization and intervention, has established iEUS as a vital tool in pancreatobiliary disease management. EUS-guided biliary drainage (EUS-BD) offers a straightforward technique for bile duct drainage, whereas EUS-guided gallbladder drainage (EUS-GBD) provides a minimally invasive solution for high-risk surgical patients with acute cholecystitis, achieving high success rates with minimal adverse events.

Regarding the long-term outcomes of EUS-BD, a Korean retrospective study analyzed the clinical outcomes of EUS-guided choledochoduodenostomy (EUS-CDS) and hepaticogastrostomy (EUS-HGS) for treating distal malignant biliary obstruction (MBO). The study included 116 patients, divided into EUS-CDS (n=56) and EUS-HGS (n=60) groups. Both groups exhibited high technical success rates—98.2% for EUS-CDS and 96.7% for EUS-HGS. Clinical success was also significant, at 96.4% for EUS-CDS and 88.3% for EUS-HGS. The EUS-CDS group showed a significantly longer average stent patency of 770.3 days compared to 165.5 days for the EUS-HGS group. The only independent risk factor for stent dysfunction identified was systemic treatment following EUS-guided biliary drainage. The incidence of stent dysfunction was higher in the EUS-HGS group compared to the EUS-CDS group, with no significant differences in late adverse events. This study highlights the efficacy and safety of interventional EUS techniques in managing distal MBO, particularly emphasizing the superior stent patency associated with EUS-CDS.
In addition, a recent meta-analysis compared the efficacy and safety of EUS-GBD with percutaneous gallbladder drainage (PTGBD) in patients with acute cholecystitis. The analysis included four studies with a total of 535 patients. Although PTGBD showed a slightly higher technical success, EUS-GBD was associated with fewer adverse events, reduced unplanned readmissions, and a lower need for reinterventions, indicating its potential as a safer and more effective alternative to PTGBD, especially for patients at high surgical risk.

The adoption of iEUS has not only enhanced the safety and efficacy of treating pancreatobiliary diseases but also significantly improved patient comfort and recovery times. As technology and expertise in this field continue to evolve, iEUS is poised to play an increasingly central role in a multidisciplinary approach, promising even better patient outcomes and broader applications in gastroenterology.

Biliary6 Interventional EUS for Biliary Diseases

Biliary6-5

Dr. Saburo Matsubara

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Japan

Biliary access in interventional EUS

Endoscopic retrograde cholangiopancreatography (ERCP) is the gold standard method for biliary drainage worldwide. However, the biliary access is sometimes impossible due to the failed biliary cannulation, the duodenal invasion of the tumor, or the surgically altered anatomy. Endoscopic ultrasound-guided biliary drainage (EUS-BD) has recently emerged including transmural drainage, antegrade stenting and rendezvous with ERCP; transmural drainage includes EUS-guided choledochoduodenostomy (EUS-CDS), EUS-guided hepaticogastrostomy (EUS-HGS), EUS-guided hepaticojejunostomy (EUS-HJS), and EUS-guided hepaticoduodenostomy (EUS-HDS). In unresectable malignant biliary obstruction, transmural drainage and antegrade stenting can be a good alternative for failed ERCP. On the other hand, transpapillary approach using EUS-guided rendezvous (EUS-RV) is desirable for benign biliary diseases such as benign biliary strictures or choledocholithiasis.

EUS-RV is a rescue technique for the failed biliary cannulation in ERCP, which was firstly reported by Mallery et al. in 2004. After the puncture of the bile duct, a guidewire is inserted into the bile duct and subsequently manipulated to pass the stricture and the sphincter of Oddi. After the placement of the guidewire in the duodenum, an echoendoscope is exchanged to a duodenoscope keeping the guidewire left in place. Finally, the transpapillary biliary cannulation is attempted with the help of the EUS-placed guidewire.

In EUS-RV, there are four approach routes: the puncture of the distal extrahepatic bile duct (EHBD) from the duodenal second part with a stretched (short) scope position, the puncture of the proximal EHBD from the duodenal bulb with a pushed (long) scope position, the puncture of the left intrahepatic bile duct (IHBD) from the stomach with a short scope position, and the puncture of the right IHBD from the duodenal bulb with a long scope position. The puncture of the distal EHBD from the duodenal second part is likely to be the best approach route, because the maneuverability of the guidewire is favorable due to the short distance between the puncture site and the papilla, and the favorable direction of the needle. Rates of technical success and adverse events of EUS-RV were reported as 82% and 13%, respectively.

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Summary

Biliary7 Hot Topics in PSC

Biliary7 Hot Topics in PSC

Biliary7-1

Dr. Itaru Naitoh

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Japan

Diagnostic criteria for primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown cause that is characterized pathologically by an inflammatory and fibrotic process centered on the epithelium, leading to diffuse biliary stenosis and increased wall thickness throughout the intra- and extra-hepatic biliary trees. The diagnostic criteria for PSC proposed by the Mayo Clinic have been used internationally in the diagnosis of PSC for a long time.

Japanese nationwide survey in 2015 revealed that several clinical aspects of PSC differed between Japan and Western countries. The Intractable Hepato-Biliary Diseases Study Group in Japan proposed Japanese diagnostic criteria in 2016 (PSC2016). The PSC2016 consisted of the major and minor items. Major items are directly related to bile duct changes based on biliary tract imaging and an increased alkaline phosphatase (ALP) level. Minor items consist of an association with inflammatory bowel disease and liver histology. It is necessary to exclude IgG4-related sclerosing cholangitis (IgG4-SC), secondary sclerosing cholangitis caused by diseases with an obvious pathogenesis, and malignant diseases such as biliary cancer.

Several years have passed since PSC2016 was published, and several limitations were found in PSC2016. Firstly, it is difficult to diagnose pediatric patients because only ALP is incorporated in the evaluation of increased biliary enzyme. Secondly, small duct PSC cannot be diagnosed. Thirdly, PSC recurrence following liver transplantation cannot also be diagnosed. New findings and knowledge have accumulated after the proposal of PSC2016.

The Intractable Hepato-Biliary Diseases Study Group of the Committee of Research on Measures for Intractable Diseases in Japan established a working group consisting of researchers specializing in PSC. The working group develops tentative revised diagnostic criteria for PSC to overcome these limitations of PSC2016. Revised criteria also consist of four items. They are 1) biliary finding, 2) association with inflammatory bowel disease, 3) increased biliary enzyme, and 4) liver histology. Revisions are as follows; 1) Cholangiographic finding is revised to biliary finding to use other modalities (EUS, IDUS, POCS) in addition to ERC/MRCP. 2) Gamma-glutamyl transpeptidase is incorporated in addition to ALP for the evaluation of elevated biliary enzyme. 3) Diagnostic criteria for PSC recurrence following liver transplantation are added. The working group is going to propose the revised diagnostic criteria for PSC after the discussion and public hearing.

Biliary7 Hot Topics in PSC

Biliary7-2

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Japan

Anti-Integrin αvβ6 Autoantibodies in Patients with Primary Sclerosing Cholangitis

Patients with primary sclerosing cholangitis (PSC) possess autoantibodies against biliary epithelial cells. However, the target molecules remain unknown. In addition, although diffuse biliary stricture is the most important finding for diagnosing with primary sclerosing cholangitis (PSC), some cases have potential to be misdiagnosed with other biliary diseases. Therefore, the development of specific diagnostic markers for PSC is needed.

We recently found that PSC patients possessed anti-integrin αvβ6 autoantibodies. By enzyme-linked immunosorbent assays (ELISA), anti-integrin αvβ6 antibodies were detected in 49/55 (89.1%) patients with PSC and 5/150 (3.3%) controls ($P < 0.001$), with a sensitivity and specificity of 89.1% and 96.7%, respectively, for PSC diagnosis. When focusing on the presence or absence of IBD, the proportion of the positive antibodies in PSC with IBD was 97.2% (35/36) and that in PSC alone was 73.7% (14/19) ($P = 0.008$). Integrin αvβ6 was expressed in bile duct epithelial cells. Immunoglobulin (Ig)G from 15/33 patients with PSC blocked integrin αvβ6-fibronectin binding through an RGD (Arg–Gly–Asp) tripeptide motif. In conclusion, autoantibodies against integrin αvβ6 were detected in most patients with PSC; anti-integrin αvβ6 antibody may serve as a potential diagnostic biomarker for PSC.

We proceeded studies further. Our study above was conducted on patients from only two institutions. Therefore, a validation research in multi-centers is needed to eliminate selection bias. In addition, the study was examined using our conventional in-house enzyme-linked immuno-sorbent assay (ELISA) method. To compare the data from different facilities, development of a universal kit for the antibody measurement is needed.

The Intractable Hepato-Biliary Diseases Study Group in Japan has conducted the nation-wide PSC registry study “Establishment of disease registry of primary sclerosing cholangitis for investigation of clinical features, natural history, and prognostic factors” to prospectively register clinical information and sera of patients with PSC in Japan. Using these serum samples and clinical information, we examined diagnostic value of anti-integrin αvβ6 autoantibody for PSC as a Japanese nation-wide validation study.

In addition, we collaborated with Medical and Biological Laboratories CO., LTD. to establish Anti-Integrin αvβ6 ELISA Kit which enables easier detection of the anti-integrin αvβ6 antibodies. The use of monoclonal antibody for integrin αvβ6 with known concentration facilitated the standardization of anti-integrin αvβ6 autoantibody titers.

I will show these results in this section.

Biliary7 Hot Topics in PSC

Biliary7-3

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Endoscopic Treatment in PSC

Primary sclerosing cholangitis (PSC) is a challenging clinical condition which is required a good and proper diagnosis before deciding the best strategy approach as it can lead to malignancy condition. Liver transplantation is still the best treatment for PSC; however, regular endoscopic approach is the most routine procedure in daily practice. Despite the imaging innovation, such as magnetic resonance cholangiopancreatography (MRCP), other innovations in endoscopy, such as transpapillary biopsy, fluorescence in-situ hybridization (FISH) method from the brush material, intraductal biopsy using innovation and dedicated cholangioscope have increased the diagnostic value, especially for cholangiocarcinoma (CCA) early detection. Biliary stenting through endoscopic retrograde cholangiopancreatography (ERCP) procedure is the main procedure in daily practice for PSC management.

Endoscopic luminal radiofrequency ablation (ELRA) is one of innovation treatment for biliary stricture, especially to maintain biliary stent patency in intraductal CCA.

Biliary7 Hot Topics in PSC

Biliary7-4

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Japan

Mucosal findings of PSC by per-oral cholangioscopy

In the diagnosis of PSC, it is important to pay attention to the abnormality of the biliary image and scrutinize it. Although the characteristic ERCP findings of PSC are well known, the biliary mucosa findings that can be observed by per-oral cholangioscopy (POCS) have not been fully examined. In this presentation, we introduce our results on the POCS findings in PSC in addition to previous reports.

POCS findings vary according to the condition and stage of disease. In the active phase, findings such as mucosal erythema, ulceration, fibrinous white exudate, and an irregular surface are observed and may reflect strong inflammation in the biliary epithelium. On the other hand, findings such as scarring, pseudodiverticula, and bile duct stenosis appear in the chronic phase and may reflect fibrosis and stenosis resulting from repeated inflammation. However, active phase findings such as mucosal erythema, ulceration, fibrous white exudate, and irregular surface were significantly increased in patients with cholangitis and intense inflammation even in those with a long course, suggesting that findings in the active phase may appear in accordance with the state of inflammation regardless of the progression of PSC pathology. In addition, dilated abnormal vessels are frequently found in patients with cholangiocarcinoma, and when this finding is found, attention should be paid to the coexistence of cholangiocarcinoma. Observation of inside the bile duct by POCS might confirm the current PSC activity.

When comparing ERC and POCS findings, multiple POCS findings coexisted for one ERC finding, and the actual changes of the biliary mucosa were different even if the same ERC finding was presented. However, because “Beaded appearance” and “Band-like stricture” in the ERC image often showed stenosis, “Shaggy appearance” often showed scar, and “Diverticulum-like formation” often showed false diverticulum, it was considered that these findings were the main cause of each finding in the ERC image.

Because POCS offers not only information regarding the diagnosis of PSC and PSC-associated cholangiocarcinoma but also the current statuses of biliary inflammation and stenosis, POCS could significantly contribute to the diagnosis and treatment of PSC.

Biliary7 Hot Topics in PSC

Biliary7-5

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Recent advances in medical treatment for PSC

Primary sclerosing cholangitis (PSC) is a disease characterized by fibrotic strictures of intra- and extrahepatic bile ducts, leading to liver cirrhosis due to bile stasis. While its pathogenesis involves presumed autoimmune mechanisms, it remains incompletely understood. At present, liver transplantation stands as the sole definitive treatment, but opportunities for deceased donor liver transplantation are limited, and living donor liver transplantation pose significant challenges. Additionally, graft failure due to a high recurrence rate after transplantation remains a concern. Though no established pharmacological treatment exists, various studies are underway with promising outcomes expected.

Ursodeoxycholic acid (UDCA) represents the most extensively studied pharmacotherapy, demonstrating reduction in hepatic and biliary enzymes in numerous randomized controlled trials. However, due to reported increased mortality and liver transplantation at high doses, it is not considered standard therapy in various national guidelines. Nonetheless, recent reports associating decreased serum ALP levels with prognosis have renewed interest in the potential of UDCA to improve outcomes. Retrospective analyses using nationwide surveys in Japan have reported improved transplantation-free survival rates associated with UDCA therapy.

Bezafibrate, a medication for dyslipidemia, acts as an agonist for Peroxisome Proliferator-Activated Receptor alpha (PPARα) and has been reported to decrease hepatic and biliary enzymes in PSC. However, its evidence remains limited to a few cases, lacking established confirmation.

Other pharmacotherapies include a Phase II randomized trial showcasing improvement in hepatic and biliary enzymes with cilofexor, a farnesoid X (FXR) receptor ligand, followed by an ongoing Phase III trial.

Recent advances reveal the involvement of the gut microbiota in PSC pathogenesis, driving research toward pathophysiology-based treatments. Reduced diversity in the gut microbiota of PSC patients has been reported, with expectations that restoring diversity through fecal microbiota transplantation may lead to therapeutic benefits. Moreover, Klebsiella pneumoniae is frequently detected in the intestines of PSC patients, prompting investigations into its role in causing liver inflammation via bacterial translocation. Studies on bacteriophage therapy targeting K. pneumoniae are also underway.

Progress in understanding PSC's pathophysiology fuels optimism for further advancements in treatment-related research in the foreseeable future.

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Summary

Biliary8 Endoscopic Management of Hilar Obstruction

Biliary8 Endoscopic Management of Hilar Obstruction

Biliary8-1

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The revised TOKYO criteria for hilar biliary obstruction

The consensus-based TOKYO criteria were introduced as a standardized reporting system to address the inconsistent documentation of outcomes of endoscopic transpapillary biliary drainage. The main aim was to solve issues arising from heterogeneous reporting practices across different studies, which hindered the comparability and interpretation of stent outcomes. However, the original TOKYO criteria were less applicable to recent endoscopic biliary drainage modalities such as those based on endoscopic ultrasound or balloon endoscopy. As opportunities for managing hilar biliary obstruction and benign biliary strictures through endoscopic drainage have expanded, and biliary ablation has been introduced for both benign and malignant strictures, there is a growing need to revise the criteria. Additionally, with cancer patients experiencing prolonged survival times, there is an increased focus on evaluating overall outcomes throughout the period of endoscopic biliary drainage rather than solely concentrating on the initial stent patency.

Acknowledging these gaps, a committee within the Japan Gastroenterological Endoscopy Society has been formed to revise the TOKYO criteria to align with current clinical practices in endoscopic biliary drainage. The revised criteria propose standardized reporting items applicable to endoscopic biliary drainage as a whole, along with specific items tailored to different conditions and interventions. The term "stent-demanding time" has been introduced to encompass the entire duration of endoscopic biliary drainage, providing a comprehensive evaluation of overall stent-related outcomes. The adoption of these revised TOKYO criteria is expected to facilitate the design and reporting of clinical studies, offering a goal-oriented approach to assessing endoscopic biliary drainage.

The revised TOKYO criteria aim to evaluate the following conditions and interventions: distal biliary obstruction, hilar biliary obstruction, EUS-guided biliary drainage, biliary drainage via balloon-assisted endoscopy, benign biliary stricture, scheduled exchange of a plastic stent, biliary ablation. In this presentation, I will focus on the part of assessing endoscopic biliary drainage for hilar biliary obstruction.

Biliary8 Endoscopic Management of Hilar Obstruction

Biliary8-2

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Korea

Endoscopic Management of High-Grade Malignant Hilar Strictures

Hilar malignant biliary strictures (MBS) usually present in an already advanced and inoperable condition. Traditional external percutaneous transhepatic drainage can be possible for hilar MBS, but, avoided with successful one step internal biliary drainage by endoscopic drainage. Endoscopic biliary stenting allows adequate biliary internal drainage in most patients with MBS. Endoscopic stenting for biliary drainage through ERCP is the mainstay of endoscopic palliation for malignant biliary obstruction. Self-expandable metal stents (SEMSs) are preferred over plastic stents because of their longer patency and fewer additional endoscopic procedures. Although unilateral drainage may provide adequate drainage in some instances, bilateral drainage can provide longer cumulative patency and may drain >50% of the liver volume that is the target volume for adequate biliary drainage. However, bilateral metallic stenting for the hilar MBS remains technically challenging even for expert biliary endoscopists, especially for cases of high-grade MBS. Although the stent-in-stent method is technically difficult, recently developed stents have facilitated bilateral stenting for hilar MBS. Bilateral stenting and revision with this new SEMS were feasible and effective for hilar MBS. Endoscopic ultrasound (EUS)-guided transenteric drainage has expanded to the drainage of biliary trees, including the intrahepatic duct for high grade hilar MBS. EUS guided biliary drainage (EUS-BD) can be performed during the same endoscopy trial for the failed or impossible cases with ERCP guided conventional drainage in selected cases. Technical development and continuous evolution of dedicated procedures, accessories, and devices including stents can bring the better success and long-term results for hilar MBS.

Biliary8 Endoscopic Management of Hilar Obstruction

Biliary8-3

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Endoscopic Management of Hilar Obstruction

Hilar cholangiocarcinoma (hilar CC), a rare but prevalent form of bile duct cancer, poses significant treatment challenges due to its advanced stage at diagnosis and the historical lack of effective treatments, resulting in poor survival rates. The primary treatment approach involves surgical resection, targeting both intra- and extrahepatic bile ducts and the affected liver lobe.

Preoperative biliary decompression is crucial for patients presenting with obstructive jaundice, a common symptom of hilar CC, and scheduled for major liver surgery. Traditionally, percutaneous transhepatic biliary drainage (PTBD) has been preferred, especially in cases with additional complications such as cholangitis, malnutrition, or liver dysfunction. More recently, endoscopic methods like endoscopic nasobiliary drainage (ENBD) have become popular due to their diagnostic benefits in evaluating bile volume and characteristics. Despite its advantages, ENBD can cause bile loss and patient's discomfort, leading some clinicians to opt for endoscopic biliary stenting (EBS). However, EBS may carries a higher risk of obstructive cholangitis and postoperative issues, making ENBD the recommended first-line treatment, although EBS may still be used if it provides sufficient drainage.

In cases of inoperable hilar CC, the optimal method for liver drainage is still debated. Generally, draining more than 50% of the liver volume is advised, but the choice between plastic stents (PS) and uncovered self-expandable metal stents (uSEMS) is controversial. PS are often selected for their ease of replacement and removal, while uSEMS are preferred for their durability and longer patency. The decision between unilateral and bilateral stenting also varies, with some evidence suggesting that bilateral stenting might offer longer stent patency.

Another therapeutic consideration is intraductal radiofrequency ablation (ID-RFA), which shows promise for treating unresectable malignant biliary obstructions. However, due to the perihilar bile duct's proximity to critical vascular structures, the risk of ID-RFA-related complications may be elevated. Our research suggests using the shortest available ID-RFA probe to minimize these risks, based on findings from animal studies that showed increased bile duct perforation risk with standard ID-RFA settings.

In summary, the management of hilar CC, including preoperative and palliative biliary decompression, requires a tailored approach that considers the complexities of each case. A multidisciplinary team's expertise is crucial in determining the most appropriate treatment strategy, whether it involves surgical resection, biliary decompression, or advanced therapies like ID-RFA. Despite the advancements, a consensus on the best practices for hilar CC is still needed, underscoring the importance of individualized treatment plans supported by collaborative decision-making.

Biliary8 Endoscopic Management of Hilar Obstruction

Biliary8-4

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Suprapapillary placement of plastic stents for unresectable malignant biliary hilar obstructions

Unresectable malignant obstructions of the biliary hilum represent a significant challenge in the field of palliative pancreatobiliary endoscopy. Prior meta-analyses have favored uncovered metal stents due to their prolonged patency compared to plastic stents placed across the papilla. However, advancements in cancer treatment have rendered the uncovered design problematic because it cannot be removed. Once the metal stent becomes occluded, it induces idiopathic cholangitis which interrupts cancer therapies, reduces quality of life, and requires extremely complicated treatments since it cannot be removed.

Plastic stents, alternatively, offer reversibility, simplifying re-interventions, despite their shorter function periods when placed across the papilla. Recently, the focus has shifted to suprapapillary placement, which has been proven to be feasible in recent studies. Retrospective or single-arm studies have reported median patency periods of suprapapillary plastic stents from 99 to 190 days, making this approach a viable option.

In our multicenter, randomized control trial comparing suprapapillarily placed plastic and metal stents, we found no significant differences in the technical success, clinical success and adverse events between the groups. While plastic stents exhibited a tendency for shorter function periods compared to metal stents without statistical significance (250 vs. 361 days, $p = 0.34$), both are potential initial permanent drainage techniques, considering the removability of plastic stents.

Biliary8 Endoscopic Management of Hilar Obstruction
Biliary8-5

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Japan

Management of Hilar obstruction with EUS

Malignant hilar biliary obstruction (MHBO) is usually treated by multiple biliary stenting under endoscopic retrograde cholangiopancreatography (ERCP) guidance. Endoscopic drainage for MHBO has several concerns such as unilateral or bilateral drainage, plastic or metal stent, or side-by-side or stent-in-stent deployment? Although recent development of dilation device or uncovered self-expandable metal stent (UCSEMS), technical success rate of multiple stenting for MHBO may be relatively high, re-intervention may be still challenging due to duodenal obstruction or complex hilar stenting. In addition, because of recent development of chemotherapy, patient's survival may be also prolonged. Therefore, the rate of encountering for challenging cases may increase.

Endoscopic ultrasound-guided biliary drainage (EUS-BD) has been widely performed for patients with failed ERCP. In case of MHBO, stent patency might be favorable because SEMSs are not deployed across malignant tumor. In addition, re-intervention may be also easy. EUS-BD for MHBO can be divided into three access route, such as EUS-guided hepaticogastrostomy (HGS) (unilateral drainage), EUS-guided hepaticoduodenostomy with EUS-HGS (bilateral drainage), or bridging method (bilateral drainage). During EUS-HGS for MHBO, to obtain enough drainage area, the periphery intrahepatic bile duct should be punctured. Also, to prevent bile duct brunch obstruction, partially covered SMES should be used. EUS-HDS can be performed for isolated right intrahepatic bile duct obstruction. Usually, anterior bile duct can be detected from the duodenum. In this procedure, bile duct puncture itself may not be so challenging if the target bile duct can be detected. To detect bile duct, echoendoscope adjustment is performed under not only EUS guidance but also fluoroscopic guidance. During bridging method, guidewire deployment across stricture site is needed. This procedure step may be sometimes challenging. In challenging case, several devices may be helpful. Also, careful stent selection which is deployed stricture site is needed.

As re-intervention techniques, EUS-BD can be also performed from left or right intrahepatic bile duct drainage. According to previous reports, compared with re-intervention under ERCP guidance, stent patency may be longer in EUS-BD group. And technical success rate of EUS-BD may be higher than ERCP.

Although EUS-BD for MHBO may be feasible and safe, techniques may not be easy for all endoscopists. In the presented lecture, I would like to talk about technical tips of EUS-BD for MHBO with several videos.

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Summary

Other1 Recent Advances for Hepatitis A and E

Other1 Recent Advances for Hepatitis A and E

Other1-2

Dr. Tatsuo Kanda

Division of Gastroenterology and Hepatology, Nihon University School of Medicine

Japan

Hepatitis A and E viruses: recent advances in research and clinical practice recommendations

In 2018, there was an outbreak of hepatitis A virus (HAV) infection in Japan, and hepatitis A is also considered a sexually transmitted disease. Patients with hepatitis A should be receiving attention, and this disease needs to be prevented more than ever. Despite the development of an effective vaccine against hepatitis A, universal vaccination has not yet been performed in Japan.

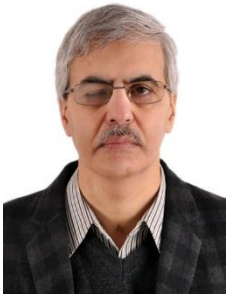
In Japan, until the early 2000s, acute hepatitis E virus (HEV) infection was considered rare until reports emerged confirming the existence of HEV genotype 3 and 4 infections. Until now, vaccines against hepatitis E have not yet become available in Japan. The Japanese National Health Insurance System does not approve anti-HAV and anti-HEV drugs.

Recently, we discovered several effective drugs against HAV infection and their mechanism by drug repositioning, in silico screening (Sasaki-Tanaka R, et al. J Virol. 2022 Sep 28; Sasaki-Tanaka R, et al. J Virol. 2023 Feb 28; Sasaki-Tanaka R, et al. Int J Mol Sci. 2023 Jun 3; Int J Mol Sci. 2022 May), etc. Although the use of off-label ribavirin for HEV infection was shown to be effective, the development of antivirals against HAV and HEV infection is urgently required.

The Japan Agency for Medical Research and Development (AMED) Hepatitis A and E viruses (HAV and HEV) Study Group has recently published the recent advances in research and clinical practice recommendations for hepatitis A. Here, the recent advances in research and clinical practice recommendations for HAV and HEV infections in Japan will be presented.

Other1 Recent Advances for Hepatitis A and E

Other1-3



Dr. Barjesh Chander Sharma
Gastroenterology, GIPMER
India

Management of Hepatic Encephalopathy with Special Reference to Combination Therapy

Hepatic encephalopathy (HE) is characterized by wide spectrum of neurological and psychiatric alterations resulting due to advanced liver malfunction. It is a neurological ailment related to hepatic insufficiency and/or portosystemic shunts. Its clinical features include neuropsychiatric dysfunction, ranges from subclinical changes to coma. Overt HE is found in 30–45% of patients with cirrhosis and 10–50% of patients with a transjugular intrahepatic portosystemic shunt (TIPS). Recurrence of HE is seen in 47-57% of patients by the end of one year despite being on treatment. Occurrence of each bout of HE results in increased morbidity, hospitalization, health care burden, poor prognosis and increased mortality. Combination of rifaximin with lactulose has favourable effect on patients with recurrent HE who have recurrent bouts of HE despite on lactulose. Thus, rifaximin along with lactulose should be considered for preventing the recurrent episodes of HE. With use of rifaximin as addition to lactulose for the prophylaxis of third and further episodes of HE, cost can be saved both from a hospital and healthcare payer's perspective. From healthcare payer's view, costs raise by adding rifaximin to lactulose is reduced due to improved survival with rifaximin causing relatively low drug and liver transplant related costs. Combination of lactulose plus albumin is also more effective than lactulose alone in the management of overt HE with more decrease in the levels of arterial ammonia, interleukin-6, interleukin-18, tumor necrosis factor-alpha, and endotoxins. Triple combination of L-ornithine L aspartate (LOLA) with lactulose and rifaximin is more efficacious than only lactulose and rifaximin in improving grades of HE, recovery time from HE and with reduced 28-days mortality. In cirrhotic patients with advanced HE adjuvant treatment with LOLA along with lactulose and metronidazole is safe and associated with fast improvement and reduced hospital stay. In conclusion combination therapy including lactulose, rifaximin, albumin and LOLA is effective in the management and prevention of recurrent HE.

Other1 Recent Advances for Hepatitis A and E

Other1-4

Dr. Khin Maung Win

Honorary Professor, Department of Hepatology, University of Medicine 1, Yangon

Myanmar

Recent Advances for Hepatitis A and E

Hepatitis A and E infections are transmitted via the faecal-oral route and still imposing significant health problems in developing countries with poor sanitary conditions as well as in the developed countries.

Hepatitis A

Hepatitis A is a disease which can be prevented by vaccine. Worldwide incidence of hepatitis A is more than 150 million.

Hepatitis A Virus (HAV) infection causes acute hepatitis and it resolves spontaneously without chronic sequelae. However, in 20% of patients develop prolonged cholestasis or relapsing hepatitis. Acute liver failure occurs in <1% of cases. Severity of the disease is influenced by host factor such as immunological status, age, pregnancy and underlying disease. Extrahepatic manifestations include rash, arthralgias and other conditions related autoimmune disease.

Laboratory abnormalities include elevations of aminotransferase (often >1000 IU/dL) followed elevations of bilirubin. The diagnosis is established by detection of Anti-HAV IgM antibodies.

Anti-HAV IgG antibodies produced in response to HAV infection persist for life whereas vaccine induced antibodies can be detected for a long time.

WHO recommend vaccination for individuals at higher risk of infection in countries with very low HAV endemicity and universal childhood vaccination in intermediate endemicity countries.

Hepatitis E

Hepatitis E is the most common cause of acute viral hepatitis worldwide. It is estimated that globally 900 million people have been infected.

Hepatitis E Virus (HEV) is a single-stranded RNA virus that is transmitted through contaminated food and water, blood transfusion and through mothers-to-infant transmission.

There are 8 classified genotypes of which genotypes 1, 2, 3 and 4 can infect humans.

High mortality was noted in acute HEV infection. Most acute HEV cases resolved spontaneously and clear the virus. Therefore, HEV was thought as self-limiting acute viral Hepatitis. But in 2008 chronic HEV infection was reported and established in immunocompromised patients such as solid organ transplanted patients.

Diagnosis was made by detection of HEV IgM antibodies. But the tests are not available commercially. Confirmation or gold standard test of the HEV infection is HEV RNA testing.

The management of acute HEV is usually supportive. However, solid organ transplant patients, a reduction of immunosuppressive therapy should be tried for 12 weeks. If HEV RNA remains detectable after reduction of immunosuppressive therapy, ribavirin monotherapy should be used.

The HEV vaccine has been developed but not widely available. Therefore, it is advised for the international travelers to endemic areas to avoid drinking water of unknown purity and avoid uncooked or undercooked meat.

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Summary

Others2 New Paradigm of Delta Infection

Others2 New Paradigm of Delta Infection

Other2-2

Dr. Naoya Sakamoto

Department of Gastroenterology and Hepatology Faculty and Graduate School of Medicine

Hokkaido University

Japan

Recent prevalence and characteristics of patients with hepatitis delta virus in Japan

Although hepatitis delta virus (HDV) coinfection with hepatitis B virus (HBV) is a global health concern, the prevalence of HDV infections remains unknown due to insufficient data in many countries. In Japan, HDV prevalence has not been updated for over 20 years. We aimed to investigate the recent prevalence of HDV infections in Japan. Methods: We screened 1,264 consecutive patients with HBV infection at Hokkaido University Hospital between 2006 and 2022. Patients' serums were preserved and subsequently tested for IgG-HDV antibody. Available clinical information was collected and analyzed. We compared the changes in liver fibrosis using FIB-4 index between propensity-matched patients with and without the evidence of anti-HDV and corrected for baseline FIB-4 index, nucleoside/nucleotide analog treatment, alcohol intake, sex, HIV coinfection, liver cirrhosis, and age. Results: After excluding patients without properly stored serums and those lacking appropriate clinical information, 601 patients with HBV were included. Of these, 1.7% of patients had detectable anti-HDV. Patients with positive anti-HDV showed significantly higher prevalence of liver cirrhosis, lower prothrombin time, and higher prevalence of HIV coinfection than those who were negative for anti-HDV. A propensity-matched longitudinal analysis revealed that liver fibrosis (FIB-4 index) progressed more rapidly in patients with positive results for anti-HDV antibody tests. Conclusions: The recent prevalence of HDV infections in Japanese patients with HBV was 1.7% (10/601). These patients experienced rapid liver fibrosis progression, highlighting the importance of routine HDV testing.Others2 New Paradigm of Delta Infection

Others2 New Paradigm of Delta Infection

Other2-3

Dr. Robert Gareth Gish
Hepatitis B Foundation
USA

New Paradigm of Delta Infection

Hepatitis D virus (HDV) is an RNA “sub-virus” that infects patients with co-existing hepatitis B virus (HBV) infections. HDV burden is estimated to be approximately 15-20 million people worldwide. Despite HDV severity, screening for the HDV remains inadequate. HDV screening would benefit from a revamped approach that automatically reflexes testing when individuals are diagnosed with HBV if HBsAg+, to anti-HDV total and then to quantitative HDV-RNA polymerase chain reaction (PCR) rather than only testing those at high risk sequentially. There are no current treatments in the United States (US) that are Food and Drug Administration (FDA)-approved for the treatment of HDV; and one approved therapy in the EU by the EMEA with conditional approval; however, bulevirtide and is under review with the US FDA. Current treatment strategies in many countries are centered on the use of pegylated interferon alfa-2a (PEG-IFNa-2a). There are other therapies in development globally that have shown promise, including lonafarnib (LNF) and the NAP: REP 2139. LNF has shown substantial response in the LOWR trials, but trials halted due to some liver toxicity risk. BLV is a well-tolerated drug, but it is not finite therapy and has shown significant on-treatment HDV RNA responses in the multiple MYR clinical trials, and the FDA cited concerns with the manufacturing and patient preparation of the drug that have delayed approval. The PDUFA date for BLV in the US is mid-2024. Current studies with both BLV and LNF are limited in providing sustained virological response (SVR); future trials will need to demonstrate more substantial SVR with possible triple combination trials as options. REP 2139 is in compassionate use trials in the EU region. In summary, HDV/HBV is a very high-risk viral infection and justifies a test all approach and a treat all approach who are HDV RNA+. Interferon remains a global tool for HDV treatment with response rates in the 20% range with newer therapies in evolution.

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Summary

Others3 Coinfection of Viral Hepatitis and HIV

Others3 Coinfection of Viral Hepatitis and HIV

Other3-2

Dr. Takeya Tsutsumi
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The University of Tokyo
Japan

Clinical features and vaccine efficacy of hepatitis A virus infection in HIV infection

In 2018, there was an outbreak of hepatitis A virus (HAV) infection in Japan, following outbreaks in foreign countries such as European countries, Unites States, and Taiwan. Most of infected patients were men who have sex with men (MSM) including human immunodeficiency virus (HIV)-infected patients. HAV is usually transmitted through fecal-oral infection, and the outbreak was probably spread by unique sexual activities of MSM. A similar HAV outbreak was observed among MSM in Japan around 2000. About 20 years passed, and the treatment strategy for HIV infection has been developed, leading to better immunological condition of people living with HIV (PLWH). Accordingly, the clinical presentation of HAV infection in PLWH was different from the previous outbreak.

To prevent HAV infection, HAV vaccine is generally useful. Centers for Disease Control and Prevention (CDC) recommends HAV vaccine for MSM as well as people traveling to endemic countries. However, the efficacy of HAV vaccine to obtain enough anti-HA IgG antibody (anti-HA-IgG) has been shown to be lower among PLWH compared to non-HIV-infected people. It is known that even PLWH who have a good HIV control sometimes cannot respond to other vaccines. Furthermore, compared to healthy people, PLWH have difficulty maintaining sufficient titers of anti-HA-IgG to prevent HAV infection.

As mentioned above, the clinical characteristics of HAV infection in PLWH, including my own experience, will be introduced

Others3 Coinfection of Viral Hepatitis and HIV

Other3-3

Dr. Lai Wei

Hepatopancreatobiliary Center, Beijing Tsinghua Changgung Hospital,

School of Clinical Medicine, Tsinghua University

China

Co-infection of HCV and HIV control in China

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) co-infection is common due to same transmission route and common risk factors. It is estimated that HCV coinfection prevalence was around 8.0% in Hong Kong and around 25.5% in general HIV cohorts in China. Recent studies showed 24.7% HCV prevalence among HIV-infected individuals in 2020. A cohort study of HIV patients in Guangxi Zhuang Autonomous Region reported that 8.1% co-infected with HCV in 2022. A cross-sectional survey in Yunnan Province reported 6.5% of a total of 5,922 HIV/AIDS cases were infected with HCV in 2021. The number of people living with HIV in China reached 1.14 million and is still increasing in 2021, implying that there might be 74,100–281,580 cases of HIV/HCV co-infection in China.

What is more, natural history study found that a higher risk of end-stage liver disease (ESLD)-related death and rapid progression of liver fibrosis in HIV/HCV coinfected patients HCV mono-infected patients. During HIV/HCV coinfection, HIV infection may aggravate HCV-associated liver injury.

China government takes national-wide actions for both of HCV infection prevention and control and HIV infection prevention and control. The State Council of the People's Republic of China released Healthy China 2030 plan in 2016, in which high endemic infectious diseases including HCV and HIV infection were raised. National-wide health education and training of health personnel was initiated for prevention of sexual contact transmission including managed MSM and people with multiple partners, as well as universal condom use, also provided proper sex education to adolescents. Surveillance site for HIV and hepatitis C were established by China Center for Disease Control and Prevention (CDC) system covering all types of high-risk populations national-wide.

Engagement of communities and civil societies also act in China for HCV and HIV control. Protection of rights and interests was put into government policy. Gender equality improved significantly.

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Summary

Global Steatosis Liver Disease Symposium APASL/AASLD/EASL/ALEH

Global Steatotic Liver Disease Symposium APASL/AASLD/EASL/ALEH
GS1-2

Dr. Aleksander Krag
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University of Southern Denmark & Odense University Hospital
Denmark

Role of Alcohol in Steatotic Liver Disease

Steatotic Liver Disease (SLD), former known as fatty liver disease, encompasses a range of liver conditions with fat accumulation in the liver. However, the role of alcohol in the progression and exacerbation of SLD is significant and multi-faceted. Alcohol consumption, particularly chronic and heavy use, directly contributes to the development of Alcohol-Related Liver Disease (ArLD), a subset of SLD. ArLD progresses from simple steatosis (fatty liver) to more severe forms like alcoholic hepatitis, fibrosis, and cirrhosis. The liver, responsible for metabolizing alcohol, undergoes oxidative stress and inflammation due to the toxic metabolites produced during this process. This stress damages liver cells, leading to fat accumulation, inflammation, and eventually scarring. The interplay between alcohol and other risk factors for SLD, such as obesity, metabolic syndrome, and diabetes, can accelerate liver damage. These risk factors are synergistic. Alcohol exacerbates insulin resistance, a key component of metabolic syndrome, which in turn contributes to the progression of Metabolic dysfunction Associated Steatotic Liver Disease (MASLD), another form of SLD. Furthermore, alcohol can influence gut microbiota, affecting metabolic functions and promoting liver inflammation.

The threshold of alcohol consumption that leads to ArLD varies among individuals, influenced by genetic factors, gender, overall health, and concurrent metabolic conditions. This variability complicates the management and prevention strategies for SLD. Biomarkers play a crucial role in diagnosing and managing Alcohol-Related Liver Disease (ArLD). They enable early detection of liver damage, monitor disease progression, and assess the response to treatment.

Management of SLD, particularly ArLD, involves lifestyle interventions with a focus on reducing alcohol intake. Complete abstinence is often recommended for individuals with ArLD, as even moderate alcohol consumption can aggravate liver damage. Moreover, addressing other metabolic risk factors, such as obesity and diabetes, is crucial in managing SLD.

Dr. Graciela Elia Castro-Narro
Latin American Association for the Liver Study (ALEH),
Department of Hepatology and Transplant at Médica Sur Hospital,
Department of Gastroenterology at the National Institute of Medical Sciences and Nutrition "Salvador Zubirán"
Mexico

MASLD in a Global Context: Latin American Experiences

Latin America is of the first places in the world in terms of obesity and diabetes, and a constant increase has been observed in its global rates. This increase has also been reflected in metabolic-associated steatotic liver disease (MASLD), with a prevalence of 30.45% in 2016 and reaching 68% in 2022, depending on the diagnostic method and the population studied. This high prevalence and the tendency to continue increasing in the coming years make it one of the main public health problems in Latin America and the world, with a large burden of disease. This increase in prevalence has been recorded in various age groups, increasingly at a younger age.

In Latin America, a prevalence of 7.11% of Metabolic Steatohepatitis (MASH) is reported in the general population and up to 16.02% (95% CI: 3.24 – 52.08%) in patients with MASLD, making it one of the main etiologies of chronic liver disease, overcoming the viral etiology that is progressively decreasing.

In the Latino population, genetic factors play an important role in the development and progression of MASLD since a greater presence of PNPLA3 polymorphisms associated with MASH and Fibrosis is found.

Hepatocellular carcinoma (HCC) related to MASLD is reported in up to 9% in Latin America, although this number could be higher if HCC related to cryptogenic liver cirrhosis is taken into account. In South America, a significant increase, reaching up to 28%, of MASLD has been observed in patients with HCC without cirrhosis.

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Summary

State-of-the Art Lecture

State-of-the Art Lecture

SAL1-2

Dr. Lai Wei

Hepatopancreatobiliary Center, Beijing Tsinghua Changgung Hospital,

School of Clinical Medicine, Tsinghua University

China

Should be Digital Pathology in MASLD now

Historically, the diagnosis of nonalcoholic steatohepatitis (NASH) is based on the presence and pattern of specific histological characteristics on liver biopsy. Up to now, liver biopsy is still the surrogate endpoint for NASH specific agent to be approved by United States Food and Drug Administration and and the European Medicines Agency, although it is an invasive approach. However, a few of score systems were used, and inter-observer as well as intra-observer disagreement exists. Therefore, there is a significant unmet need for developing objective, and quantitative technique for diagnosis, even for assessment of treatment response objectively on liver histology to bypass interpreted subjectively.

Artificial intelligence promotes digital pathology development. Recently, machine learning has made integration of artificial intelligence and digital pathology, it brings us to a new ear to understand deeply histology that were limited and not replaced by radiology.

There have been increasing efforts to leverage on advances in artificial intelligence (AI) and digitized whole-slide images to develop various AI-assistive tools to improve/replace manual histopathologic interpretation. Recent endeavors include machine learning models based on deep convolutional neural networks requiring pixel-level annotations for supervised model training, and algorithms based on second harmonic generation (SHG)/2-photon excitation fluorescence laser microscopy, which allows the identification, localization, and characterization of collagen fibers.

We developed an automated tool that accurately quantifies the critical components of NASH histological assessment, named as qFIBS, which offers a tool that could potentially aid reproducibility and standardization of liver biopsy assessments required for NASH therapeutic clinical trials. In which, qFibrosis provides more benefits, including reducing inter-observer as well as intra-observer disagreement, find more histology response information (location, quantitation, etc).

Recently, metabolic dysfunction-associated steatotic liver disease (MASLD) was proposed to including more patients under Steatotic Liver Disease (SLD) umbrella, the digital pathology maybe a good tool to help us to understand histology more for MASLD patients, find new mechanism, explant the rational and interaction among sub-groups.

State-of-the Art Lecture

SAL2-1

Dr. Tawesak Tanwandee

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Thailand

Can Blood-Based Biomarker HCC Surveillance Replace Ultrasound?

Hepatocellular carcinoma (HCC), a leading cause of cancer mortality globally, especially in Asia, often presents at advanced stages with limited therapeutic options. Current surveillance standards recommend ultrasound in conjunction with alfa-fetoprotein, yet the effectiveness of ultrasound is notably reduced in patients with advanced cirrhosis or obesity, and is subject to radiologist interpretative variability. Advances in HCC screening, such as short protocol CT or MRI, demand complex equipment and experienced radiologists.

Recent studies have explored multi-biomarker blood tests (mt-HBT) for HCC surveillance, especially in compensated cirrhosis patients. These include biomarkers like AFP-L3, PIVKAII, and algorithms such as GALAD, GAAD, and ASAP score. Risk-based surveillance approaches have also been investigated for enhanced cost-effectiveness. Additionally, emerging research on cell-free DNA-based tests shows higher specificity for HCC. This body of evidence suggests that mt-HBT significantly outperforms ultrasound in early-stage HCC detection. Hypothetical models indicating improved adherence to blood-based biomarkers further underscore their potential advantages.

These findings could revolutionize HCC surveillance protocols, enhancing detection efficiency and potentially improving long-term patient outcomes. However, current studies have not extensively examined implementation in real-world settings, leaving questions about potential false positives and negatives unaddressed.

In conclusion, while blood-based HCC surveillance appears promising, offering increased sensitivity and reduced interpretative bias, its efficacy in replacing ultrasound as the standard practice requires further validation in real-world applications.

State-of-the Art Lecture

SAL2-2

Dr. Diana Alcantara-Payawal

Department of Internal Medicine, Fatima University Medical Center

Hepatology Committee, Cardinal Santos Medical Center

Philippines

Unraveling the Crosstalk: Understanding the Interplay Between MAFLD Pathogenesis and Treatment Strategies

MAFLD is a complex condition characterized by the accumulation of fat in the liver in individuals who consume little or no alcohol. MAFLD is a disease resulting from dysregulated metabolism, lipotoxicity, genetic variants, and changes in the gut microbiome

The pathogenesis of MAFLD involves a multifactorial interplay of genetic, metabolic, environmental, and lifestyle factors. Understanding this cross-talk between pathogenesis and treatment is crucial for developing effective therapeutic strategies. MAFLD is closely linked to obesity. Insulin resistance plays a central role in the pathogenesis of MAFLD. This identifies a metabolic mechanism resulting in an imbalance of liver energy metabolism due to an excess delivery of lipids and carbohydrates to the organ that overcomes its ability to oxidize these substrates or to export them as incorporated into very low-density lipoproteins (VLDL). It leads to increased lipolysis in adipose tissue, resulting in elevated free fatty acid (FFA) levels. Excess FFAs are taken up by the liver, leading to hepatic steatosis. Accumulation of lipids in the liver triggers oxidative stress and inflammatory responses. This involves the activation of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), and the recruitment of immune cells, contributing to hepatocyte injury and fibrosis. Alterations in the gut microbiota composition can influence the development and progression of MAFLD. Dysbiosis leads to increased gut permeability, promoting the translocation of bacterial products (e.g., lipopolysaccharides) into the liver, exacerbating inflammation and metabolic dysfunction. Genetic polymorphisms and epigenetic modifications contribute to individual susceptibility to MAFLD. Variants in genes involved in lipid metabolism, insulin signaling, and inflammation influence disease progression and treatment response.

Treatment:

1. Lifestyle Modifications: Dietary interventions, weight loss, and regular exercise remain the cornerstone of MAFLD management. Caloric restriction, particularly reducing intake of refined carbohydrates and saturated fats, can improve insulin sensitivity and reduce hepatic fat accumulation.
2. Pharmacotherapy: Several pharmacological agents are being investigated to treat NAFLD/NASH. These include insulin sensitizers (e.g., pioglitazone, metformin), lipid-lowering agents (e.g., statins, fibrates), antioxidants (e.g., vitamin E), and agents targeting inflammation and fibrosis (e.g., pentoxifylline, obeticholic acid).
3. Targeting Gut Microbiota: Probiotics, prebiotics, and antibiotics are being explored to modulate gut microbiota composition and improve MAFLD outcomes. These interventions aim to restore gut barrier function, reduce bacterial translocation, and mitigate inflammation.
4. Novel Therapeutic Targets: Emerging research is uncovering novel molecular targets implicated in MAFLD pathogenesis, such as bile acid receptors, inflammasomes, and fibrogenic pathways. Targeting these pathways holds promise for developing more effective and specific therapies for MAFLD.

MAFLD is a complex disease with diverse pathogenic mechanisms and variable clinical outcomes. Effective management requires a multifaceted approach targeting the underlying drivers of disease progression. On one side is the development of liver steatosis in the context of a systemic metabolic derangement and its impact on the clinical manifestations and outcomes . On the other is the development of a chronic liver disease with possible evolution to liver cirrhosis.

Future research should focus on elucidating the intricate interplay between these pathogenic factors and identifying novel therapeutic targets to improve MAFLD treatment outcomes. Personalized medicine approaches considering individual genetic, metabolic, and environmental factors may enhance treatment efficacy and precision in MAFLD management.

State-of-the Art Lecture

SAL3-1

Dr. Jacob George

Robert W. Storr Professor of Hepatic Medicine at the Storr Liver Centre,

Westmead Institute for Medical Research, University of Sydney

Australia

Metabolic (dysfunction) Associated Fatty Liver Disease (MAFLD): From concept to practice

In 2020, the term Metabolic (dysfunction) Associated Fatty Liver Disease or MAFLD) to describe liver disease characterized by steatosis in the context of systemic metabolic dysregulation was introduced. Subsequently, a framework for defining the disease was published, rapidly followed by widespread endorsement in national and pan-national clinical practice guidelines. This was led by APASL which published the first MAFLD CPG in 2020 and forms the basis for diagnostic and clinical considerations as well as clinical research in our region.

While there are many positive attributes to the framework that is MAFLD, singular among them is the move from a disease of exclusion to one that is based on a simple set of positive criteria. Gone was the requirement to exclude other liver diseases for a diagnosis of MAFLD to be entertained, and in was the necessity to consider every patient from a holistic perspective about all the liver diseases they might harbour, and the need to treat each liver disease on its own merits. To enable this leap forward, the term dual (or more) aetiology liver disease was introduced to encompass patients who might have MAFLD and another disease such as that related to alcohol, viral hepatitis or autoimmune liver disease. Dual aetiology liver disease is common and numerous studies highlight the independent impact of each of the component disease on the on disease progression and outcomes. Importantly, the diagnostic criteria for alcohol-related liver disease was left to experts in the alcohol field, with future research on the interaction of MAFLD and alcohol expected to deliver novel insights on outcomes. Moreover, the introduction of three diagnostic groupings (overweight/obese, health weight MAFLD, and MAFLD arising in the context of type 2 diabetes) was introduced to reduce the obvious heterogeneity of fatty liver disease when considered as a single entity. Subsequent studies have shown that the three sub-types of MAFLD have different presentations, disease trajectories and outcomes, enabling further research and dissection of mechanistic pathways and potential treatment algorithms. As we sit we on the cusp of novel diagnostics, big-data insights, artificial intelligence-based algorithms and pharmacotherapies, MAFLD will be an enabler for precision medicine.

State-of-the Art Lecture

SAL3-2

Dr. Kiyoshi Hasegawa

Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery,

Graduate School of Medicine, the University of Tokyo

Japan

Surgical resection following systemic therapy for advanced hepatocellular carcinoma

Surgical resection has been established as a curative treatment option for hepatocellular carcinoma (HCC). However, the recurrence rate is high (70% within 3 years even after curative resection), which remains an unsolved problem. Recently, the advance of systemic therapy using immune-checkpoint inhibitors and/or molecular target agents is remarkable, which is now inducing another paradigm shift in the therapeutic approach for HCC.

According to the BCLC guidelines, only systemic therapy is recommended for advanced HCC with macroscopic vascular invasion (MVI), however, the MST was not satisfactory (shorter than 2 years). Japanese liver surgeons have challenged to treat HCC with MVI by surgery, and reported much better survival than systemic therapy. To obtain even better outcomes, preoperative systemic therapy was introduced for advanced HCC. Recently, we have conducted several prospective phase II trials to evaluate efficacy of combination strategy of systemic therapy followed by surgical resection for advanced HCC.

In my presentation, I will show the current role of surgical resection using the recent advance of systemic therapy for HCC.

State-of-the Art Lecture

SAL4-1

Dr. George Lau

Humanity and Health Clinical Trial Center, Humanity and Health Medical Group,

Hong Kong SAR, China

APASL initiative to reshape the discipline of Hepatology in Asian-Pacific region beyond 2024

Till 2023, liver diseases remain a major health threat in Asian-Pacific region,
accounting for two-third of the global deaths due to acute-on-chronic liver failure, end-staged liver cirrhosis and hepatocellular carcinoma. The major aetiology of liver diseases are chronic hepatitis B and C, metabolic dysfunction-associated (MAFLD) and alcoholic fatty liver disease (AFLD). Asian-Pacific Association for the Study of Liver (APASL) is the premier Asian-Pacific liver society set up in 1978 aiming to create and to disseminate the best evidence-based clinical knowledge to relieve patients' suffering from liver diseases. Sharing the same vision, APASL is in alliance with European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD) and Latin American Association for the study of the liver (ALEH). In the past few decades, there have been rapid advancement and availability of laboratory, imaging diagnostic and endoscopic technology, more stringent and transparent conduct of clinical trials, development of sophisticated computation and big data collection (with artificial intelligence-AI) and change in social-economic environment. Very importantly, machine learning (ML) and AI algorithms can help to address data integrity by ensuring consistency and reliability across various data sources and over time. In the age of AI, where machine learning models continuously learn and evolve, maintaining data integrity is not just a one-time effort; it's an ongoing discipline that requires robust strategies and advanced technological support. New drug development is anticipated to be supercharged with AI. With the digitalisation of medical data, more personalised medical care can be provided to our patients, especially those living in resource-limited areas. With AI-assisted robotics, medical procedures can also be more effectively and safely performed. Skills and knowledge are also necessary to perform ultrasound-based examination for liver and how to read CT-based or MRI-based imaging data. Basic sciences related to laboratory techniques used to provide clinical data should be understood. The application of AI to guide screening, diagnosis and treatment of patients with liver diseases should be enhanced. Therefore, it is now time to reshape the discipline of hepatology to update knowledge and skills which will allow us to advance our clinical management to our patients. Finally, it is of great importance to integrate the art of humanities into medical practise to reshape and modernise professional hepatology discipline with emphasize on empathy, communication, and teamwork.

State-of-the Art Lecture

SAL4-2

Dr. Ryuji Hamamoto

National Cancer Center Research Institute

Japan

AI research for clinical application: from research planning to regulatory approval

Expectations for artificial intelligence (AI) have been rising in recent years due to advances in machine learning technology, particularly deep learning, the emergence of inexpensive, high-performance GPUs (Graphics Processing Units), and the expansion of public databases as the Big Data era begins, making it easier to utilize large data sets. In the long history of AI research, however, it has not been smooth sailing. There have been periods of high expectations for AI, known as the "AI boom," and then a period of "AI winter," when AI failed to technologically meet those high expectations, leading to widespread disappointment in AI. On the other hand, an important aspect of the third AI boom, which began with the advent of deep learning, is that social implementation is progressing. AI is now being utilized in a wide range of fields, such as face recognition for airport security, automatic translation, automatic voice recognition, and home appliances. The medical field is no exception, and the development of SaMDs (software as medical devices) utilizing AI is underway around the world, and many products have been approved as medical devices and are being used in clinical practice. In 2016, we launched the project "Development of an Integrated Cancer Medical System Using Artificial Intelligence " as a JST CREST research project, and have been working on various medical AI research and development projects. As a result, our AI-based endoscopy diagnosis support software was approved as a medical device in Japan in 2020, and later conformed to the CE Mark in Europe, and is already in clinical use in Japan and Europe. In addition to AI-based endoscopy-assistive software, the company has also published a variety of other medical AI-related results that have led to clinical applications. In this presentation, I will introduce the current status and future possibilities of medical AI based on our experience in promoting the entire process from research planning to actual clinical application.

State-of-the Art Lecture

SAL5-2

Dr. Fu-Sheng Wang

Department of Infectious Diseases and Liver diseases, the Fifth Medical Centre of Chinese PLA General Hospital, National Clinical Research Center for Infectious Diseases

China

Baseline age for antiviral treatment influences functional cure of chronic hepatitis B in young children

Current data including real-world evidence suggest that early initiation of antiviral treatment promotes functional cure in children with chronic hepatitis B (CHB) though some data did not support the notion. The reasons may be that there are few data from randomized controlled trials of antiviral therapy in young children with CHB.

First, our real-world study enrolled 372 children aged 1–16 years, with active CHB who underwent either nucleos(t)ide analog monotherapy or combination therapy with interferon-α (IFN-α) for 24–36 months. Longitudinal investigation revealed more rapidly dynamic reduction in HBV DNA, HBeAg, and HBsAg levels in children aged 1– < 7 years than in those aged ≥ 7–16 years with CHB. According to further age-stratified analysis, HBsAg loss rates were successively reduced in the children with CHB who were 1– < 3, 3– < 7, 7– < 12, and 12–16 years old (62.61% vs. 41.13% vs. 25.45% vs. 1.64%, respectively; $p < 0.0001$). No serious adverse events were observed throughout the study period.

Second, we recently conducted a meta-analysis that focused on the association between baseline age to initiate antiviral treatment and the functional cure of CHB in children. The result, from 18 studies with 2459 children with CHB, showed that children aged 1-7 years exhibited better treatment response than the counterparts aged 8-18 years old, especially among immune clearance phase children with CHB. In addition, some studies also showed the same notion in immune tolerance phase children with CHB.

Why is the cure rate high in young children with CHB receiving antiviral treatment? Major factors influencing the functional cure rate of CHB in younger children receiving antiviral therapy are as follows: hepatocyte proliferation, smaller and lower complexity of viral pool and immunological characteristics in children.

In conclusions, the available data demonstrated that baseline age at initiation of antiviral treatment is significantly associated with higher functional cure rate in young children with CHB though some data did not support the notion. Therefore, future prospectively randomized controlled trials are needed to further confirm the findings and explore the unmet mechanisms underlying the cure of the disease.

State-of-the Art Lecture

SAL7-1

Dr. Tatsuhiro Shibata

Laboratory of Molecular Medicine, The Institute of Medical Science, The University of Tokyo

Japan

Epigenetic liquid biopsy

Currently, mutation-based liquid biopsy is widely used in the clinical management of advanced and recurrent cancers. In particular, monitoring emergency of therapy-resistant clones or evaluation of minimal residual tumors have provided significant information in clinical practice. In contrast, epigenetic liquid biopsy (DNA methylation and fragmentomics) provides unique cellular information about the status of tumor cells (such as tumor origin, tumor differentiation or degree of inflammation), which is complementary to mutation-based liquid biopsy and will open a new opportunity for cancer screening. A large-scale prospective cohort study (PATHFINDER test) has demonstrated the diagnostic significance of epigenetic liquid biopsy for early cancer detection. In this talk, I will present the current and future direction of epigenetic liquid biopsy.

State-of-the Art Lecture

SAL7-2

Dr. Jin-Lin Hou
State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University,
School of Basic Medical Sciences, Southern Medical University, Guangzhou.
Institute of Cellular Medicine, Newcastle University Medical School,
Medical College of Georgia, Augusta University
China

China steers towards HBV mother-to-child transmission elimination

Hepatitis B virus (HBV) infection is a major global public health issue. In 2016, WHO released the Global Health Sector Strategy on Viral Hepatitis, which proposed to eliminate hepatitis as a public health threat by 2030[1]. Mother-to-child transmission (MTCT) is the predominant transmission route of HBV. Although remarkable progress in preventing MTCT has been made, there is still a last mile to achieve the elimination goal.

In the recent issue of Nature Medicine, Yin et al demonstrated a real-world implementation of a multilevel interventions program to prevent HBV MTCT in China[2]. They found that the comprehensive interventions among HBV-infected pregnant women were feasible and effective in dramatically reducing MTCT. SHIELD program provided an example of accelerating the elimination of HBV MTCT. Three measures for implementing PMTCT are essential elements. First, the management algorithm for preventing HBV MTCT should be standardized according to international consensus and be applied in the practice of PMTCT. Following that, digital health could be used as a management tool to follow up participants and collect data. Finally, the implementation process can be rolled out in multiple stages, including pilot, implementation and community scale-up stages, regardless of geographic, socioeconomic statuses, and hospital settings.

China accounts for around 1/3 of hepatitis B infection all over the world. More than 50 000 newborns in China are infected with HBV annually[3]. With the beginning of the hepatitis B vaccination program for newborns and infants in 1992 and expanded program on immunisation in 2002 (the free-vaccine policy), up to 2015, the vaccination coverage had an great increase to over 95%. As a result, the HBsAg prevalence in the population aged 1–4 years was sharply declined to 0.32%[4].

In 2010, National Health Commission began to integrate and standardize prevention of MTCT efforts for HIV, syphilis and HBV. Subsequently, the ministry initiated the Chinese National Integrated Prevention of Mother-to-Child Transmission of HIV, Syphilis, and Hepatitis B Program (iPMTCT Program) nationwide[5]. The services are provided through a collaboration between maternal and child health clinics, the national and local Centers for Disease Control and Prevention, and general hospitals. Integrated PMTCT services proved to be feasible and effective, and they are now part of the routine maternal and child health services provided to infected women.

However, what can not be ignored is the strength of nongovernmental organizations, medical communities and health providers. Before 2015, a standardized management algorithm was lacking, SHIELD Program organized experts in the field of infectious diseases, hepatology, immunology, obstetrics, and public health to make the algorithm for preventing HBV MTCT and the algorithm has been adopted in clinical practice in China[6]. In addition, SHIELD Program investigated a novel mobile health tool called SHIELD, which breakdown barriers among hepatologists, gynaecologists, and HBV-infected mothers. SHIELD Program not only provides health benefits for patients, but also has great impact on the decision making and resource allocation of the government, such as treatment during pregnancy.

Elimination of viral hepatitis will require a shifting emphasis from a focus on individual patients to an emphasis on a coordinated public health approach to prevention. Especially, the Framework for the Triple Elimination of Mother-to-Child Transmission of HIV, Hepatitis B, and Syphilis offers a coordinated approach towards achieving triple elimination of MTCT of HIV, hepatitis B, and syphilis through access to quality reproductive, maternal, newborn, and child health (RMNCH) services for all women, their children and families, in the context of universal health coverage. SHIELD Program also provides important support and cooperation. In 2022, National Health Commission released the Action Plan for the Elimination of Mother-to-child Transmission of AIDS, Syphilis and Hepatitis B (2022-2025), which clearly promoted the elimination assessment work by the province. Up to the end of 2023, Beijing, Guangdong Province, Hunan Province, Jiangsu Province, Yunnan Province have been validated on MTCT elimination.

Based on the successful experience from iPMTCT Program and SHIELD Program, China is steering towards HBV MTCT elimination and zero HBV MTCT is an achievable target. We believe that, a future without hepatitis B will come from dream to reality in the near future.

State-of-the Art Lecture

SAL8-1

Dr. Ji-Dong Jia

Liver Research Center Beijing Friendship Hospital, Capital Medical Unviversity

China

Update on the management of primary biliary cholangitis: something old, something new

Primary Biliary Cholangitis (PBC) is a chronic autoimmune liver disease characterized by progressive non-purulent destructive inflammation of intrahepatic bile ducts, leading to cholestasis, fibrosis and finally cirrhosis. The treatment landscape for PBC encompasses various modalities, ranging from traditional approaches to emerging therapies. Ursodeoxycholic acid (UDCA) remains the first-line therapy. It promotes bile flow, reduces liver enzymes, and may slow disease progression. However, a significant proportion of patients exhibit incomplete response to UDCA. Farnesoid X receptor (FXR) is a nuclear receptor that plays a crucial role in regulating bile acid synthesis, transport, and metabolism. Activation of FXR by obeticholic acid (OCA) modulates these processes, leading to a reduction in bile acid accumulation and subsequent hepatocellular injury. Now it has been regarded as a second-line therapy for PBC. Clinical trials have demonstrated its efficacy in reducing ALP levels and potentially slowing disease progression, especially in patients with inadequate response to UDCA. Peroxisome proliferator-activated receptor (PPAR) activation may modulate inflammation and improve liver function. Therefore, a pan-PPAR agonist, bezafibrate, and a PPAR alpha agonist, fenofibrate, have been explored as a monotherapy or in combination with UDCA. The clinical trials and real-world clinical studies showed that these agents could improve the liver biochemistry as indicated by remarkable reduction in serum levels of alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT). It has been demonstrated that the addition of the fibrates to UDCA may provide additional benefits in terms of histological and survival improvement. Novel PPAR agonists including seladelpar (□), elafibranor(□□□□ and saroglitazar (□□□□ also show promising results in clinical trials. Norursodeoxycholic Acid (norUDCA), a side-chain-shortened derivative of UDCA, has been studied for its potential to improve bile flow and reduce liver injury in PBC patients. As a fibroblast growth factor 19 (FGF19) analog, NGM282 regulates bile acid synthesis and has demonstrated potential in reducing liver biochemistry and improving histological features in PBC patients. These diverse treatment modalities reflect the evolving understanding of PBC pathogenesis and the ongoing efforts to improve outcomes for patients. Ongoing research aims to refine existing therapies and identify novel targets for intervention.

State-of-the Art Lecture

SAL9-1

Dr. Massimo Giuseppe Colombo

EASL International Liver Foundation,Geneva Switzerland

Italy

Towards risk stratified screening of hepatitis C related hepatocellular carcinoma(HCC)

Detection of early stage HCC through surveillance is lifesaving as it allows scaling up curative treatments. In the era of hepatitis C virus (HCV)elimination, the exponential growth of HCV-cured individuals who need surveillance has fostered the race towards cost-effective screening programs grounded on the identification of patients with advanced liver disease (and co-morbidities), who retain the greatest risk of developing HCC independently of HCV eradication. The more widely adopted strategy has been through the use of the FIB-4 score, a simplified scoring system which assesses liver disease severity by combining the routine chemistries transaminases and platelet count with patient age. Due to the high number of patients with undetermined scores with FIB-4, a second-line noninvasive staging of liver disease is often deemed necessary using elastography techniques. This notwithstanding, development of performant biomarkers for risk-stratified screening of individuals at risk of developing HCC stands as a prerequisite for the implementation of cost effective programs of surveillance. At present a heterogeneous array of experimental blood-based biomarkers are under scrutiny for improving prediction of HCC in both viraemic and cured individuals. Standing as more promising biomarkers were vehicles of small RNA clusters like the extracellular vesicles, cell free DNA combined with gender, age, AFP and decarboxylated prothrombin DCP, methylation markers of 28 genes combined with AFP,AFP-L3,DCP, age and sex, all demonstrating at least 90% specificity and from 74% to 100% sensitivity. Recent attempts to reinforce clinical algorithms for HCC prediction through the incorporation of polygenic scores were met with little success. Noticeably, risk-stratified screening might be used with a collateral scope, like to provide less intensive screening to low-risk individuals in order to reduce the unnecessary harms and costs of over-screening, tailoring screening age range, frequency, and method, including CT scan and abbreviated MRI, to each risk group. The implementation of a risk-stratified surveillance program for HCC is scattered with multiple barriers which include the histological and molecular heterogeneity of the tumor, the lack of external validation and calibration of the current biomarkers, except for alpha-fetoprotein, and the time dependence of the outcomes.

State-of-the Art Lecture

SAL10-1

Dr. Jia-Horng Kao

Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine

Hepatitis Research Center, National Taiwan University Hospital

Taiwan

Precision Management of Patients with HBV Infection

Precision medicine is defined to understand a disease at a more detailed level to guide the diagnosis and prevention, to develop targeted therapies, and to predict disease outcome more precisely to achieve a customized healthcare for a subgroup of patients. Precision medicine is a paradigm shift from guideline-specific therapy toward patient-specific ones. The strategies of precision management in chronic hepatitis B (CHB) are focused on prediction and action. Currently, several hepatitis B viral biomarkers are discovered to serve as predictors for disease progression, risk of hepatocellular carcinoma (HCC) occurrence, and responses to nucleos(t)ide analogue (NA) therapy. In this presentation, three serum biomarkers, quantitative HBsAg, HBcrAg, and HBV RNA, for the precision management of patients with CHB will be summarized and discussed. Quantitative HBsAg provides prediction in staging clinical phases, HBsAg seroclearance, relapse after cessation of NA therapy, and risk of HCC development. Several studies highlight the potential role of HBcrAg as a biomarker for predicting functional cure, risk of HCC development, and relapse after NA withdrawal. HBV RNA may predict HCC risk and relapse after NA withdrawal; however, the data remain limited. Currently, clinical medicine, basic biomedical research, as well as new sources of health-related data (e.g. wearable devices with biosensors, internet of things, and networks) generate huge amount of biomedical and health-related data, which exceed the limit of analysis by humans, necessitating the help of machines to help the analysis. Artificial intelligence (AI) is thus providing a paradigm shift toward the practice of precision medicine. In summary, novel HBV biomarkers and future application of AI are promising to predict clinical outcomes of untreated and treated CHB patients, including antiviral therapy response, relapse after cessation of therapy, risk of HCC development, and functional cure.

State-of-the Art Lecture

SAL10-2

Dr. Norihiro Kokudo

National Center for Global Health and Medicine

Japan

Role of liver resection in the era of advanced systemic therapy for hepatocellular carcinoma

The recent dramatic progress in systemic therapy for hepatocellular carcinoma (HCC) provides the possibility of a combination of surgery and systemic therapy including adjuvant, neoajuvant, or conversion settings. After the turn of the century, there have been at least three negative studies testing adjuvant therapies after curative resection or ablation, including Uracil-Tegafur an oral chemotherapeutic drug, sorafenib, and peretinoin, a synthetic retinoid that may induce apoptosis and differentiation of liver cancer cells. Using more potent immuno-checkpoint inhibitors (ICIs), there are at least 4 phase-III trials ongoing for adjuvant immunotherapy: Nivolumab, Durvalumab/Bevacizumab, Pembrolizumab, and Atezolizumab+Bevacizumab. Very recently, the last one showed significantly better RFS for adjuvant Atezolizumab+Bevacizumab. Another promising combination of surgery and systemic therapy is neoadjuvant therapy for potentially resectable cases or conversion strategy for oncologically unresectable cases. There have been 2 neoadjuvant trials for technically or oncologically unresectable HCCs ongoing in Japan: LENS-HCC trial using Lenvatinib and RACB study using Atezolizumab+Bevacizumab. Although we may need longer follow-up, OS in resected cases seems much higher than that for unresectable cases. Recently, Japan Liver Cancer Association (JLCA) and the Japanese Society of HPB Surgery (JSHPBS) created a joint working group on “so-called borderline resectable HCC.” They compiled a Japanese consensus on this issue and it has been published on the websites of JLCA and JSHPBS. The definition of resectability or borderline resectability provides the common language on advanced HCC for investigators and it is a useful tool for future clinical trials.

APASL 2024 Kyoto

The 33rd Annual Meeting the Asian Pacific Association for the Study of the Liver

Summary

Basic and Clinical Research of Cholangiocellular Carcinoma

Basic and Clinical Research of Cholangiocellular Carcinoma

BCR1-1

Dr. Cosmas Rinaldi Adithya Lesmana

Department of Internal Medicine, Hepatobiliary Division,

Dr. Cipto Mangunkusumo National General Hospital, Medical Faculty Universitas Indonesia, Indonesia

Innovation on Clinical Management of Hepatocellular Carcinoma in the era of Systemic Therapy

Hepatocellular carcinoma (HCC) is still becoming a major burden all over the world due to increase of metabolic liver disease despite hepatitis virus B and C infection. Metabolic dysfunction associated fatty liver disease (MAFLD) is an emerging disease, where it can lead to portal hypertension, liver cirrhosis, as well as liver cancer development. Most of the patients have come in the late stage of the disease. Therefore, early detection is still the main key for a success disease control and prolong patient's survival, however, in the case of MAFLD, it is not always easy to find early cancer development due to standard screening methods limitations. Innovation in endoscopic ultrasound (EUS) can be a promising secondary tool not only for confirming diagnosis, but also in the advance management.

Surgical approach is still the best treatment for managing liver cancer, however, the post-surgical recurrence rate is still high. In the intermediate stage of HCC, the combination of loco-regional therapy with immunotherapy as well as oral systemic therapy have shown a satisfaction result when compared to loco-regional therapy alone.

The new concept of neo-adjuvant therapy after resection has opened the new horizon in the liver cancer management. Recently, adjuvant therapy has been proposed to prevent tumor recurrency after surgery. This might be a promising concept for the future beyond the guidelines. It would still need further and larger study to conclude that this concept would be incorporated in the clinical practice guideline.

Basic and Clinical Research of Cholangiocellular Carcinoma

BCR1-2

Dr. Tatsuya Kakegawa

Gastroenterology & Hepatology, Tokyo medical university

Japan

Current diagnosis of intrahepatic cholangiocarcinoma -From tumor localization to genetic abnormalities-

The incidence of intrahepatic cholangiocarcinoma(ICC) is increasing, with the highest rates seen in Eastern Asia when compared with Western countries. It is asymptomatic in the early stages, and about 20% of ICC are diagnosed incidentally, and no effective screening method has been established yet. It is important to know risk factors including primary sclerosing cholangitis and non-bile duct specific diseases as chronic hepatitis C virus and hepatitis B virus infection, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, alcoholic liver disease, and autoimmune hepatitis. Screening these populations by clinical examination, tumor markers, and abdominal ultrasound may aid in early diagnosis. On clinical examination, persistently elevated bilirubin levels, hepatobiliary enzymes, and the tumor markers CA19-9 and CEA are useful for auxiliary diagnosis. Contrast-enhanced CT(CECT) is widely used for differential diagnosis and localization evaluation of ICC from the viewpoints of simplicity, dissemination, and cost. Also Gd-EOB-DTPA contrast-enhanced MRI is useful for localization diagnosis because it shows the tumor as a clear low-signal area in the hepatocellular phase. The Kupffer phase of contrast-enhanced US(CEUS) depicts the tumor as a clear defect image, and its detection sensitivity is reported to be high. However, CEUS is only an adjunct to CECT and MRI due to the presence of blind spots and reproducibility problems. The most common extra-hepatic metastases of ICC are lung, bone, and distant lymph node metastases. The advantage of FDG-PET/CT is that it allows systemic search for these metastases in a single examination. Meta-analysis shows that "vascular invasion" is one of the prognostic factors, and it is important to accurately determine the presence or absence of vascular invasion. EUS is excellent for the diagnosis of hilar cholangiocarcinoma and is particularly useful in predicting the extent of bile duct invasion in cases of specific resection. Cholangiography has good spatial resolution and is useful in diagnosing the extent of cancer invasion. In ICCs near the porta hepatis, mapping biopsy under direct view with cholangioscopy can diagnose the extent of bile duct invasion and reduce the number of positive cases of surgical resection margins. Liver tumor biopsy is also an option for atypical cases on imaging and for non-resected cases that require systemic therapy. Biopsy can help identify ICC-specific driver gene abnormalities, such as FGFR2 fusion gene and IDH1/2 mutations, and aid in the selection of therapeutic agents.

Basic and Clinical Research of Cholangiocellular Carcinoma

BCR1-3

Dr. Shun Kaneko

Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University (TMDU)

Japan

The Progress of Internal Medicine for Intrahepatic Cholangiocarcinoma

Cholangiocarcinoma (CCA) is the second most common liver cancer after hepatocellular carcinoma. CCAs are a group of heterogeneous tumors classified as either intrahepatic or extrahepatic (perihilar and distal) based on its location in the biliary tract. Globally, the incidence of intrahepatic CCA (ICC) is increasing. ICC is a highly aggressive malignancy that arises within the liver and presents with features of biliary differentiation. The sole potentially curative treatment is surgical resection. However, due to the late manifestation of clinical symptoms, fewer than one-third of patients are eligible for surgery. Unfortunately, ICC is inherently highly resistant to chemotherapy, with a median overall survival below one year under palliative chemotherapy (gemcitabine+ cisplatin). Though unresectable ICC exhibits very poor prognosis, the development of novel therapeutic agents is emerging, as the genomic profile of ICC comes to light. Second-line therapies are available to target pathways associated with specific gene mutations (e.g., FGFR2, IDH1, NTRK). Notably, the combination of durvalumab with chemotherapy (gemcitabine + cisplatin) has shown significant improvements in overall survival, progression-free survival, and objective response rate compared to a placebo in conjunction with chemotherapy, as first-line therapy. In addition to these advancements in systemic therapy, the background liver disease and liver function are focused on prognosis associated with liver function in the context of ICC, including our data. This presentation provides an overview of internal medicine treatment in relation to ICC.

Basic and Clinical Research of Cholangiocellular Carcinoma
BCR1-4

Dr. Shunichi Ariizumi
Dept. of surgery, Institute of Gastroenterology, Tokyo Women's Medical Univ.
Japan

What is the optimal indication of surgery with adjuvant therapy for intrahepatic cholangiocarcinoma?

Abstract. Background/Aim:
The optimal indication of hepatectomy with adjuvant therapy for intrahepatic cholangiocarcinoma (ICC) has not been evaluated in detail.

Patients and Methods:
We retrospectively studied 224 patients with ICC who underwent hepatectomy between 2000 and 2019. Prognostic factors for overall survival (OS) were evaluated by univariate and multivariate analysis. A total of 127 patients were treated with adjuvant therapy (62 patients with chemotherapy and 65 patients with immunotherapy) after hepatectomy, and 97 patients were treated with hepatectomy alone.

Results:
Intrahepatic metastasis (IM), lymph node metastasis (LNM) of ICC, adjuvant chemotherapy, and adjuvant immunotherapy were significant prognostic factors for OS on multivariate analysis. In 127 patients with neither IM nor LNM, the 5-year OS rate was significantly higher in 36 patients with adjuvant chemotherapy (81%) and in 34 patients with adjuvant immunotherapy (68%) than in 57 patients with hepatectomy alone (45%).

Conclusion:
The absence of IM or LNM is the optimal indication for hepatectomy with adjuvant therapy in patients with ICC.

APASL 2024 Kyoto

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Summary

Comprehension of Asian HCC by A-HOC Study and APASL HCC Guideline

Comprehension of Asian HCC by A-HOC Study and APASL HCC Guideline

HOC1-1

Dr. Hitoshi Mochizuki

Genome Analysis Center / Department of Gastroenterology, Yamanashi Central Hospital

Japan

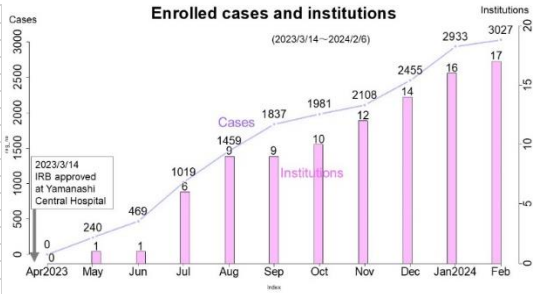
A-HOC Start-up and Current State

The A-HOC (APASL Hepatology/Oncology Consortium) study is planned to enter 10,000 cases from countries and regions in the Asia-Pacific region that are important for the development of APASL guidelines, to understand the actual situation in each country and the efficacy of new therapeutic agents such as immune checkpoint inhibitors.

This study began in January 2023 with President Omata as the principal investigator, and the first IRB was approved in March 2023.

By February 2024, 17 centers in 6 countries and regions (JPN, TUR, IDN, CHN, MNG, TWN) have participated in the study, and 3221 cases have been enrolled.

Yamanashi Central Hospital (JPN)
Okayama University (JPN)
The University of Tokyo (JPN)
Kagawa University (JPN)
Gazi University (TUR)
Dharmais National Cancer Center (IDN)
Happy Veritas Hospital (MNG)
Matsudo City General Hospital (JPN)
Beijing Tsinghua Changgung Hospital (CHN)
Nagasaki Medical Center (JPN)
Teikyo University (JPN)
Chiba University (JPN)
Yamagata University (JPN)
Humanity & Health Medical Group (CHN)
Taipei Veterans General Hospital (TWN)
Juntendo University (JPN)
Mochtar Riady Comprehensive Cancer Center Siloam Hospitals Semanggi (IDN)

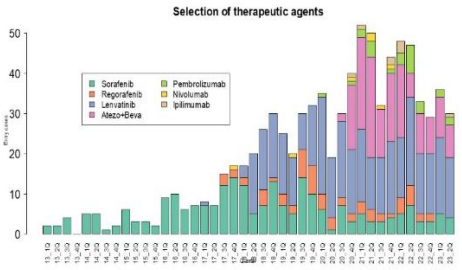


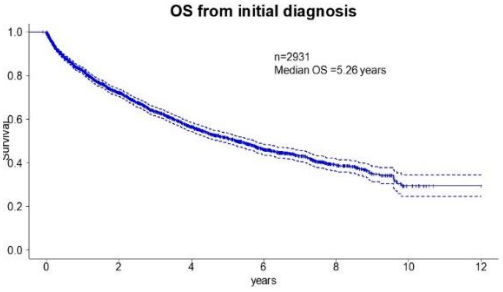
This study uses REDCap（Research Electric Data Capture）, which is highly confidential and is a revolutionary clinical research support tool that is becoming a global standard in academic medical research.

In addition, many registered researchers can view the status of their data in real time using the provided functions.

Analysis of these data shows that liver cancer, background liver, and treatment conditions vary widely from country to country and region to region, and even within the same country, there are differences between institutions, and this heterogeneity must be taken into account when formulating APASL guidelines.

In addition, treatment drugs are changing rapidly with the times, and prompt response to these changes is required.





Comprehension of Asian HCC by A-HOC Study and APASL HCC Guideline

HOC1-2

Dr. Amarsanaa Jazag

Department of Medicine OMIS school of Medicine

Mongolia

Assessment of triple therapy for NAFLD and NASH in Mongolia

Background: Although it is commendable that hepatitis caused by viruses have recently decreased in Mongolia, it is expected that liver steatosis and cirrhosis related to unhealthy lifestyles will increase. Therefore, we conducted a study to determine the results of the triple therapy of NAFLD for the first time in our country.

Methods: Before treatment, the degree of steatosis was determined using the Fibrotouch /transient elastography/ device and patients with higher than normal values of steatosis were included, and then a triple medical therapy and lifestyle modifications were recommended for 1 month, and a second measurement was performed after treatment. The treatment was performed at the outpatient clinic of Happy Veritas Hospital. Treatment consisted of atorvastatin 20-40 mg once a day, ursodeoxycholic acid 250 mg 2-3 times a day, vitamin E 400 IU, 2 capsules per day after meals. The lifestyle advice included cutting down on carbohydrates /flour, rice, potatoes, and sugar/, increasing physical activity, and losing excess weight. From the total of 150 people who participated in the study, the information of 148 eligible citizens was processed.

Results: 147 patients showed a decrease in fatty liver of 99.3%, and decrease in CAP values varied between 2 and 168 db/m respectively. Steatosis decreased in n=133 (89%) patients by at least one stage, 15 or 11% decreased by few db/m within the steatosis stage, and only in one patient (0.67%) steatosis did not decrease at all. There were patients (20.4%) whose steatosis reduced but the liver stiffness increased after treatment.

Conclusion: Triple therapy that consisted of lifestyle modifications plus statins, vitamin E and ursodeoxycholic acid was highly effective in Mongolian NAFLD patients. But there is need to re-assess why stiffness increases in certain group of patients.

Comprehension of Asian HCC by A-HOC Study and APASL HCC Guideline

HOC1-3

Dr. Muhsin Murat Muhip Harputluoglu

University Medical Faculty Liver Transplant Institute,

Transplant Hepatology and Gastroenterology Dept

Turkey

Evaluation of data from the A-HOC (APASL Hepatology/Oncology Consortium) study of patients with hepatocellular cancer in Turkey

A-HOC (APASL Hepatology/ Oncology Consortium) study is the abbreviated name of study of 'Survey on Current Status and Treatment of Hepatitis and Liver Cancer in the Asia-Pacific Region'. This international multicenter study examines the actual incidence and treatment of hepatocellular cancer in Asia Pacific countries, the background of viral and non-viral hepatitis, the actual situation of health and medical problems, and the development of new treatment methods in each country.

Aim of this presentation is to evaluate Turkey data in the A-HOC study. Basic patient data, physical examination findings at the time of carcinogenesis, blood and biochemical tests at the time of carcinogenesis, tumor characteristics, treatment methods and dates and prognostic informations of the patients entered into the A-HOC REDCap system from centers in Turkey were analyzed.

Comprehension of Asian HCC by A-HOC Study and APASL HCC Guideline

1-4

Dr. Imelda Maria Loho

Division of Gastroenterology and Hepatology, Dharmais Hospital,

Indonesian National Cancer Center

Indonesia

Hepatocellular Carcinoma in Indonesia – Where are We Now?

Hepatocellular carcinoma in Indonesia represents a significant health challenge, characterized by a high disease burden and a poor outcome. As there was no liver cancer registry in Indonesia, the Indonesian Association for the Study of the Liver took the initiative in September 2022 to establish the Indonesian National Liver Cancer Registry (RINKAS) in order to reduce the burden of liver cancer. Throughout the year, twenty hospitals across 14 provinces in Indonesia collaborated, successfully registering 2035 patients in the database. The online REDCapTM (Research Electronic Data Capture) platform was utilized. The database incorporated various features, encompassing general patient information (such as gender, age, demographics, etc.), risk factors, medical history, laboratory parameters, imaging, and therapeutic strategies.

Out of the total 2035 patients, this study focuses on 222 patients (169 male, median age 56) diagnosed with HCC between 2015 and 2022 at Dharmais Hospital, Indonesian National Cancer Center. These cases were recorded in the APASL Hepatology/Oncology Consortium (A-HOC) database and are presented in this report. Hepatitis B virus (HBV) infection remains the most common cause of HCC, affecting 133 patients (62.4%), followed by non-B non-C HCC (24.2%) and hepatitis C (12.2%), respectively. The median AFP level was 908 ng/mL, while the median largest diameter of tumor was 10 cm. A total of 156 patients (78.8%) exhibited multiple nodules, and 123 patients (63.7%) were categorized with albumin-bilirubin (ALBI) grade 1 liver function at the time of diagnosis. As many as 78 (49.1%) and 62 (39%) presented with intermediate and advanced stage according to the Barcelona Clinic Liver Cancer (BCLC) staging system, respectively. The most common initial treatment approaches included transarterial chemoembolization (TACE) and lenvatinib, administered to 48 patients (34.3%) and 40 patients (28.6%), respectively. A total of 26 patients (18.6%) underwent best supportive care. One-year overall survival rate was 61.4%. In conclusion, more rigorous efforts are needed to lower the burden of HCC in Indonesia, particularly in increasing the number of early-stage HCC to prolong survival.

Dr. Ming Yang
Hepatopancreatobiliary Center, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University
China

Comprehension of HCC in Central Asia (China)

The burden of hepatocellular carcinoma (HCC) is heavy in China, and most patients are in the middle and advanced stage when diagnosed. We should carry out early screening for patients at high risk of HCC. Systematic anti-tumor therapy is an important therapeutic strategy for patients with advanced HCC. With the rapid development of targeted, immune and other drugs, it brings more therapeutic options for patients with HCC. Translational descending treatment is also very popular in China, and some patients can get surgery through descending treatment to prolong survival.

APASL 2024 Kyoto

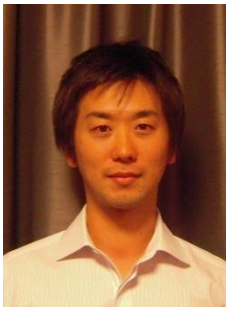
The 33rd Annual Meeting the Asian Pacific Association for the Study of the Liver

Summary

Advances in Hepatobiliary Imaging

Advances in Hepatobiliary Imaging

AHI1-1



Dr. Keitaro Sofue

Department of Radiology Kobe University Graduate School of Medicine

Japan

Applications of artificial intelligence for hepatobiliary MR imaging

Global interest in artificial intelligence (AI) applications for MR imaging is growing rapidly, fueled by significant advances in computing power and new deep learning algorithms. Recently, deep learning reconstruction (DLR) algorithms have been developed for MRI that are trained to improve image quality, and the combination of DLR with various sequences has produced favorable results in hepatobiliary MR imaging. DLR has been proven successful in reconstructing MR images with a high signal-to-noise ratio from undersampled k-space data to reduce acquisition times while maintaining high image quality. Additionally, a newly developed deep learning reconstruction method for upscaling resolution of low-resolution (superresolution) has been implemented into the MR machine. These DLR algorithms may help to improve visualization and characterization of hepatobiliary diseases. In this presentation, I would like to present our attempts to apply AI to improve image quality for hepatobiliary MR imaging.

Advances in Hepatobiliary Imaging
AHI1-3

Dr. Yasunori Minami
Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine
Japan

Challenging Precise Ablation: US-US Overlay Fusion Guidance

Fusion imaging has also emerged as valuable guide for ablating small HCC tumors that have poor ultrasound conspicuity. Use of CT/MR–US fusion imaging techniques for targeting can increase operator confidence, the accuracy of the procedure, and technical success rates. With more advances in imaging technology, US fusion imaging can be used to monitor treatment response during ablation. US-US fusion imaging shows the real-time 2D US image (post-ablation) and MPR US image (pre-ablation) side-by-side, while US–US overlay fusion can visualize the ablative margin because the tumor image is projected onto the ablative hyperechoic zone. At present, the imaging guidance systems of US-US fusion imaging have been already supported by some manufacturers. This feedback helps operators to recognize residual tumors or an insufficient ablative margin area during ablation. US-US overlay fusion guidance can be used to achieve a good safety margin for ablation therapy of HCC, promising a lower risk of local tumor progression. Therefore, US–US overlay fusion can accelerate the development of the so-called “precise ablation”.

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Summary

Big Data and AI for Hepatology

Big Data and AI for Hepatology

BD1-1

Dr. Hitoshi Mochizuki

Genome Analysis Center / Department of Gastroenterology, Yamanashi Central Hospital

Japan

The usefulness of AI for tumor microenvironment analysis in HCC.

[Introduction]

The tumor mass consists not only of a heterogeneous population of cancer cells but also a variety of resident and infiltrating host cells, secreted factors, and extracellular matrix proteins, collectively known as the TME(tumor microenvironment). The recent advances in machine learning are essential to elucidate what cells make up a TME and how these cells change and organize into different cellular communities in response to the signaling environment.

[Aims]

In this study, we will evaluate TME based on DNA and RNA analysis and compare HCC with other cancer types, predict the efficacy of immune checkpoint inhibitors, and discuss issues in evaluating TME.

[Methods]

DNA and RNA were extracted from 441 surgical samples of Tumor (including 333 HCCs) during treatment.

T cell prevalence can be estimated (General Additive Model) by sequencing the rearranged T cell receptor-α gene (T Cell ExTRECT).

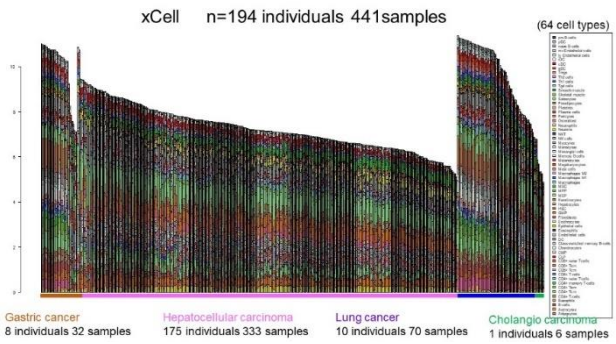
Transcriptome analysis makes it possible to estimate the abundance of cells with well-known mRNA expression profiles, such as immune cells, from bulk RNAseq data (CIBERSORT: 22 cell types, xCell: 64 cell types).

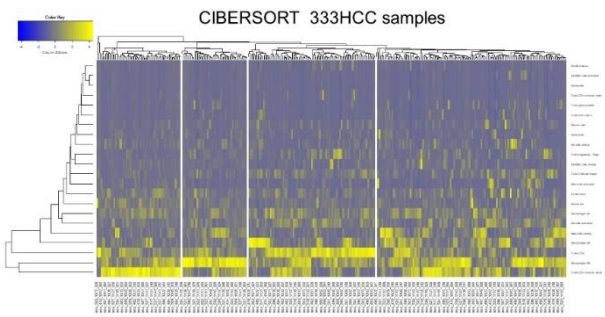
Moreover, we analyzed using EcoTyper, a machine-learning framework for large-scale identification and validation of cell states and multicellular communities from bulk, single-cell, and spatially resolved gene expression data.

[Results]

The use of AI in TME Analysis of Tumors elucidates fundamental units of cellular organization in HCC and provides a framework for large-scale profiling of cellular ecosystems in any tissue.

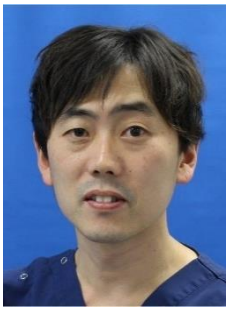
From a real-world clinical perspective, it was also shown that irAE caused by ICI(Immune Checkpoint Inhibitors) is caused in specific clusters.





Big Data and AI for Hepatology

BD1-4



Dr. Masaya Sato

Department of Clinical Laboratory Medicine, Graduate School of Medicine,

The University of Tokyo

Japan

Application of Machine Learning in the Diagnosis and Management of Liver Disease

While there has been significant progress in developing therapies for liver diseases, the prognosis for hepatocellular carcinoma (HCC), especially in advanced-stage patients, remains very poor. Artificial intelligence (AI), which combines computer science and mathematics, involves creating computer algorithms to improve the performance of computer programs. It does this by using various data sources and employing analytical or probabilistic models. The intersection of machine learning (ML) and the medical field has great potential to revolutionize diagnostic methods, particularly in laboratory medicine. Because liver diseases are complex and multifaceted, an ML approach that integrates multiple factors seems promising. This approach aims not only to improve diagnostic accuracy but also to predict how patients will respond to treatment and their future prognosis. Electronic medical records contain a wealth of data crucial for advancing medical research. By using AI and ML techniques and incorporating various factors into the analysis, we can enhance the precision of decision-making processes. This not only refines diagnostic accuracy but also helps predict outcomes in the intricate network of factors associated with liver diseases. In this presentation, we will explore the potential use of AI and laboratory medicine in the field of liver disease.

APASL 2024 Kyoto

The 33rd Annual Meeting the Asian Pacific Association for the Study of the Liver

Summary

Robotic Surgery Summit at APASL 2024 Kyoto Supported by Intuitive

Robotic Surgery Summit at APASL 2024 Kyoto Supported by Intuitive
RS1-1

Dr. Yutaro Kato

Robotic Surgery will be the Standard Approach to Highly Complex Minimally Invasive Liver Resection

Background: We have standardized surgical techniques of minimally invasive complex anatomic liver resection (MICAR) by extrahepatic Glissonean approach and hepatic vein root-at first cranial-to-caudal parenchymal dissection, based on Laennec's capsule.

Methods: We performed 260 MICAR including 3 trisectionectomies, 58 hemihepatectomies, 4 bisectionectomies, 70 monosectionectomies and 125 segmentectomies (laparoscopic: LCAR 180; robotic: RCAR 80) at our institution. Indications were HCC (n=151), metastatic tumors (n=73), intrahepatic cholangiocarcinoma (n=13) and others (n=23). Posterosuperior lesions were resected in 170 cases (65.4%). Repeat hepatectomies and reconstructive procedures were performed in 40 (15.4%) and 8 (3.1%) cases, respectively.

Results: In the entire MICAR cohort, the median operative time was 593 min and blood loss was 246g. Open conversion, major morbidity, bile leak/collection and 90-day mortality were 3.5%, 9%, 6.5% and 0.4%, respectively. Between propensity score-matched cohorts (64:64), compared to LCAR, RCAR had a lower rate of bile leak (1.6% vs. 11.1%, P=0.028), with comparable operative time, blood loss, conversion rate, morbidity, mortality and hospital stay. In MICAR for posterosuperior lesions and repeat hepatectomy, RCAR, which had worse tumor and procedural backgrounds than LCAR, still had comparable outcomes with LCAR. Reconstructive procedures were highly difficult laparoscopically, and no reconstruction-related complications were observed in RCAR. Postoperative long-term outcomes in newly developed HCC were comparable between LCAR (n=90) and RCAR (n=26).

Conclusions: Robotics may potentially improve safety of MICAR by technical dexterity, particularly for posterosuperior lesions, redo hepatectomy and reconstructive procedures, with comparable long-term outcomes in HCC with laparoscopic surgery. Robotic surgery will be the standard approach to MICAR.

Robotic Surgery Summit at APASL 2024 Kyoto Supported by Intuitive
RS1-2

Dr. Satoshi Ogiso
Division of Hepato-Biliary-Pancreatic surgery and Transplantation, Department of Surgery, Graduate School of Medicine, Kyoto University
Japan

Role of Minimally-Invasive and Robotic Hepatectomy in Managing Hepatocellular Carcinoma

Treatment strategy of hepatocellular carcinoma (HCC) has been recently changing due to the development of effective systemic therapy and, accordingly, survival outcomes of HCC, mainly survival-after-recurrence (progression) rather than recurrence (progression)-free-survival, have been improved. Patients with HCC is often complicated with background liver damage and their liver functional reserve has vital impacts on the choice of treatment and short- and long-term outcomes. When performing hepatectomy, extensive parenchymal retrieval or massive bleeding poses the risk of post-hepatectomy liver failure, which is directly associated with immediate morbidity after hepatectomy and also with long-term impairment of liver function. Minimally-invasive hepatectomy may potentially have some benefits over open counterpart by decreasing blood loss or surgical trauma and optimizing treatment for recurrence. To data, laparoscopic hepatectomy has been globally used to date, offering better short-term outcomes as well as similar survival outcomes compared to open hepatectomy, while providing excellent local control over ablative procedures. Robotic hepatectomy has several technical advantages over laparoscopic hepatectomy, such as increased range of motion, dexterity, and control, and is becoming popular and popular. Excellent short-term outcomes of robotic hepatectomy have been increasingly reported, but long-term outcomes are still in the process of being clarified as data continues to be accumulated. In this presentation, we review the long-term outcomes of conventional and minimally-invasive hepatectomies and discuss the role of robotic hepatectomies in the modern multimodal treatment of HCC.

Robotic Surgery Summit at APASL 2024 Kyoto Supported by Intuitive
RS1-3

Dr. Taiga Wakabayashi

Robot-Assisted Limited Anatomic Liver Resection: A Report on the Current Status

[Background] Since the inclusion of robot-assisted liver resection (R-LR) in insurance coverage, the number of cases has gradually increased in Japan. This report outlines the current status of minimally invasive liver resection (MI-LR) at a leading robotic hospital in Japan.
[Methods] In our institution, the Glissonean approach (GA) and indocyanine green negative staining (ICG-NS) are employed as fundamental techniques in minimally invasive anatomic resections (MI-AR). We aimed to analyze long-term outcomes of MI-AR and describe our approach for R-LR.
[Results] Among 112 patients undergoing laparoscopic AR, the 5-year OS rates were 73% for hepatocellular carcinoma (HCC) and 60% for colorectal liver metastasis (CRLM). Of 42 R-LR cases (December 2021 to December 2023), 24 involved anatomic liver resection, 18 involved partial resection. Operative time averaged 384 minutes, blood loss 358ml, complications (≥Calvien-Dindo IIIa) occurred in 7 cases but were successfully treated. The average postoperative hospital stay was 14 days.
[Conclusion] MI-AR exhibits favorable oncologic outcomes for HCC and CRLM. R-LR's advantages lie in its flexible approach to Glissonean pedicle and vessels due to multi-joint functionality. Ongoing improvements in near-infrared light cameras and liver transection devices anticipate the safer implementation of R-LR.

Robotic Surgery Summit at APASL 2024 Kyoto Supported by Intuitive
RS1-4

Dr. Takahisa Fujikawa
Department of Surgery, Kokura Memorial Hospital
Japan

An Efficient Saline-linked Cautery (SLiC) Method for Robotic Liver Parenchymal Transection Using Simultaneous Activation of Saline-linked Cautery and Robotic Suctioning: A Detailed Technical Aspects and Short-term Outcomes

Introduction: Although there are a number of benefits to using robotics in liver surgery over conventional open and laparoscopic approaches, liver parenchymal transection is still the most difficult aspect of robotic liver resection (RLR) due to the limitations of the currently available robotic instruments and the lack of a standardized method. This study presents a detailed technical aspects of our novel saline-linked cautery (SLiC) method for RLR and assessed the short-term outcomes for both non-anatomical and anatomical RLRs in our institution.

Methods: Among 82 cases that underwent RLR utilizing the SLiC method at our hospital from September 2021 to December 2023, 44 patients with hepatocellular carcinoma (HCC) were examined. The included patients were divided into two groups; the RAH group underwent robotic anatomical hepatectomy (n=22) and the RNAH group received robotic non-anatomical hepatectomy (n=22). Short-term outcomes including intraoperative and postoperative complications were compared between the groups.

Surgical Technique: We present a novel SLiC method for robotically transecting the liver parenchyma employing simultaneous activation of the SLiC and robotic suctioning. The dissection and hemostasis were advanced while low-temperature heat coagulation of the superficial layer of the dissection surface was performed by dripping saline droplets from the assistant side. The multi-joint scissors or bipolar cautery were used to scrape liver parenchyma back and forward to continuously promote thin-layer dissection of the liver parenchyma. Alternatively, the parenchyma was scraped by short pitch movement of the cautery tip in the case of parenchymal transection around the major vessels.

Results: There were no differences in patients' background characteristics. RLR was performed without Pringle's maneuver in more than 80% of cases in the RNAH group, and more than 80% in the RAH group required only 4 or less 15-min Pringle's maneuvers. Although the RAH group had more operative and console time, higher difficulty scores, and slightly more surgical blood loss than the RNAH group, there were no conversions to open liver resection and no cases of Grade B or C post-hepatectomy liver failure, and mortality was zero in the whole cohort. Two postoperative complications with Clavien-Dindo class 3a or higher occurred (small bowel obstruction in 1 and intraabdominal hemorrhage in 1), but no differences in the frequency of complications were found between the groups.

Conclusions: The SLiC method utilizing simultaneous activation of SLiC and robotic suctioning is a safe and practical procedure for liver parenchymal transection in RLR. In order to standardize and broadly implement RLR into normal patient treatment, this unique approach enables an advanced, locally controlled preparation of intrahepatic vessels and bile ducts.

APASL 2024 Kyoto

The 33rd Annual Meeting the Asian Pacific Association for the Study of the Liver

Summary

Symposium: Robotic Liver Resection for Liver Cancer

Symposium: Robotic Liver Resection for Liver Cancer
SR1-1

Dr. Naoto Gotohda
Department of Hepatobiliary and Pancreatic Surgery, National Cancer Center Hospital East
Japan

Robotic Liver Resection using Clamp Crushing technique

【Background】
Robotic liver resection (RLR) is now widespread throughout the world. RLR requires a completely different technique for liver surgeons using CUSA in Laparoscopic liver resection (LLR). However, we have performed LLR using the Clamp Crushing technique (CCT). We are able to perform RLR using a familiar technique.

【Purpose】
In this symposium, we will show RLR with CCT.

【Key points of the Technique】
In robotic surgery, the dissection and incision are usually performed in the bipolar soft mode with high-leveled. After crushing the liver parenchyma with the Maryland forceps, we adjust the bipolar soft mode that the exposed vessels are not divided but sealed. Sealed vessels are sharply divided with the Scissors. In order to perform this procedure, we hold the Maryland forceps in the right hand and the Scissors in the left hand during liver resection. An assistant is in responsible for aspiration through the assist port.

Symposium: Robotic Liver Resection for Liver Cancer

SR1-2

Dr. Kazuharu Igarashi

Department of General-Pediatric-Hepatobiliary Pancreatic Surgery, Kitasato University School of Medicine

Japan

Robotic versus laparoscopic liver resection for liver tumor

Background:

The advantages of the robotic approach in minimally invasive liver surgery (MILS) are still debated. This study compares the short-term outcomes between laparoscopic (LLR) and robotic (RLR) liver resections.

Methods:

This retrospective study included patients who underwent LLR or RLR for benign and malignant liver lesions at our hospital and affiliated hospital between January 2018 and February 2024.

Results:

Five hundred eleven patients underwent MILS (LLR = 461; RLR =50).

Of the 50 patients who underwent RLR, 34 had non-anatomic liver resections and 16 anatomic liver resections (11HrS, 5Hr2). RLRs had significantly less blood loss (80 vs. 151 ml, p = 0.0002) vs. LLRs. In RLRs compared to LLRs, operative time (378 vs. 350 min, p = 0.13), Pringle's cumulative time (69 vs. 70 min, p =0.66), major morbidity (6% vs. 5.6%, p = 0.92), mortality (2% vs. 0.4%, p=0.17) and hospital stay (8 vs. 8, p=0.11) were no significantly differences.

Conclusion:

RLR is feasible and safe for patients with benign or malignant liver lesion.

Further case accumulation is needed to validate its usefulness.

Symposium: Robotic Liver Resection for Liver Cancer
SR1-3

Dr. Masayuki Kojima
Fujita Health University Hospital
Japan

Standardization of Robot-Assisted Right Side Hepatectomy in our Hospital

(Introduction) Robotic-assisted liver resection surgery is now being introduced in many hospital. However, a standardized global approach has not been universally established due to limited device availability. Leveraging our institutional experience, we summarize our techniques.
(Material) Beginning in December 2009, our hospital pioneered robot-assisted hepatectomies, conducting 191 cases by September 2023. This involved 32 cases with Da Vinci S, 20 cases with Si, 138 cases with Xi, and 2 cases with hinotori. Due to the different port configurations of each device, only 96 right-sided liver resections, mainly using the Xi system, were included in this study.
(Port Placement) Fundamental port placement for right side hepatectomies includes a semi-lateral decubitus position, inserting ports in a semicircular arc pattern centered around the hepatoduodenal ligament following EZ access insertion on the lateral side of the rectus abdominis. The camera port is positioned slightly towards the left upper quadrant from the umbilicus. The surgery is conducted with the patient in a head-up position.
(Liver Transection) Following the Pringle maneuver, liver parenchyma is transected using a combination of monopolar scissors and the crush-clamp technique with a Maryland dissector. In anatomical resections, Gleason sheath is secured by 'the peel off and sweep method' using Fenestrate and Maryland. Firefly mode was used in the ischemic area for the parenchymal dissection line of the liver.
(Results) Among the 96 Xi system cases, 41 involved partial resections, while 55 underwent anatomical resections.
(Conclusion) Presently, utilizing the outlined approach, we ensure the safe conduct of nearly all cases.

Symposium: Robotic Liver Resection for Liver Cancer
SR1-4

Dr. Yukio Tokumitsu

Surgical Techniques of Liver Parenchymal Transection in Robot-Assisted Liver Resection

Background:
Liver parenchymal transection is the most important process in liver resection. Current study shows our clamp–crushing technique for robot-assisted liver resection (RLR) and evaluates its perioperative outcomes.
Methods:
The da Vinci Surgical System Xi robot is used for RLR. During clamp-crushing technique, the right hand uses a Maryland bipolar connected to the Force Triad Macro mode on arm No.3 or No.4. The EndoWrist One Suction Irrigator is used on arm No.1 to perform all suction and irrigation with the surgeon's left hand. During this solo-surgery, after crushing with the Maryland bipolar in the right hand, suction is performed with the left hand. Small vessels are cauterized and separated with the Maryland bipolar, and vessels larger than 3 mm in diameter are clipped. When bleeding occurs, hemostasis could be efficiently achieved by using a bipolar system while suction and irrigation. A good surgical field of view could be maintained by alternately using suction and Maryland bipolar to hold up or down the liver dissection plane.
Results:
From August 2022 to December 2023, a total of 17 patients underwent RLR. Median total operation time was 384 min, median console type was 305 min and median blood loss was 50 ml. There were no CD>3 postoperative complications, and median hospital stay was 10 days.
Conclusion:
RLR could be safely performed by a clamp–crushing technique using EndoWrist One Suction Irrigator.

Symposium: Robotic Liver Resection for Liver Cancer
SR1-5

Dr. Kazuhiro Matsuda

Robot-Assisted Liver Resection Guided by ICG Fluorescence Imaging and Artificial Intelligence

【Background】
Although the number of robot-assisted liver surgery (RALS) has increased in recent years, the lack of haptic feedback remains an issue. Indocyanine green (ICG) fluorescence imaging has proven to be a high potential navigation tool and may be a way to overcome the limitation. Furthermore, we have developed a surgical support artificial intelligence(AI) system to improve the recognition accuracy of vascular structures. This study aimed to investigate the feasibility and clinical application of ICG fluorescence imaging and AI to guide RALS.

【Methods】
11 patients who underwent RALS with fluorescence imaging for liver tumor were included. The da Vinci Xi system's Firefly mode was used to observe fluorescence, liver transection was performed under IOUS and ICG fluorescence guidance. The AI algorithm was evaluated at Anaut Inc.

【Results】
The subjects included 4 hepatocellular carcinoma, 6 colorectal liver metastasis, and one focal nodular hyperplasia. The mean operative time and blood loss was 354 minutes and 105g, there were no postoperative complications and mortality. In all cases, ICG fluorescence imaging successfully identified tumor localization and aiding in liver transection guidance. The pathological findings of all tumors indicated negative margins, defined as R0. The AI model accurately recognized vascular structures of any size in real-time and indocyanine green fluorescent imaging without visual discrepancies.

【Conclusion】
The ICG fluorescence imaging is a promising navigational tool, that can potentially overcome the limitations of RALS. Although this AI system is currently limited to preclinical application, these results may support the realization of more accurate real-time navigation.

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Summary

Medical Tourism in the Asia-Pacific Region

Medical Tourism in the Asia-Pacific Region (by Kinshukai)
MT1-2

Dr. Yutaka Yata
Department of gastroenterology, Hanwa memorial hospital
TO BE ANNOUNCED.

The proposal of Japanese medical tourism in Kansai region in the future

Medical tourism is a form of travel that aims to enjoy tourism together with health care and treatment through high-quality medical services. Japan has advanced medical technology, high-quality Japanese hospitality, beautiful nature and abundant culture. Especially in the Kansai region, Osaka has many of Japanese leading commercial and entertainment facilities, Kyoto has cultural facilities such as many traditional temples and Buddha statues, and culture such as zazen meditation. Hyogo has also many hot springs. Therefore, through the medical tourism in Kansai, it is possible not only to provide high-quality medical services, but also to provide medical tourism that visits tourist destinations and restores the mind and body through relaxation and cultural experiences. In addition, the progress of medical tourism will lead to the revitalization of not only the medical economy but also the regional economy, and it could be expected to develop as part of international exchange. Although there are likely to be many potential users, due to the impact of overseas travel restrictions because of the Covid19 pandemic, medical tourism in Japan is still not active and further development is required. In this symposium, we would like to discuss the proposal of Kansai-style medical tourism that takes advantage of the characteristics of Kansai, mainly Osaka, Kyoto and Hyogo prefectures which is expected to grow significantly in the future. In addition, we would like to propose the export of Japanese excellent health checkup system.

APASL 2024 Kyoto

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Summary

Joint Symposium Current Status of Ablation

Joint Symposium Current Status of Ablation

JS1-1

Dr. Takeshi Hatanaka

Department of Gastroenterology, Gunma Saiseikai Maebashi Hospital

TO BE ANNOUNCED.

Ablation therapy for hepatocellular carcinoma

Ablation therapy stands as one of the standard treatments for early-stage hepatocellular carcinoma (HCC). It is recommended as curative treatment for early-stage HCC according to recent guidelines. The pivotal randomized controlled SURF trial demonstrated comparable efficacy of ablation therapy and surgical treatment for patients with early-stage HCC. Image-guided ablation therapy, widely accepted for small HCCs, provides potential curative benefits, minimal invasiveness, and ease of repeatability for recurrence. Ultrasound and/or computed tomography are the most widely used guided imaging techniques. In cases where HCC is adjacent to other organs, such as the lung and gastrointestinal tract, artificial pleural effusion and artificial ascites may be required to avoid thermal injury to other organs. In ultrasound-guided modalities, contrast-enhanced ultrasonography and fusion imaging have proven to be useful for accurately identifying tumor locations and assessing ablation margins.

One of the sought-after capabilities in ablation devices is the prompt attainment of an extensive ablation zone. Additionally, given the spherical or nearly spherical shape of many tumors, achieving an ablation as close to spherical as possible is crucial. Furthermore, it is imperative to avoid excessively broad ablation to prevent thermal damage to other organs and vessels. In summary, the ability to predict the ablation area, ensure consistent reproducibility, and promptly attain an extensive ablation zone is critical. Future developments are expected in devices with these capabilities.

In recent years, significant progress has been made in systemic chemotherapy, including immunotherapies and multikinase inhibitors. Tumor shrinkage and downstaging have become achievable even in advanced HCC. However, achieving a complete tumor response through systemic therapy alone is still challenging. Following tumor reduction, ablation therapy serves as a curative conversion therapy expected to prolong survival. The combination of systemic therapy and ablation therapy is also anticipated as a promising treatment approach.

APASL 2024 Kyoto

The 33rd Annual Meeting the Asian Pacific Association for the Study of the Liver

Summary

Luncheon Seminar

Gilead

LS1-1

Dr. Masao Omata
University of Tokyo,
Gastroenterology Department, Yamanashi Prefectural Hospital Organization
Japan

Path to eliminating viral hepatitis

The World Health Organization (WHO) has set ambitious goals to eliminate viral hepatitis as a public health threat by 2030. This initiative, outlined in the Global Health Sector Strategy on Viral Hepatitis, targets a 90% reduction in incidence and a 65% reduction in mortality from hepatitis infections. To guide progress, interim 2020 targets were established, aiming for a 10% reduction in mortality, a 30% diagnosis rate, and a 10% treatment rate.

Despite these goals, the disease burden of Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) remained significant in 2019, with approximately 3 million new infections and around 1.1 million deaths globally. In terms of mortality updates, the target reduction has been achieved for HCV but not for HBV. This discrepancy highlights the challenges in combating these viruses and the need for intensified efforts, particularly against HBV.

Regionally, the Western Pacific and South-East Asia did not meet the 2020 diagnosis and treatment targets for HCV. More concerning is that all regions fell short of the 2020 targets for HBV diagnosis and treatment. These shortfalls underscore the uneven progress towards the WHO's 2030 elimination goals across different parts of the world and different types of viral hepatitis.

Although there has been considerable progress in addressing viral hepatitis, the path to elimination requires more concerted and targeted efforts. The global health community must mobilize resources, implement effective public health strategies, and ensure access to necessary medical interventions to overcome these challenges and move closer to eliminating viral hepatitis as a public health threat.

Gilead

LS1-2

Dr. Chun-Jen Liu

Department of Internal Medicine, National Taiwan University College of Medicine

Hepatitis Research Center and Clinical Trial Center, National Taiwan University Hospital

Taiwan

Global and regional elimination update

Efforts to combat viral hepatitis by 2030 are undermined by gaps in prevention, diagnosis, treatment access, and treatment efficacy. Nonetheless, targeted global initiatives offer promising solutions across these areas.

Prevention: The MINMON project simplifies Hepatitis C Virus (HCV) treatment by forgoing pre-treatment genotyping and ongoing clinical monitoring, achieving comparable results to traditional methods. This suggests that effective HCV management can be streamlined.

Diagnosis: The "100 Million Healthy Lives" initiative demonstrates the power of national campaigns for free hepatitis testing and treatment, significantly lowering infection rates through widespread screening.

Access to Treatment: The Relink program focuses on re-engaging patients diagnosed with HCV but not yet in care, thereby enhancing treatment engagement and outcomes through global efforts.

Treatment: TraP HepC has shown remarkable success in controlling HCV by implementing a nationwide program that rapidly expands testing, treatment, and prevention, highlighting the feasibility of large-scale efforts to enhance care access.

For Hepatitis B Virus (HBV), similar strides have been made:

Prevention: The Hepatitis B Control Program combines universal childhood vaccination with mass screening and immunization to stop HBV transmission.

Diagnosis: The UHEP pilot project proves that large-scale screening and care linkage is achievable in low- and middle-income countries, enhancing HBV care.

These programs illustrate that despite the challenges, effective strategies can address the care cascade gaps for hepatitis elimination. While these achievements mark significant progress, the journey towards completely eradicating viral hepatitis necessitates further action to bridge the remaining gaps, serving as models for future public health efforts.

Gilead

LS1-3

Dr. Young-Suk Lim

Department of Gastroenterology Asan Medical Center, University of Ulsan College of Medicine

Korea

HBV: The case for simplified and earlier treatment

The care cascade for Hepatitis B Virus (HBV) faces significant challenges, notably the complex treatment guidelines that contribute to many diagnosed individuals awaiting treatment. Approximately 30% of patients are in a "gray zone" or indeterminate phase, where eligibility for treatment varies between guidelines and high viral load does not always qualify for therapy. This complexity is problematic given the non-linear relationship between baseline HBV DNA levels and the risk of Hepatocellular Carcinoma (HCC).

Efforts to simplify HBV treatment criteria, such as the progressive 2022 CSH HBV guidelines, aim to broaden treatment eligibility. Simplifying these guidelines can significantly increase the proportion of patients eligible for therapy, offering potential benefits in outcomes. For instance, adjusting treatment guidelines to include a wider range of patients could potentially save thousands of lives by reducing the incidence of HCC.

The risk of HCC is notably higher in patients within the indeterminate phase compared to those in the inactive phase. Broadening treatment criteria to encompass those in the gray zone could cut the risk of HCC by 70% for these patients.

Hence, there is a clear need for more inclusive treatment guidelines and earlier therapeutic intervention to address the gaps in HBV management effectively. Simplifying treatment access and criteria is essential to improve health outcomes for HBV patients, underscoring the importance of global health community action towards more accessible and expansive treatment guidelines.

Gilead
LS1-4

Dr. Qing Xie
Department of Infectious Disease, Ruijin Hospital, Shanghai Jiaotong University School of Medicine
Severe Viral hepatitis Clinical Center, Shanghai Jiaotong University School of Medicine
Shanghai Clinical Quality Control Center of Infectious Diseases
China

Overcoming challenges: Special populations

Achieving the WHO's 2030 hepatitis elimination goals demand targeted strategies for key populations, particularly People Who Inject Drugs (PWID) and those at risk of Mother-to-Child Transmission (MTCT). Addressing these groups' unique needs is vital for the global eradication efforts against Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV).

PWID face high HCV prevalence, yet HCV is curable in this group despite potential adherence issues. Programs like Trap HepC have proven effective in reducing HCV rates among PWID by ensuring access to Direct-Acting Antivirals (DAAs), highlighting the need to scale-up treatment and overcome care barriers.

For MTCT prevention, enhancing access to HBV vaccines and tackling challenges in screening, treatment eligibility, and antiviral prophylaxis are crucial. Interventions need to be broad, addressing HBV at all pregnancy stages to significantly reduce MTCT risks.

Addressing Hepatitis Delta Virus (HDV) in individuals with HBV through routine screening emphasizes the importance of a comprehensive approach in hepatitis management, recognizing the interconnectedness of hepatitis viruses.
Simplifying access to treatment and preventive measures for these special populations can significantly contribute to the WHO's elimination targets. This focused approach, combining innovation in program implementation and policy support, is essential for overcoming the barriers to hepatitis care and achieving global health objectives.

Gilead

LS2-1

Dr. Masayuki Kurosaki

Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital

Japan

Eliminating viral hepatitis C: Not to leave anyone behind from HCV cure

Hepatitis C remain important background for liver-related mortality. HCV cure improve liver function and may reduce mortality in decompensated cirrhosis if treated before the point of no return. Identification of high-risk cases for HCC after HCV cure is important to personalize surveillance. Situation of DAA treatment for HCV patients complicated with active HCC may differ between countries due to lack of evidence. These points will be discussed.

TAISHO PHARMACEUTICAL HOLDINGS CO., LTD.

LS4-1

Dr. Takumi Kawaguchi

Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine.

Japan

Diabetes and the Liver: Diverse Actions of SGLT2 Inhibitor

Sodium-glucose cotransporter 2 inhibitor (SGLT2i) is an anti-diabetic medication. Besides the glucose-lowering effect, SGLT2i exerts various pleiotropic effects including inhibition for the progression of heart failure and chronic kidney disease. In addition, SGLT2i has been reported to exert beneficial effects on the liver. Several meta-analyses demonstrated that SGLT2i decreased serum levels of alanine aminotransferase (ALT) in patients with diabetes mellitus and liver injury. Single-arm trials and open-label prospective studies have reported that SGLT2i ameliorates hepatic steatosis. Furthermore, retrospective studies and randomized controlled trials support the efficacy of SGLT2i in improving hepatic fibrosis. Moreover, we recently performed a pooled meta-analysis using 5 phase III clinical trials of luseogliflozin, an SGLT2i. Hepatic steatosis and fibrosis indexes were significantly improved by a 24-week treatment with luseogliflozin in diabetic patients with liver injury. Moreover, luseogliflozin exhibited positive impacts on various cardiometabolic risk factors and hepatic inflammatory markers. Since metabolic dysfunctions and inflammation promote the progression of MAFLD, luseogliflozin may be beneficial for improving MAFLD in patients with diabetes.

Recent studies have shown that SGLT2 occurs in tumor cells including human hepatocellular carcinoma (HCC) tissue. SGLT2i has been reported to exert antitumor effects. SGLT2i-induced suppression of HCC was reported in vitro and in vivo studies as well as a case report. However, the underlying mechanisms remain elusive. We performed a multi-omics analysis of metabolomics and absolute quantification proteomics (iMPAQT). We found that SGLT2i suppressed the proliferation of HCC cells through alterations in mitochondrial oxidative phosphorylation metabolism and fatty acid metabolism. Additionally, SGLT2i directly inhibits the release of tumor-promoting cytokines (CXCL1, CXCL8, CXCL10, and M-CSF) in Hep3B and Huh7 cells, suggesting its potential to influence the tumor microenvironment. Thus, SGLT2i may suppress HCC through modulation of tumor mitochondria and tumor microenvironment.

In this luncheon seminar, I will introduce and discuss the diverse hepatic actions of SGLT2 inhibitors, highlighting the potential therapeutic implications for metabolic disorders, particularly MAFLD, and HCC.

TAISHO PHARMACEUTICAL HOLDINGS CO., LTD.

LS6-1

Dr. Toshinari Takamura

Department of Endocrinology and Metabolism,

Kanazawa University Graduate School of Medical Sciences

Japan

Pathology of diabetic steatohepatitis in humans and mice

Diabetes may be a cause and consequence of nonalcoholic fatty liver disease (NAFLD). We hypothesized diabetic steatohepatitis (DiSH) based on the following clinical observations.

1. In the clinical course of post-transfusion hepatitis C, type 2 diabetes comorbidity accelerated the risk for cirrhosis, hepatocellular carcinoma (HCC), postoperative HCC recurrence, and liver-related death (Metabolism 56: 1682, 2007; Am J Gastroenterol 102:1, 2007).
2. In a serial liver biopsy study in patients with NAFLD, elevated HbA1c promoted liver fibrosis independently of BMI (Diabetes Care 33:284, 2010).
3. In the livers of patients with advanced NAFLD with advanced liver fibrosis, zone 3 liver sinusoidal endothelial cells (LSEC) are damaged (Diabetes 2023. doi: 10.2337/db22-0933).
4. An SGLT2 inhibitor improves NAFLD histology and LSEC impairment in patients with NAFLD (Diabetes Care 45:2064, 2022).

So far, we have established two experimental steatohepatitis models that have been used in NASH research worldwide: methionine-choline deficient diet + high-fat diet (+OLETF rats) (Gastroenterology 132:282-93, 2007) and cholesterol + cholic acid + high-fat diet (Hepatology 46:1392-1403, 2007).

Here, we have established a mouse DiSH model to elucidate the detailed mechanism by which diabetes promotes the pathology of steatohepatitis (Am J Pathol, in press).

1. Steatohepatitis is induced by the administration of carbon tetrachloride (CCl4) in C57BL/6J mice fed a high-fat diet (HFD). Insulin-dependent diabetes mellitus was induced by multiple low-dose streptozotocin.
2. Diabetes accelerates steatosis, ballooning, necrosis, and regenerative nodular formation in the liver.
3. Diabetes upregulates inflammatory cytokines (TNF-α, IL6) in the liver.
4. Diabetes elevates the M1/M2 polarity of macrophages in the liver.
5. Single-cell RNA sequence (scRNAseq) analysis shows decreased Kupffer cells, increased bone marrow-induced Ly6Hi inflammatory macrophages, and upregulated expression of RAGE agonists.
6. Diabetes reduces LSECs with upregulated RAGE agonists, adhesion factors, and apoptotic factors.

These findings suggest that DiSH may be recognized as a diabetic vascular complication.

Abbott

LS7-1

Dr. Chee Kiat Tan

Department of Gastroenterology and Hepatology Singapore General Hospital

Singapore

Basic Understanding of MAFLD-related Hepatocellular Carcinoma

With the current effective treatment for viral hepatitis, metabolic dysfunction-associated fatty liver disease (MAFLD) is becoming the predominant liver disease globally. Fatty liver disease itself comprises two distinct subgroups, alcoholic-related and metabolic dysfunction-related, that are different with regards to hepatocellular carcinoma (HCC). For alcoholic liver disease and non-MAFLD patients, HCC develops predominantly when there is cirrhosis, which is the classical risk factor for HCC. Hence, surveillance for HCC in these patients is an established strategy, similar to that of viral-related HCC. However, for MAFLD, up to 40% of HCCs develop in the absence of cirrhosis. We will try to understand why this is so and whether that then allow us to develop strategies to deal with the difficult problem of HCC in MAFLD. The different pathogenesis of HCC development in MAFLD vs non-MAFLD will be discussed.

Abbott

LS8-1

Dr. Chee Kiat Tan

Department of Gastroenterology and Hepatology Singapore General Hospital

Singapore

Basic Understanding of MAFLD-related Hepatocellular Carcinoma

With the current effective treatment for viral hepatitis, metabolic dysfunction-associated fatty liver disease (MAFLD) is becoming the predominant liver disease globally. Fatty liver disease itself comprises two distinct subgroups, alcoholic-related and metabolic dysfunction-related, that are different with regards to hepatocellular carcinoma (HCC). For alcoholic liver disease and non-MAFLD patients, HCC develops predominantly when there is cirrhosis, which is the classical risk factor for HCC. Hence, surveillance for HCC in these patients is an established strategy, similar to that of viral-related HCC. However, for MAFLD, up to 40% of HCCs develop in the absence of cirrhosis. We will try to understand why this is so and whether that then allow us to develop strategies to deal with the difficult problem of HCC in MAFLD. The different pathogenesis of HCC development in MAFLD vs non-MAFLD will be discussed.

Miltenyi Biotec

LS10-1

Dr. Jana Soyka
Miltenyi Biotec B.V. & Co. KG
Germany

Challenges and Opportunities in Utilizing Primary Hepatocytes: Navigating Limitations in Liver Research

Primary hepatocytes are indispensable tools in biomedical research, providing valuable insights into liver physiology, drug metabolism, and toxicity. However, their acquisition remains a challenge, particularly through the gold standard in vivo liver perfusion technique. The limitations of this method, excluding the use of individual organs in multiple experimental settings, such as cellular, molecular, and imaging assays, necessitate innovative solutions. Here, we present a novel semi-automated perfusion technology designed to address these challenges, facilitating gentle, rapid, and efficient generation of a single-cell suspension from rodent livers ex vivo.

The gentleMACS Perfusion Technology represents a significant advancement in the field, offering an alternative to traditional methods by simplifying, streamlining, and parallelizing the isolation process of hepatocytes while maintaining cell viability and functionality. This technology is also applicable to disease models, including Non-Alcoholic Steatohepatitis (NASH) and fibrotic liver conditions. It allows for the isolation of cells from single liver lobes thus facilitating the use of the same liver in multiple parallel experimental setups.

Furthermore, we introduce the MACSima Spatial Biology platform, that enables researchers to relate scientific findings at the single-cell level to spatial contexts. By incorporating spatial information, researchers gain a deeper understanding of the liver microenvironment, allowing for more comprehensive investigations into disease mechanisms and medical treatment.

In summary, our innovative perfusion technology addresses the challenges associated with primary hepatocyte isolation, offering a versatile and efficient method for obtaining single-cell suspensions from rodent livers. Combined with the MACSima Spatial Biology platform our tools open new avenues to gain novel insights into liver biology in health and disease.

Novo Nordisk Pharma Ltd.
LS11-1

Dr. Wah-Kheong Chan
University of Malaya
Malaysia

Patient care pathways: The importance of multidisciplinary care

Obesity and type 2 diabetes are frequent comorbidities in patients with metabolic dysfunction-associated steatohepatitis (MASH), existing in 82% and 44% of these patients, respectively. As a result, there is a need for a multidisciplinary clinical care approach to this disease. A holistic approach to effectively manage MASH would include early risk identification, comprehensive assessment and management of comorbidities as well as lifestyle interventions. This talk will provide an overview of the current multidisciplinary care in MASH and discuss how the different care pathways that can be implemented in clinical settings to improve identification and referral of high-risk patients with MASH.

Novo Nordisk Pharma Ltd.

LS11-2

Dr. Lai Wei

Hepatopancreatobiliary Center, Beijing Tsinghua Changgung Hospital,

School of Clinical Medicine, Tsinghua University

China

Patient case: Spotlight on obesity in patients with MASH

Obesity is the most common metabolic comorbidity in patients with MASH. Due to the increased risk of developing MASH, patients living with obesity should be screened for the disease, regardless of liver enzymes, and treatment should include targeted weight loss via lifestyle interventions and/or medical treatment. In this talk, a unique clinical case of a patient with MASH and obesity will be presented. Alongside detailing the pathophysiological interplay between MASH and obesity, the case study will also highlight practical aspects of screening, diagnosing and monitoring patients with MASH and obesity; the reasons for choosing various management options will also be discussed.

Novo Nordisk Pharma Ltd.
LS11-3

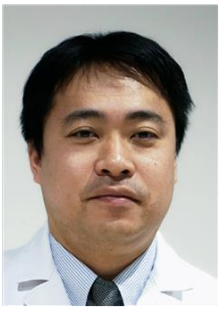
Dr. Kathryn Williams
University of Sydney, Nepean Blue Mountains Local Health District
Australia

Patient case: Spotlight on diabetes in patients with MASH

MASH is considered the hepatic manifestation of the metabolic syndrome, highly linked to type 2 diabetes (T2D). Approximately 44% of patients with MASH have T2D, and international guidelines recommend that patients with T2D are actively evaluated for MASH. The presence of T2D can play a key role in choosing the appropriate treatment when aiming to improve MASH prognosis. In this talk, a unique clinical case of a patient with MASH and T2D will be presented to discuss the interplay between these chronic diseases. The case will demonstrate the practical challenges associated with screening, diagnosing and monitoring MASH in this patient population. Finally, management and care pathways will be reviewed.

GE HealthCare

LS13-1



Dr. Nobuhito Taniki

Keio University, School of Medicine, Division of Gastroenterology and Hepatology,

Department of Internal Medicine

Japan

Advances of Ultrasound in Locoregional Therapy for Hepatocellular Carcinoma using LOGIQ E10x

The recent progress of ultrasound diagnostic imaging systems has been remarkable, and the quality of echo images is particularly important for safe locoregional therapy of liver cancer.GE Healthcare Japan's high-end model is equipped with cSound 2.0, which further improves cSound Architecture. In cSound 2.0, it has new functions related the image quality, cBand HI, which enables homogeneous images from near to far field, and Advanced SRI, which improves visibility through intelligent image processing. The benefits of cSound 2.0 also include full-focus contrast enhancement for uniform image rendition. We report on our experience with the top-of-the-line LOGIQ E10x.

Roche

SS15-1

Dr. Jacob George

Robert W. Storr Professor of Hepatic Medicine at the Storr Liver Centre,

Westmead Institute for Medical Research, University of Sydney

Australia

Evolving goals in HCC management: Improving HCC surveillance and shifting from palliative to curative approaches

This session explores the evolving landscape of hepatocellular carcinoma (HCC) management. We will examine how advancements in systemic therapies have transformed clinical practice from merely prolonging survival to potentially achieving a cure. Additionally, we will highlight the crucial role of early diagnosis in transitioning advanced cases to early and intermediate stages, thereby improving HCC outcomes. We will also discuss the latest advancements in biomarkers and digital algorithms for the early detection of HCC, which can help tailor treatment approaches. This sets the stage for more effective intervention strategies to maximize the survival of HCC patients in a real-world setting.

Eisai Co., Ltd.

LS16-1

Dr. Haruki Uojima

Department of gastroenterology, Kistasato university Hospital

TO BE ANNOUNCED.

Treatment strategies for intermediate stage
- What is LEN-TACE role in the Intermediate stage ? -

Lenvatinib, a multi-targeted tyrosine kinase inhibitor (TKI), has demonstrated efficacy in the treatment of advanced HCC and is approved for use as a first-line systemic therapy. Administering lenvatinib prior to transarterial chemoembolization (TACE) in patients with a high tumor burden is a sequential therapy aimed at first addressing the systemic component of the disease. This can potentially reduce tumor burden and stabilize the disease before TACE is used to residual tumors. A Phase 2 study, which is prospective, multicenter and single-arm of LEN-TACE sequential therapy, evaluated the efficacy and safety of a systemic therapy, a lenvatinib followed by TACE in patients with HCC. The sequential therapy has gained traction, especially for patients with intermediate-stage HCC who exceed the up-to-seven criteria. The results from clinical trials have contributed to the development of treatment guidelines and recommendations for managing patients with high tumor burden HCC.

However, it's essential to consider potential disadvantages or challenges associated with this sequential approach, such as a treatment toxicities and cost implications. As with any treatment strategy, the decision to administer lenvatinib prior to TACE should be individualized based on the patient's overall health, liver function, tumor characteristics, and treatment goals. Furthermore, close collaboration among multidisciplinary teams, including hepatologists, oncologists, interventional radiologists, and other specialists, is essential to optimize treatment for patients with HCC.

Eisai Co., Ltd.

LS16-2

Dr. Yusuke Kawamura

Head Physician, Department of Hepatology, Liver Disease Center, Toranomon Hospital

Japan

Multidisciplinary treatment strategy to achieve Cancer Free & Drug Free in future hepatocellular carcinoma treatment

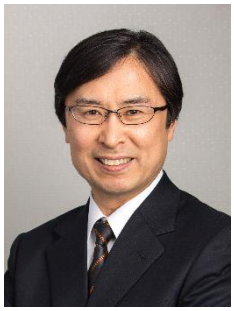
The Barcelona Clinic Liver Cancer (BCLC) algorithm is used widely for staging HCCs, with current treatment strategies dependent on the results. For advanced stage HCC (BCLC stage C), systemic therapy is recommended as first-line to later-line treatment. In fact, systemic therapy is the definitive treatment strategy for advanced stage HCC. However, it is questionable why control of intrahepatic targets in patients with BCLC stage C HCC using various treatment procedures is not the main topic of discussion. In contrast, the importance of intrahepatic tumor control in patients with extrahepatic tumor spread is reviewed. Since the introduction of lenvatinib, encouraging results have been reported on its highly synergistic effect with transarterial chemoemboli-zation (TACE) and hepatic arterial infusion chemotherapy (HAIC) based on anti-tumor vessel effects and high treatment efficacy in patients with oncologically aggressive HCC. A recent report suggested that TACE is preferred for patients with tumors within the Up-to-7 criteria who have good liver function. In addition, several clinical trials, and the current AASLD guidelines have reported that up-front molecularly-targeted therapy followed by TACE is a useful treatment option in patients with high tumor burden beyond the Up-to-7 criteria.

Moreover, many clinical trials have reported the possibility of achieving Cancer-free and Drug-free in advanced-stage HCC treated by combined use of lenvatinib and interventional radiology therapy / surgical resection.

In this seminar, we will examine the usefulness of lenvatinib in combination with IVR and resection based on its drug characteristics, and finally discuss the importance of a multidisciplinary approach in systemic chemotherapy.

Medicaroid, Inc.

LS18-1



Dr. Minoru Tanabe

Department of Hepatobiliary and Pancreatic Surgery, Tokyo Medical and Dental University

Japan

Japan-made hinotori™: the best choice for liver resection?

The DaVinci surgical robotic system was first developed in 1999, and since then it has been repeatedly upgraded and is now used in a variety of surgeries around the world. Until recently, the DaVinci from Intutive Surgical Inc. was the only choice for surgical robots, however, several other companies have released new robots in the last few years, expanding the range of options available. In Japan, Medicaroid Corporation developed a novel surgical robotic system, named hinotori™, which was approved by the Ministry of Health, Labour, and Welfare in 2020. Since then, more than 1,000 surgeries have been performed with this newly invented robot in the fields of urology and upper and lower GI. For liver resection, the hinotori™ has more recently been approved for insurance coverage in Japan. Although hinotori™ is similar to DaVinci in its basic configuration, it has several functional features that DaVinci™ does not have. This session will introduce the basic functions of hinotori™ and discuss how the features of this new robot can be used effectively in liver resection.

Medicaroid, Inc.

LS18-2

Dr. Takeshi Takahara

Department of Surgery, Fujita Health University

Japan

Experience with hinotoriTM liver resection

We have performed liver resection in six cases using hinotoriTM. The average BMI of the patients was 22.5 kg/m2, with a median Difficulty Index of 4 according to the Iwate Criteria. Partial resection was performed in five cases, and anatomical resection in one case. The average surgical time was 305 minutes, with an average blood loss of 92 ml. The median time from the start of surgery to initiation of console operation was 32 minutes. The average length of hospital stay was 12 days, and no postoperative complication of Clavien-Dindo grade IIIa or higher were observed in any cases.

The fundamental techniques of liver resection, including dissection of the perihepatic supporting ligaments, parenchymal transection, and vascular handling, were found to be almost equally feasible when compared to the da Vinci Surgical System. At the present, the advantage lies in the hinotoriTM pivot system, which gives the impression of less interference of the arms, particularly in slender patients, without the need to ensure the distance between each port as long as with the da Vinci Surgical System. This docking-free system can provide a large space around the trocars. Additionally, we perform parenchymal transection under Pringle's maneuver using the Maryland clamp-crushing method, in conjunction with coagulation/cutting using the double bipolar devices. In comparison to the da Vinci Surgical System, the default generator appeared to match well with our liver transection method. However, due to the somewhat time-consuming process of changing the robotic forceps and the absence of a vessel sealing device designed for hinotoriTM, the role of the patient-side assistant was deemed more crucial compared to the da Vinci Surgical System.

To promote the safe adoption of robot-assist liver resection, we want to actively share information, leveraging the advantage of being domestically produced.

Medtronic

LS19-1

Dr. Kai-Wen Huang

Centre of Mini-invasive Interventional Oncology, National Taiwan University Hospital

Taiwan

Local Tumor Ablation for Liver Cancers in Taiwan

Tumor ablation technology has evolved rapidly during the past several decades, with substantial technical and procedural improvements that can help improve clinical outcomes and safety profiles. With the significant evolution of imaging devices and ablation modalities during the last two decades, image-guided tumor ablation has become an ever more increasingly employed means for definitive treatment of focal malignancy in Taiwan. It has allowed larger ablation sizes with smaller instruments, and new technologies have enabled mini-invasive ablation with potential advantages in patient safety and treatment efficacy. As these technologies mature, the indications for percutaneous ablation continue to expand, and ablation promises to increasingly supplant surgery for local tumor therapy.

Bayer

LS20-1

Dr. Bo Hyun Kim

Department of Radiology, Seoul St. Mary's Hospital College of Medicine,

The Catholic University of Korea

Korea

Clinical value of EOB-MRI for colorectal liver metastases diagnosis and treatment follow-up

This lecture explores the practical applications and clinical relevance of hepatobiliary-phase on EOB- MRI in the context of diagnosing and monitoring colorectal liver metastases (CRLM). Colorectal cancer often leads to liver metastases, presenting challenges in accurate diagnosis and treatment evaluation. The presentation delves into the specific clinical value of EOB-MRI, focusing on its ability to enhance diagnostic precision by differentiating CRLM from different types of liver lesions met in clinical practice. Moreover, it investigates the role of EOB-MRI in post-treatment follow-up, assessing treatment response and detecting potential recurrence. Practical insights derived from this examination are poised to significantly impact clinical decision-making, aiding in the optimization of patient management.

APASL 2024 Kyoto

The 33rd Annual Meeting the Asian Pacific Association for the Study of the Liver

Summary

Sponsored Seminar

Abbott

SS1-3

Dr. Atsushi Hiraoka

Department of Gastroenterology Ehime Prefectural Central Hospital

Japan

Medication Adherence of DAA and How It May Affect the Outcome (tentative)

HCV was discovered in 1988 and we tried to treat it with different kinds of medicine such as Interferon and Ribavirin. In the early days of treatment, we struggled to treat HCV patients with the medication that was available in those day, having the difficulty to complete the treatment until the end while being successful with the treatment varied from patient to patient. Now, we have what we call DAA, or Direct Acting Anti-viral. By correctly using DAA, it became possible to treat HCV patients in shorter treatment period while having less adverse events and higher SVR rates. The introduction of DAA has made HCV infection a disease that could be cured.

There are 3 DAAs available in Japan, Glecaprevir / Pibrentasvir (MAVIRET), Sofosbuvir / Ledipasvir (SOF/LED), Sofosbuvir / Velpatasvir (SOF/VEL). In my presentation, I would like to share with you the characteristics of MAVIRET, especially from safety perspective. We all know that HCV non-cirrhotic could be treated with MAVIRET in 8 weeks, but we are not all aware of the safety profile of MAVIRET which has been available in Japan for more than 6 years. I hope my presentation would be of help for you to provide appropriate treatment to HCV patients.

Gilead

SS2-1

Dr. Sammy Saab

Departments of Medicine and Surgery at the David Geffen School of Medicine at UCLA

USA

Elimination of Hepatitis C Through Simplicity

Since the first description of hepatitis C (HCV) was first described over thirty years ago, HCV has become an important cause of morbidity and mortality across the globe. Hepatitis C is an important reason for liver complications such as cirrhosis, hepatocellular carcinoma and liver failure. In fact HCV remains one of the most common indications for liver transplantation across the globe. In addition to liver complications, HCV is associated with extra-hepatic complications such as insulin resistance, cryoglobulinemia, and kidney injury.

Hepatitis C antiviral therapy with direct acting agents are safe, effective and tolerable. Hepatitis C cure is associated with improved survival and patient related outcomes. Hepatitis C cure has also led to improve liver function, fibrosis regression, reversal of cirrhosis, decreased portal pressure, and reduced incidence of hepatocellular carcinoma. In fact, in the United States, antiviral therapy has changed the relative importance of indications for transplantation. Whereas HCV had been the most common indication for liver transplantation for over two decades, successful HCV antiviral therapy lead to its change in its relative importance as an indication for liver transplantation. Today, HCV is now the 3rd lead indication for transplantation instead of the most common one.

Despite the advances in antiviral therapy, a large cohort of patients infected with hepatitis C exists. Many of the individuals were infected several decades. The increasing age possess a number of challenges to therapy. First, with increasing age comes increasing number of co-morbidities. As patients age, they are more likely to develop other chronic medical conditions that subsequently require therapy. For instance, older patients are more likely than younger patients to be treated for hyperlipidemia and hypertension. Successful HCV elimination of this cohort will require regimens that do not burden patients with increased daily pill burden or potential drug-drug interactions that may lead to adverse effects. Second, the years of being infected likely has resulted in increasing burden of fibrosis. Risk of advanced fibrosis is directly related to the years of infections. These patients with advanced fibrosis may be at risk of portal hypertension, and thus a regimen that is safe in patients with portal hypertension is essential.

Patients with HCV need a regimen that is simple, effective and free of protease inhibitor drug-drug interactions. Thus a regimen could be used for all.

CHUGAI PHARMACEUTICAL CO., LTD.

SS7-1

Dr. Hideki Iwamoto

Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume University, Iwamoto Internal Medicine Clinic

Japan

Understanding Atezolizumab + Bevacizumab Combination Therapy and Multidisciplinary Treatment

Systemic therapy for unresectable hepatocellular carcinoma (HCC) has changed from the era of molecular-targeted agents to combination immunotherapy. The combination immunotherapy such as atezolizumab plus bevacizumab that activates the tumor immune microenvironment is a first-line treatment in systemic chemotherapy for HCC. Much evidence of systemic therapy for unresectable HCC has been reported, but further understanding of the combination immunotherapy and establishing proper use of each drug and sequential therapy are needed to prolong patients' survival in real-world clinical practice.

Now, a therapeutic strategy that aims "cancer-free" by performing curative conversion therapy initially starting from atezolizumab and bevacizumab therapy is attracting attention. The "REPLACEMENT" study revealed that atezolizumab and bevacizumab therapy was more effective than TACE in progression-free survival for intermediate HCC with beyond up-to-7 criteria. Moreover, the combination or sequential therapy of TACE or hepatic arterial infusion chemotherapy (HAIC) with immunotherapy are also attracting attention. It has been reported that locoregional treatments such as TACE and HAIC may induce cancer immune activity, suggesting the significance of combining locoregional treatments and immunotherapy.

In this lecture, real-world clinical practice data of atezolizumab + bevacizumab therapy and the combination or sequential therapy of atezolizumab + bevacizumab therapy and locoregional treatments, such as TACE and HAIC will be introduced. Furthermore, the impact of cancer-immune activation due to atezolizumab and bevacizumab will be discussed from both basic and clinical perspectives.

CHUGAI PHARMACEUTICAL CO., LTD.

SS7-2

Dr. Kaoru Tsuchiya

Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital

Japan

Atezolizumab plus bevacizumab therapy for unresectable HCC ~ Clinical Practice and Future Perspectives~

In Japanese and international guidelines, combination immunotherapy is positioned as the standard first-line treatment for unresectable hepatocellular carcinoma (HCC) if there are no contraindications to immunotherapy. Atezolizumab plus bevacizumab (Atezo + Bev) is listed as first-line therapy unless there is a high risk of bleeding in AASLD Practice Guidance. Although Atezo + Bev and durvalumab plus tremelimumab are listed together as first-line therapy in Japanese Clinical Practice Guidelines for Hepatocellular Carcinoma, as the efficacy and safety data are clearly stated, it is necessary to understand the risks and benefits of the regimen when selecting treatment. The evidence of Atezo + Bev has been accumulated from the phase 3 trial (IMbrave150) and clinical practice data. Our hospital and the Japan Red Cross Liver Study Group have also reported efficacy and safety.

Management of immune-related adverse events (irAEs) is essential in combination immunotherapy, considering sequence therapy after the first-line treatment. It has been reported that the frequency and profile of irAEs differ depending on the immune checkpoint inhibitor regimen, and it is necessary to understand and manage the differences between regimens. In particular, it is important to manage proteinuria as an adverse event related to bevacizumab, a VEGF inhibitor, in the case of Atezo + Bev. Many patients with HCC are elderly and may have various complications, so careful monitoring is required to prevent proteinuria from becoming serious. It is also essential to pay attention to esophagogastric varices, which can lead to bleeding risks. Atezo + Bev suggests similar efficacy regardless of the presence of varices. To prevent bleeding, patients with varices should undergo upper gastrointestinal endoscopy regularly and receive appropriate treatment before starting treatment.

As systemic therapy for unresectable HCC, combination immunotherapy and combination with locoregional therapy have been developed, and it is expected that treatment outcomes will continue to improve in the future. In this lecture, I will introduce clinical data and treatment strategies of Atezo + Bev, as well as future prospects for the treatment of unresectable HCC.

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SS8-1

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Management of immune-related adverse events (irAE) in combination cancer immunotherapy

In recent years, the successful clinical development of immune checkpoint inhibitors (ICIs) has led to the expansion of their indications in many types of cancer, and they have become one of the standard of care.

ICIs attack cancer cells by inhibiting immune checkpoint molecules, which are co-inhibitory molecules (receptors) that are expressed on T cells activated by the recognition of cancer antigens, thereby sustaining T cell activation.

ICIs cause immune-related adverse events (irAEs). It is recognized that irAEs occur when residual autoantigen-specific lymphocytes in the body are activated by ICIs and attack autologous cells and tissues.

Among irAEs, skin rash, thyroid dysfunction, and enteritis/diarrhea are reported to be relatively frequent. Although most of the adverse events are infrequent, they occur throughout the body, and it is difficult to predict the timing of their onset, so it is necessary to organize a team approach in the management of irAEs.

In this lecture, I will review the mechanisms, characteristics, diagnosis, and management of immune-related adverse events, including recent information.

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SS8-2

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Managing the Adverse Events of Combination Therapy with Atezolizumab and Bevacizumab to Improve Prognosis in Patients with Unresectable Hepatocellular Carcinoma

In recent years, the development and clinical application of systemic treatment for unresectable hepatocellular carcinoma (uHCC) has accelerated. The combination of atezolizumab, an anti–PD-L1 antibody, and bevacizumab, a molecular targeted agent (MTA) against vascular endothelial growth factor (VEGF) (Atez/Bev), has been a first-line systemic treatment for uHCC. Compared with sorafenib, Atez/Bev therapy significantly prolonged progression-free survival and overall survival, with an increased response rate, in a Phase III randomized controlled trial (IMbrave150). On the other hand, Atez/Bev treatment is associated with several characteristic adverse events. Bev induces proteinuria, a prognostic factor in clinical practice that makes it difficult to continue treatment. Risk factors for proteinuria include poor functional hepatic reserve, the need for additional lines of treatment, and the presence of hypertension or type 2 diabetes. However, it has been reported that the appropriate withdrawal and resumption of Bev in patients with proteinuria improve prognosis (Kudo M, et al.: ASCO- GI 2023 #538). Regarding immune-related adverse events (irAEs) caused by Atez, data from both the IMbrave150 trial and real-world settings indicate that immune checkpoint inhibitor (ICI)-induced liver injury is the most common irAE during Atez/Bev treatment, and it can be fatal. Furthermore, types of liver injury due to ICIs include ICI-induced immune-related sclerosing cholangitis, which is associated with corticosteroid resistance. Hence, early detection and appropriate treatment of severe irAEs are important for improving prognosis in patients with uHCC treated with Atez/Bev. At our hospital, an irAE-focused multidisciplinary toxicity team was established to detect severe ICI-induced liver toxicity. Our systematic consultation rules can help doctors who use ICIs in each department consult with specialists to manage this type of toxicity while reducing the therapeutic effect of ICIs as little as possible. In this lecture, we will review the importance of managing adverse events to improve the prognosis of uHCC patients receiving Atez/Bev combination therapy.

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SS11-2

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The Potential of Lenvatinib to Recruit Cytotoxic GZMK+ CD8 T Cells in Hepatocellular Carcinoma

In recent years, combination immunotherapy using immune checkpoint inhibitor (ICI) and angiogenesis inhibitor has been approved for hepatocellular carcinoma (HCC), playing a central role in the treatment of HCC. Despite the success of this combination, the underlying mechanisms of their synergistic effects remain unclear. To address this gap, we analyzed surgically resected human HCC samples after lenvatinib treatment.

Following lenvatinib administration and subsequent surgical resection (median 43 days, IQR 28-62 days), analysis was performed on HCC specimens from five cases (lenvatinib group) and ten control cases (matched for age, gender, tumor size, and etiology) without prior treatment. Immunohistochemical analysis revealed increased infiltration of CD8+ T cells in the lenvatinib group. RNA-seq analysis uncovered significant suppression of VEGF-related pathways in the lenvatinib group, particularly pathways inducing vascular permeability, potentially improving immune cell infiltration. Furthermore, several pathways in HCC progression were also inhibited in the lenvatinib group.

In the previous single cell RNA-seq study using HCC samples, infiltrating T cells were classified into 11 subsets. Using this data as a reference, we performed an integrative analysis of our bulk RNA-seq data and identified GZMK+ CD8 T cells infiltrating in the lenvatinib group. GZMK, associated with precursor exhausted T cells, is known to respond to ICI therapy and exhibit proliferative capacity. High GZMK expression in liver cancer patients correlated with a favorable prognosis. The increase in GZMK+ CD8 T cells induced by lenvatinib suggests a potential contribution to improved prognosis.

However, RNA-seq analysis has limitations in providing spatial information. To address this, Digital Spatial Profiling (DSP) was employed to analyze the impact of lenvatinib on the tumor immune microenvironment. This technique integrates gene expression and spatial information, revealing the influence of lenvatinib on tumor immune microenvironment changes. Specifically, CD8+GZMK+ regions showed elevated expression of chemokine CXCL9 and macrophage marker CD68, indicating macrophage-secreted CXCL9 may contribute to GZMK+ CD8 T cell infiltration.

Despite these positive outcomes, CD8 T cells in the lenvatinib group exhibited a limited localization, predominantly at the tumor edge, suggesting an "exclusion" state. Analysis suggested the activation of extracellular matrix-related pathways in lenvatinib-treated cases, potentially leading to T cell exclusion by cancer-associated fibroblasts. Overcoming this challenge could enable more effective combination immunotherapy.

The study, utilizing lenvatinib-treated specimens, provides valuable insights into the modifications induced by lenvatinib in the tumor immune microenvironment, offering potential applications in optimizing combination immunotherapies for HCC.

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SS12-1

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Pushing the Envelope for Surgical Management of Advanced Hepatocellular Carcinoma

Recent introduction of effective systemic therapy has been changing the landscape of multidisciplinary treatment for hepatocellular carcinoma (HCC), while it remains unclear whether or not surgical intervention as a part of multidisciplinary treatment is truly beneficial for patients with advanced HCC. Since introduction of lenvatinib in 2017, increasing number of papers regarding the concept of conversion surgery have been published. However, lack of consensus on resectability of HCC has precluded constructive discussion on an optimal treatment strategy in the era of effective systemic therapy. In 2023, the working group between JLCA and JSHBPS launched new criteria for oncological resectability of HCC as the Expert Consensus Statement 2023, and several validation studies are currently on going. In this talk, updated clinical evidence and future perspective of multidisciplinary treatment for advanced HCC will be discussed from the standpoint of surgery.

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SS13-1

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Introducing Japan’s Novel RFA system, arfa RF ABLATION SYSTEM

Japan is a country of the origins of various therapeutic procedures of liver cancer including systematic hepatectomy, percutaneous ethanol injection (PEI), microwave coagulation therapy (MCT) and allegedly transcatheter arterial (chemo)embolization (TA(C)E).

The "arfa RF ABLATION SYSTEM" is the first and, at the present moment, the only radiofrequency ablation (RFA) system developed in Japan based on the voices of numbers of Japanese physicians. The features and advantages of "arfa" will be presented in the lecture along with a brief background of the manufacturer, Japan Lifeline.

JAPAN LIFELINE Co., Ltd.

SS13-2

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Radiofrequency Ablation by Japan Lifeline: Clinical Results with arfa RF ABLATION SYSTEM

Radiofrequency ablation (RFA) has been established as a minimally invasive therapeutic modality for hepatocellular carcinoma (HCC). It has gained prominence since its introduction in the 1990s and subsequent approval for insurance coverage within Japan in 2004. In the liver cancer study group of Japan clinical practice guidelines, RFA is recommended as the first-line treatment for HCC, with up to three lesions measuring 3 cm or less, as well as resection. The SURF trial, a phase III randomized controlled trial comparing surgical resection with RFA for the treatment of primary HCC, elucidated non-inferior recurrence-free survival (RFS) rates associated with RFA in comparison to surgical resection, thereby affirming the equivalence of safety profiles and therapeutic efficacies between these modalities. RFA is widely adopted domestically and internationally due to its advantages, such as the potential for high treatment efficacy through complete ablation of lesion tissue, low invasiveness as a percutaneous treatment, and ease of repeated treatment during recurrence. Historically, the apparatus utilized for RFA encompassed monopolar and bipolar needles. However, 2019 witnessed the introduction of "arfa RF ABLATION SYSTEM" the inaugural domestically manufactured RFA device in Japan, distinguished by its "variable" model, which permits the meticulous adjustment of the ablation zone via alteration of the non-insulated segment's length at the electrode tip. It is a "variable" model that allows for flexible adjustment of the ablation zone by changing the length of the non-insulated portion of the electrode tip. It allows for settings of the output increase per minute during ablation and the decrease in output after a break, as well as two methods of output increase during ablation: a stepwise method where the output increases to the set value every minute and a linear method where the output gradually increases over one minute to the set value. This latest system achieves greater ease of use and simplicity than conventional methods. In this report, we summarize our initial experience and treatment outcomes using RFA with "arfa" at our institution. This seminar delineates our experiences and clinical outcomes s after implementing the "arfa", highlighting its prospective clinical utility and implications.