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EXPERT OPINION

A Post-International Gastrointestinal Cancers' Conference (IGICC) Position Statements

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Abstract: Hepatocellular carcinoma (HCC), the most prevalent liver tumor, is usually linked with chronic liver diseases, particularly cirrhosis. As per the 2020 statistics, this cancer ranks 6th in the list of most common cancers worldwide and is the third primary source of cancer-related deaths. Asia holds the record for the highest occurrence of HCC. HCC is found three times more frequently in men than in women. The primary risk factors for HCC include chronic viral infections, excessive alcohol intake, steatotic liver disease conditions, as well as genetic and family predispositions. Roughly 40–50% of patients are identified in the late stages of the disease. Recently, there have been significant advancements in the treatment methods for advanced HCC. The selection of treatment for HCC hinges on the stage of the disease and the patient's medical status. Factors such as pre-existing liver conditions, etiology, portal hypertension, and portal vein thrombosis need critical evaluation, monitoring, and appropriate treatment. Depending on the patient and the characteristics of the disease, liver resection, ablation, or transplantation may be deemed potentially curative. For inoperable lesions, arterially directed therapy might be an option, or systemic treatment might be deemed more suitable. In specific cases, the recommendation might extend to external beam radiation therapy. For all individuals, a comprehensive, multidisciplinary approach should be adopted when considering HCC treatment options. The main treatment strategies for advanced HCC patients are typically combination treatments such as immunotherapy and anti-VEGFR inhibitor, or a combination of immunotherapy and immunotherapy where appropriate, as a first-line treatment. Furthermore, some TKIs and immune checkpoint inhibitors may be used as single agents in cases where patients are not fit for the combination therapies. As second-line treatments, some treatment agents have been reported and can be considered.

Keywords: hepatocellular carcinoma, screening, imaging, diagnosis, treatment, immunotherapy, tyrosine kinase inhibitors

Introduction

Hepatocellular carcinoma (HCC) is the most frequently occurring primary liver tumor, accounting for over 80% of all liver cancers. The development of HCC is often (>80%) associated with chronic liver diseases, primarily cirrhosis. It ranks as the 6th most common cancer globally and the third leading cause of cancer-related deaths, based on 2020 data.[1] A significant majority of HCC cases (72.5%) are found in Asia. The remaining cases are distributed across Europe (9.8%), Africa (7.7%), North America (5%), Latin America/The Caribbean (4.6%), and Oceania (0.4%) (1). Men are

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three times more likely to have HCC compared to women. The average age of HCC diagnosis is generally higher in North America and Europe, typically over 60 years, compared to 30–60 years in Asia and Africa.[2,3]

Approximately 20–40% of patients are only identified in the late stages. Generally, many beginning-stage diseases proceed to a severe phase throughout the course of the illness, frequently leading to a decrease in liver performance. Over the past few years, progress has been made in creating more efficient therapies for patients suffering from both localized and advanced illnesses.[2,4] In this article, we aimed to comprehensively evaluate current treatment options for focal and advanced hepatocellular cancer.

Clinical Features

HCC is primarily attributed to persistent liver disease. HBV and HCV infections, excessive alcohol intake, and steatotic liver disease conditions like metabolic syndrome, obesity, and type 2 diabetes are the main culprits.[4,5] Other risk factors include exposure to aflatoxins, anabolic steroids, and tobacco consumption.[6]

Although most underlying factors are lifestyle or environmental, genetic and familial tendencies, developmental or congenital anomalies may also be responsible for the development of HCC. Hepatocellular adenomas may also undergo malignant transformation (5%). The presentation of the patient may vary from being asymptomatic to presenting with ascites, jaundice, and bleeding as a part of a life-threatening clinical picture. Individuals suffering from HCC may also exhibit syndromes that are not directly related to a carcinoma, leading to symptoms like erythrocytosis, hypoglycemia attacks, elevated calcium levels, or intense diarrhoea.[7]

Locoregional and distant metastases are not uncommon in addition to intrahepatic multifocal disease; the lungs, portal vein, portal lymph nodes, intraabdominal lymph nodes, bone, adrenal glands, and brain are the common metastatic sites.

Patients diagnosed with hepatocellular cancer may have significant comorbidities other than the primary disease, such as cirrhosis, and varicose veins due to portal hypertension, ascites, and others (coronary artery disease, stroke, uncontrolled hypertension, or embolism). Therefore, the treatment management of patients with hepatocellular cancer must be determined by multidisciplinary tumor boards, and the implementation of individualized treatment approaches is very important. The core members of an HCC multidisciplinary tumor board include liver surgeons, hepatologists/gastroenterologists, medical oncologists, radiation oncologists, interventional radiologists, and pathologists, with additional consultative experts included based on the individual needs of the patient.

Screening/Surveillance

Community-based non-selective screening is not a valid approach. Nonetheless, individuals suffering from cirrhosis and chronic hepatitis B virus infection who are at a high risk of developing HCC should be considered for regular monitoring.

Patients with advanced fibrosis (F3) may also be considered for surveillance even if they are not cirrhotic based on a detailed individual assessment of their risk regardless of etiology.[8,9] The grading for liver fibrosis according to Knodell and Ishak scoring system is given in Table 1.[10,11] The imaging method suggested for screening and monitoring is liver

Table 1 The Grading for Liver Fibrosis According to Ishak (Modified Knodell) Scoring System

Finding	Score	Reference
No fibrosis	0	[10,11]
Fibrous expansion of some portal areas, with or without short fibrous septa	1	
Fibrous expansion of most portal areas, with or without short fibrous septa	2	
Fibrous expansion of most portal areas, with occasional portal to portal bridging	3	
Fibrous expansion of portal areas with marked bridging (portal to portal) as well as portal to central	4	
Marked bridging (portal to portal and/or portal to central) with occasional nodules (incomplete cirrhosis)	5	
Cirrhosis, probable or definite	6	

ultrasound (US), performed every six months. Nonetheless, for some patients, dynamic computerized tomography (CT) or dynamic magnetic resonance imaging (MRI) of the liver, which has a greater sensitivity for detecting HCC, might be the preferred choice.[9] In addition, serum alpha-feto protein (AFP) should also be a part of radiological imaging-based screening and surveillance. Serum AFP level is above the normal limits in 70–90% of HCC cases. The sensitivity of serum AFP elevation is 60%, with a specificity of 90%. For patients with HCC high risks, serum AFP levels >400 ng/mL are nearly diagnostic, and specificity of >95%. However, around 20% of patients with HCCs have such AFP levels. Additionally, elevated AFP levels are not specific to HCC and may be due to viral hepatitis, decompensated liver disease, and pregnancy. Therefore, AFP can be used for screening, diagnosis, and follow-up of recurrences and evaluating responses to treatment with the aforementioned limitations.[12–16]

Radiological Imaging

Hepatocellular carcinoma (HCC) can be identified based on imaging standards using CT scan with multiple phases of contrast enhancement, MRI, or ultrasonography. Because detection of HCC at an early stage offers more options for fully curative treatments, a feasible and robust diagnostic tool is required; therefore, an MRI can easily detect the presence of abnormalities in the liver which might be cancer. There are gadolinium-based, hepatocyte-specific MRI contrast agents that provide functional and structural information about the hepatobiliary system as well as the dynamic contrast enhancement pattern of the focal lesion in the liver. Unlike standard extracellular contrast agents, which distribute only in the extracellular space, these contrasts distribute into hepatocytes and are shortly excreted into the biliary system. MRIs performed with these contrast agents may be a potential screening tool for HCCs in the future due to their high sensitivity and superior tissue contrast.[17] In general, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of MR imaging for HCC are better than CT, but a statistically significant superiority has been demonstrated, especially in terms of sensitivity, accuracy, and negative predictive values. Therefore, the diagnostic efficiency of MRI is better than CT, especially in the diagnosis of small HCC.[17,18] For HCC patients, history of liver cirrhosis, tumor stage, and portal vein thrombosis are prognostic factors, the efficiency and accuracy of imaging are also gaining importance, and MR imaging is superior to CT in the evaluation of these features. Personalized comprehensive treatment approaches according to these conditions are effective in extending the life expectancy of HCC patients.[17]

For most patients at high risk, solitary diagnosis with imaging should be regarded as the golden standard. In this context, the Liver Imaging Reporting and Data System (LI-RADS) was created, and this system provides a solid method to classify the HCC risk among patients who have been screened. However, LI-RADS is not applicable to patients with cirrhosis due to congenital hepatic fibrosis, vascular disorders such as hereditary hemorrhagic telangiectasia, Budd-Chiari syndrome, chronic portal vein occlusion, cardiac congestion, or diffuse nodular regenerative hyperplasia[19] (Table 2).

Table 2 Liver Imaging Reporting and Data System (LI-RADS) Categorises the HCC Risk in Screened Patients

Category	Assessment	Reference
LR-1	Definitely benign	[19]
LR-2	Probably benign	
LR-3	Intermediate probability of malignancy	
LR-4	Probably HCC	
LR-5	Definitely HCC	
LR-M	Probably or definitely malignant, not specific for HCC	
LR-NC	Not categorizable	
LR-TIV	Tumor in vein	

Abbreviations: LR, LI-RADS; TIV, Tumor in vein; NC, not categorizable; HCC, hepatocellular cancer; M, malignant.

For liver nodule growths observed that are 10mm or larger, standardized imaging criteria have been accepted by the AASLD, EASL, and LI-RADS systems to diagnose HCC. This criterion identifies major HCC radiological characteristics such as arterial phase hyper-enhancement, non-peripheral venous or washout appearance during the delayed phase, capsular enhancement, and threshold growth. LI-RADS also outlines radiological proofs for detecting macrovascular invasion. It is pertinent to define vascular invasion since the tumor's imaging features in the vein might differ from those of parenchymal tumors.[20,21]

The imaging criteria for liver nodules is primarily intended for patients at high risk of developing HCC, such as those with liver cirrhosis, chronic hepatitis B, HCV and current or previous history of HCC. The criteria system may not be suitable for use in the general population or patients with chronic liver disease, excluding those with chronic hepatitis B who have not developed cirrhosis. The prevalence of HCC is sufficiently high in at-risk patients, to the point that lesions which meet the imaging criteria are almost certain to be HCC. The imaging criteria generally aim to have high specificity for HCC. Thus, lesions that satisfy these conditions are likely to be HCC and could be treated without requiring histological confirmation. In conclusion, these criteria have moderate sensitivity; and further yet, numerous HCCs still need to meet the required criteria, and HCC cannot be excluded in patients with radiological features not meeting the aforementioned radiological criteria.[22]

Any patient with a nodule(s) not fulfilling the radiological criteria should be evaluated individually with further imaging or histological/cytological sampling, preferably in a multidisciplinary setting.

Patients frequently present with peritoneal involvement and pulmonary, lymphatic, skeletal, and adrenal metastasis. Therefore, systemic imaging with computerized tomography (CT) of the thorax, contrast-enhanced whole abdomen CT or magnetic resonance imaging (MRI), and bone scan in the presence of skeletal symptoms are recommended in the staging of HCC. Imaging with CT has several advantages, including evaluation of response to HCC treatment, detection of calcification (eg, calcified stones, calcified metastasis, granuloma, chronic hematoma, hydatid disease), better detection of gas within the lesion (eg, necrotic tumor and abscess), and evaluation of acute bleeding or rupture. Therefore, CT is the most preferred imaging modality for initial evaluation and subsequent follow-up surveillance of potential metastatic disease after HCC diagnosis due to its ability to image the liver and sites of potential extrahepatic disease spread (ie, nodes, peritoneum, chest).[23]

It is essential that patients on the waiting list for a liver transplant receive similar screenings to monitor the progression of their disease. Regular radiological tests are also a must for patients with HCC, regardless of whether they are currently in treatment or in post-treatment observation, in order to assess their reaction, identify any relapses, or measure the advancement of the disease.[24]

For HCC, there is no need for contrast-enhanced Thorax CT; however, if concurrently contrast-enhanced abdominal/pelvic CT is required, then thorax CT with contrast can be acquired. If an abdominal MRI is planned, thorax CT may be obtained without contrast. 18-fluorodeoxyglucose (FDG) PET/CT can be performed in cases with uncertain findings with radiological imaging. For HCC, FDG-PET/CT has high specificity but a modest sensitivity, and its sensitivity ranging from 36 to 70% in patients with HCC. Increased metabolic activity in FDG PET/CT correlates with the aggressiveness of HCC biology. Because [^{18}F] FDG PET-CT has limited sensitivity to certain extrahepatic and intrahepatic HCC metastases, the [^{11}C]Choline ([^{11}C]CH) tracer of cell membrane lipid metabolism has been evaluated to overcome this. Different types of HCC show a high proliferation and metabolic activity in cell membrane components, leading to an increased choline uptake. For [^{11}C]Choline ([^{11}C]CH) tracer, clinical studies have reported better detection rates than [^{18}F]FDG PET/CT for well to moderately differentiated HCC lesions (84%). Therefore, studies that will evaluate the role of dual-tracker PET imaging with [^{18}F]FDG and [^{11}C]CH PET/CT for clinical decision-making in patients diagnosed with hepatocellular cancer are awaited.[25] MRI imaging technique might also predict a less optimal response to locoregional therapies.[26,27]

Multiphasic dynamic multiphasic MR imaging with liver-specific contrast agents is the mainstay in patients with HCC workup, not only to detect small lesions but also to asses the functional liver reserve with delayed phased images.

For the quality of MR imaging, patients' compliance is required. Dynamic CT imaging should be preferred for uncompliant patients.

To detect extrahepatic disease, CT imaging is advised as HCC frequently manifests with metastasis to the lungs, bone, lymph nodes, and adrenal glands

Radiological Imaging for Treatment Response Evaluation Assessment

The thorax CT scan is helpful for detecting metastasis in the chest. Whole abdomen multiphasic contrast CT scan and/or contrast-enhanced MRI scan are recommended because they are reliable for the assessment of intra-nodular arterial vascularity, which indicates residual or recurrent tumours. Nevertheless, nodule size alone is not a reliable indicator of response to treatment. An effectively treated lesion can be stable in terms of its size or even appear bigger after treatment.[28]

Contrast enhancement and the largest tumor diameter are the key parameters to define imaging response for any given treatment. The widely used 1.1 RECIST criteria is less accurate in showing response to treatment when compared to EASL or modified RECIST criteria. During the period of immunological checkpoint inhibitor treatments, iRECIST has also been endorsed. All these evaluation techniques recognize four categories: Progressive disease (PR), Stable disease (SD), Partial response (PR), and Complete response (CR).[29]

Any extra growth spotted in subsequent scans is categorized as a progressive disease. An exact assessment of the response is necessary to avoid unnecessary modifications in treatment.

Principles of Core Needle Biopsy

Recently, biopsy has been more frequently advocated to inform on the histological and molecular features of HCC, especially for patients to be considered for enrolment in clinical trials. Core needle biopsy is the optimal diagnostic sampling for HCC. Tissue sampling should be performed from the most suspicious lesion for HCC according to radiological criteria, biopsy can also be performed on lesions not fulfilling HCC radiological criteria at optimal radiological imaging.

If the lesion observed aligns with the HCC imaging guidelines and the patient has a significant risk of developing HCC, however, if the lesion does not meet the radiologic diagnostic criteria, a biopsy should be performed. Furthermore, patients who have congenital hepatic fibrosis and cardiac cirrhosis, when a visible growth corresponds to the HCC imaging criteria and the patient is at substantial risk for HCC, it is recommended to undertake a biopsy. In addition, those with inherited conditions like hepatic fibrosis, cirrhosis due to cardiovascular diseases, Budd-Chiari syndrome, and cirrhosis from disparate vascular issues such as genetic hemorrhagic telangiectasia or nodular regenerative hyperplasia should also give serious thought to a core biopsy.

A core needle biopsy may also be considered when a patient has increased serum CA 19–9 or carcinoembryonic antigen (CEA) which may be an indicator of peripheral or intrahepatic cholangiocarcinoma (CCA) or combined HCC and CCA.

A biopsy can also be done for confirmation of metastatic disease, which may change the disease management plan. If a core needle biopsy is considered, the biopsy result must be obtained before ablative treatment. If surgery is planned, a core needle biopsy may not be needed depending on the thorough evaluation of the case.

Repetition of the core needle biopsy is required if the current biopsy specimen is non-diagnostic or if it is discordant with imaging, biomarkers, or other factors.[30–32]

However, it should be noted that liver biopsies for HCC diagnosis have multiple risks, including tumor seeding. The risk in individual studies ranges from 1.5% to 5.8%. A large meta-analysis including 1340 biopsies reported an overall incidence of tumor seeding of 2.7%.[33] The outcomes of such reports have led to frequent warnings when recommending biopsy from liver lesions suspected of HCC.

Pathological Evaluation

Gross Description of HCC

In the macroscopic pathological assessment of HCC, the surrounding liver tissue typically displays a cirrhotic look, and one can notice a clearly defined growth in a tan-yellow to green hue, featuring areas of bleeding and obvious decay.

The tumor can be solitary or have a dominant nodule with intrahepatic satellite nodule or nodules, and the tumor may also present as multiple discrete or distinct nodules.

There are four principal growth patterns for HCC on a microscopic pattern: trabecular, pseudo glandular, solid and macro trabecular. However, 50% of the cases have mixed patterns, and the macrotrabecular pattern is generally associated with the worse prognosis.[34,35]

Immunostaining

The tumor can be stained with HepPar-1, Glypican 3, Alfa-fetoprotein, arginase-1, CEA, villin and CD10, albumin ISH pan-cytokeratin and reticulin.

For HCC, arginase-1 has high sensitivity and specificity and helps confirm hepatocellular differentiation. Arginase-1 is more beneficial in differential diagnosis as compared to HepPar1, especially for poorly differentiated HCC.[34] On the other hand, HepPar1 staining is more precise. However, it should also be noted that over half of the poorly differentiated HCC lose HepPar1 expression.[36,37] In cases of poorly differentiated and cirrhotic HCC, Glypican 3 exhibits high sensitivity, whereas its sensitivity is low for well-differentiated HCC. In contrast, the non-cancerous liver does not exhibit glypican activity.

The tumour is generally negatively stained with AE1/AE3, CK7, CK13, CK19, CK20, CDX2, Monoclonal CER, Mucicarmine, MOC31 BerEP4.[38–40]

Subtypes

According to the WHO classification system, HCC has eight subtypes including steatohepatic HC, clear cell HCC, macrotrabecular-massive type, cirrhotic, chromophobic HCC, fibrolamellar type, neutrophil-rich subtype, lymphocyte rich HCC.[41]

Molecular and cytogenetic testing may be helpful in identifying specific HCC subtypes. Cirrhotic subtype is associated with TSC1/TSC2 mutations, activation of IL, and JAK/STAT is seen in steatohepatic HCC, macrotrabecular massive HCC is characterized with TP53 mutation and amplification of FGF19, fibrolamellar subtype determination of DNAJB1-PRKAC fusion gene important to show fibrolamellar HCC. The prognosis of each subtype is different; for example, steatohepatic HCC, clear cell subtype, chromophobic HCC, fibrolamellar, and lymphocyte-rich HCC conceive a better prognosis than conventional HCC. The prognosis of the cirrhotic subtype is not well established, while the trabecular subtype is the worst prognosis among all HCC subtypes.[42]

Classification of HCC

The Barcelona Clinic Liver Cancer (BCLC) system is the most commonly utilized method for establishing the stage and prognostic worth of HCC. It is frequently used to allocate treatment and has been recently modified.[43] This system identifies five stages of HCC, namely very early, early, middle, advanced, and terminal. The BCLC system takes into account factors such as tumor load, liver functionality (Child-Pugh class), clinical condition, and the presence of cancer-related symptoms to determine the stage and the appropriate therapeutic strategy.[44,45]

The Tumour, Node, Metastasis (TNM) categorization for Cancer (AJCC) is created by both the American Joint Committee and the International Union for Cancer Control (UICC). The classification is routinely updated. Although this system is the most common cancer staging system accepted by clinicians, its utility is limited for HCC staging. The TNM staging system determines the primary tumour extension, lymph node involvement and extrahepatic metastasis. Still, it does not include the patient's liver function and performance status, which are significant determinants of the outcome of the patients. Hence, the TNM system is favored in patients who have early-stage disease for surgical removal or for those being contemplated for a liver transplant.

The Model for End-Stage Liver Disease (MELD) scoring scheme utilizes lab data, such as serum bilirubin, serum creatinine, and the international normalized ratio (INR) to ascertain the severity of liver disease. This method facilitates the forecasting of survival rates based on the chronic liver disease severity score and assists in recognizing candidates for liver transplantation.

The Child-Turcotte-Pugh (CTP) classification method has been employed for many years to ascertain a patient's liver reserve capacity and forecast the outcome of those with cirrhosis. This system proves beneficial when choosing appropriate candidates for standard treatment and clinical trial participation. Among the various factors, it takes into account are measurable indicators like serum bilirubin, serum albumin, and INR. Ascites and encephalopathy are assessed as well, though these are considered less consistent as they can be influenced by numerous daily variables, including medication and dietary intake.

In recent years, ALBI and PALBI scores have been accepted as a valuable prognostic classification system. Lately, insulin-like growth factor-1 (IGF-1) serum levels have been incorporated into the CTP system. This new IGF-CTP classification system substitutes two subjective parameters, ascites, and encephalopathy, with serum IGF-1. Given that the liver generates the majority of the circulating IGF-1, the serum IGF-1 level depicts the liver's synthetic capacity. A correlation was found between the intensity of cirrhosis and the onset of HCC and low serum IGF-1 concentration.[46,47]

Surgical Treatment

According to BCLC's revised publication in 2022, for stages 0 and A, the first choice of treatment, if possible, is liver transplantation (LT). Stage 0 refers to a solitary hepatocellular carcinoma (HCC) that is less than 2 cm and accompanied by preserved Liver Function Test (LFT) results and a Performance Status (PS) of 0. If a liver transplant is not a viable option, ablation is usually the recommended treatment. On the other hand, Stage A could imply the presence of a single HCC or a maximum of three nodules, each under three centimetres, along with a consistent LFT and a PS of 0. If a liver transplant is not an option, then liver surgery could be the best treatment if both the portal blood pressure and bilirubin levels are within the normal range.[43,48]

Otherwise, ablation is the choice. Based on the prospective randomized trials or retrospective studies, no statistically significant difference was shown between RFA and Microwave Ablation (MWA) if HCC is smaller than 2–3 cm. When a lesion or part of a lesion smaller than 2 cm is located in a technically unsuitable section of the liver for ablation, it becomes essential to employ percutaneous ethanol injection (PEI). However, it has been reported that RFA is superior to PEI.[49–51]

Principles of Surgery

In patients maintaining liver functionality, particularly those in Child-Pugh Class A without portal hypertension, resection could be a viable curative method. A minor series of cases indicated the feasibility of limited resection even under mild portal hypertension, provided there is only a single lesion without significant vascular invasion.[48] Hepatic resection can be considered as a therapeutic route for those who possess a favorable future liver remnant (FLR). It is necessary for FLR to be at least 20% in patients without cirrhosis and 30%–40% for those with Child-Pugh Class A cirrhosis, given that there is sufficient vascular and biliary supply.

The practicability of hepatic resection for patients with multifocal but limited disease with significant vascular invasion is often debated. When dealing with patients who suffer from chronic liver conditions and are possible candidates for severe liver resection, the portal vein may be embolized before performing surgery.[52] Associating Liver Partition and Portal vein Ligation for Staged (ALPPS) hepatectomy. ALPPS is the most recent modification of the techniques developed for two-stage hepatectomies that allow the resection of advanced liver tumors in two steps by making use of the regenerative capacity of the human liver.[53]

Alternatively, patients with initially inoperable cancer who positively responded to systemic treatment may be directed to surgical treatment. Each case should be considered on a case-by-case basis with a comprehensive multi-disciplinary evaluation. The indocyanine green (ICG) retention test has been one of the most widely used quantitative liver function tests since the 2000s. The bolus ICG injection is applied, the dye connects with plasma proteins and taken by hepatocytes, and is finally excreted into bile. The abnormal structure or function of the liver leads to a decrease in the ICG clearance rate, which represents impaired liver reserve function. Therefore, preoperative ICG clearance testing to predict the development of postoperative liver dysfunction is applicable before major liver resection or liver transplantation.[54]

The process of selecting candidates for liver transplantation involves evaluating them against the criteria set by the United Network for Organ Sharing (UNOS). The prerequisites for liver transplantation by UNOS are ([AFP level ≤1000 ng/mL and a single lesion ranging from 2 cm to 5 cm or 2 or 3 lesions ranging between 1 cm and 3 cm] as stated on www.unos.org). Based on these criteria, a patient suffering from HCC may be considered for either cadaveric or living donation transplantation.

To assess the intensity of chronic liver disease and assign corresponding priority for liver transplantation, UNOS utilizes the Model for End-Stage Liver Disease (MELD) score.[55] The MELD score can be determined using the MELD calculator available on https://optn.transplant.hrsa.gov/resources/allocation-calculators/meldcalculator/.

Principles of Liver Transplantation

Some patients marginally fail to meet the UNOS criteria for liver transplantation, but they can still be reconsidered for transplantation.[56] Patients with HCC who are down-staged after treatment to meet the liver transplantation criteria can also be considered for transplantation.[57] A patient is qualified for a standard MELD exception if the shave lesions they have align with these parameters: a singular lesion greater than 5 cm but not exceeding 8 cm or two to three lesions that all fall within these boundaries: each lesion is not greater than 5 cm, with a minimum of one lesion exceeding 3 cm and the combined diameter of all lesions not surpassing 8 cm. This eligibility comes into play prior to beginning a locoregional therapy if they possess four or five lesions each.[58]

Bridging/Downstaging Treatment Before Liver Transplantation

Due to the lengthy wait times for liver transplant candidates worldwide, it is crucial to control the disease in these patients. Patients may progress, and the disease may exceed transplantation criteria while awaiting a suitable organ, in order to prevent this, many centers employ a kind of Bridging Therapy (BT), such as TACE and/or RFA/MVA.[58] There are many potential advantages of BT in these patients, such as disease control and by this way reducing patient dropout rates for LT because of tumor progression. BT may also reduce tumor burden, improve post-transplant oncological outcomes, and may be helpful in excluding patients with aggressive tumor biology who might not get optimal benefit from liver transplantation.[59]

Some patients present beyond the liver transplantation criteria at diagnosis but have relatively good tumor biology and may benefit from LT. Assessment of such patients becomes essential for the Multidisciplinary Tumor Board to detect these patients and address appropriate therapy to downstage the disease and then make them eligible for LT. TACE and Radioembolization (TARE), with or without systemic therapy, TACE and TARE are reported to be potential tools for downstaging and bridging to LT.[60]

Locoregional Therapy

Patients should be assessed for their suitability for potential curative ablative or surgical procedures or LT. Locoregional therapies may be viewed as a bridge or to scale down for patients, paving the way for other curative HCC treatments.[61] Ablation, radiation therapy, and hepatic artery-targeted therapies are among the available locoregional therapies. HCC's current ablation strategies encompass RFA, microwave ablation (MVA), cryoablation, high-intensity focused ultrasound (HIFU), and percutaneous alcohol injection, with RFA being the go-to local ablation method during the disease's early stages.[62] Local ablation is considered a possible curative treatment for tumors measuring 3 cm or less. The tumor's location and the lesion's accessibility can influence the treatment choice and the technique's feasibility. Tumors should occupy a location that permits percutaneous, laparoscopic, and open surgical ablation techniques. Every tumor should be amenable to ablation so both the tumor and, when it comes to thermal ablation, a portion of normal tissue is treated. A margin is not anticipated after percutaneous ethanol injection. Extreme care is needed when ablating lesions in close proximity to major blood vessels, bile ducts, the diaphragm, and other internal organs in the abdomen. In patients carefully selected with small (less than 2cm is ideal), correctly situated tumors, ablation can be deemed the definite treatment following a multi-disciplinary assessment. HIFU is a novel non-invasive ablation technique for tumors. It can be performed under MRI or ultrasound guidance. In this technique, the ultrasound beam with a high-power transducer targets tissue at a selected depth increasing local temperature to provide protein denaturation and induce necrosis.

Technically, it has similar success to RFA; however, several factors limit the applicability of HIFU which include high cost, time-consuming, and requiring either general or epidural anesthesia.[63] Cryoablation is also one of the local treatment ablation techniques for hepatocellular cancer. Cryoablation has many advantages, such as activation of cryo-immunology, no serious damage to large blood vessels, and does not cause severe pain.[64] Lesions measuring between 3 and 5 cm may be managed with artery-targeted therapies to prolong life or, where the tumor's position is accessible for ablation, using a mix of artery-targeted therapy and ablation.[65] The following considerations may be helpful for ablation; lesions greater than 5 cm can be treated hepatic arterially directed therapies, systemic therapies, or with radiotherapy if they are unresectable/inoperable. The benefit of adjuvant sorafenib use after successful ablation has not been clearly shown.[66]

Arterially Directed Therapies

Regardless of the tumor's position, arterial-focused treatment can be applied when the tumor's arterial blood supply can be distinguished without unnecessary exposure to liver treatment. HCC is a vigorously neovascular, hypervascular tumor. Both the portal vein and hepatic arteries deliver a dual blood flow to the normal liver parenchyma. Arterial-focused therapies operate on the principle that they target the tumor, which relies mostly on the hepatic arterial system for its supply while leaving the normal liver parenchyma, primarily sustained by the portal venous flow.

Transarterial bland embolization (TAE), conventional chemoembolization with lipiodol (cTACE), chemoembolization with drug-eluting beads (DEB-TACE), and transarterial radioembolization (TARE, also known as selective internal radiotherapy (SIRT)) using yttrium-90 (Y-90) microspheres are all available transarterial procedure options.[67]

Transarterial treatments are not recommended for patients with bilirubin levels above 2 mg/dl unless a segmental or super-segmental method is used. The main concern for patients with bilirubin levels over 2 mg/dl is radiation-induced liver damage caused by TARE. Alternatively, a tumoral dose of 205 Gy or higher can yield better overall survival.[68,69]

Treatments involving the arteries have been found safe for limited tumor invasions of the portal vein in a few select cases. However, there are no universally accepted selection guidelines. According to randomized control trials, for those with advanced HCC, TARE[70] is not superior to sorafenib. Due to TARE's less embolic nature compared to TACE, it may be a suitable arterial treatment option, particularly for patients with lobar or segmental portal vein thrombosis without main portal vein thrombosis. An expert opinion recently suggested that some patients with major portal vein tumor thrombosis, who have good targeting, a hepatic reserve of more than 30%, and treatment aimed at a single lobe, might benefit from TARE. Sorafenib might be a more suitable treatment choice based on some retrospective data for patients with adequate liver function who are resistant to TACE.[71] The TACTICS study revealed that PFS (Progression Free Survival) might improve in selected patients by continuing sorafenib and repeating embolization.[72] Yet, the safety of combining sorafenib with arterial treatments remains unclear, and it has not been significantly associated with OS (Overall Survival) benefit in randomized trials. Currently, Phase III randomized trials are exploring the combined treatment of systemic therapies, including immunotherapy, and transarterial treatments.[73]

Transarterial Radioembolization (TARE), also known as SIRT, could potentially be a treatment option for those with early-stage BCLC who suffer from HCC lesions that are unfit for surgical removal or ablation. Consequently, TARE could be contemplated for patients who possess preserved liver functionality and lack extrahepatic diseases but cannot undergo TACE or systemic treatment, on a case-by-case basis [III, C].[74] As per the latest advancements in radiation segmentectomy, TARE is progressively used on BCLC-A patients for curative intentions. The 2022 BCLC update suggests that TARE is favored over TACE[43] in patients, with singular lesions exceeding 8 cm. Patients who are categorized as Child-Pugh class A are said to show a more favorable response to TACE treatment, but low levels of serum albumin and the existence of portal vein thrombosis could likely lead to unfavorable overall survival rates.[75]

Principles of Radiation Treatment

The continuous improvements in medical imaging, treatment delivery methods, and knowledge of liver reactions to radiation have led to an increased amount of research into the potential uses of external beam radiation therapy (EBRT) for hepatocellular carcinoma (HCC) patients. The American Society for Radiation Oncology (ASTRO) suggests that EBRT can be considered a primary treatment option for patients with HCC confined to the liver who are not suitable for

curative treatments, used as additional therapy after liver-directed treatments provided incomplete results, or as a restorative treatment for local recurrences.[76] ASTRO guidelines also conditionally recommend EBRT for patients with multiple yet liver-confined HCC cases, unresectable HCC, or cases exhibiting macrovascular invasion, in conjunction with either systemic or catheter-based therapies. Palliative radiotherapy is suggested in symptomatic primary HCC or when HCC presents with macrovascular tumor thrombosis, and EBRT is conditionally recommended as a preliminary treatment to transplantation or surgery in carefully selected HCC patients.

Liver tumors can be treated using three-dimensional conformal radiotherapy (RT), intensity-modulated RT (IMRT), proton beam therapy (PBT), or stereotactic body RT (SBRT), regardless of their original location. The use of image-guided RT (IGRT) is strongly encouraged when applying these precision techniques, as it helps increase treatment accuracy and lessen side effects. Only highly experienced centers should carry out radiation therapy for HCC.[77]

The term hypofractionation refers to the application of a larger dose of radiation in each therapy session, which shortens the overall treatment time compared to traditional fractionation. Moderate hypofractionation involves external beam radiation therapy (EBRT) with a dose size of between 3 Gy and 5 Gy, typically spread over a span of 12 to 20 sessions. Ultra-hypofractionation, on the other hand, is characterized by EBRT, with a dosage exceeding 5 Gy, generally requiring 10 or fewer sessions. Stereotactic body radiotherapy (SBRT) is a type of hypofractionated radiotherapy, specifically classified as ultra-hypofractionation; it is delivered in five or fewer sessions. The growing research evidence suggests that SBRT is a potentially effective primary treatment strategy for intermediate hepatocellular carcinoma (HCC).[78] In a particular study, a 38% complete response rate and a 95% local disease control rate over a 2-year period were noted with SBRT.[79] If corroborated by additional clinical trials and real-world data, this technique could serve as a substitute for ablation/embolization techniques when they fail or are not feasible. Moderate hypofractionation could be evaluated for more extensive disease or larger tumors, providing that the unaffected liver and its radiation tolerance can be maintained.[80]

The need for the absence of extrahepatic disease is a mandatory requirement, and all extrahepatic involvement should be effectively handled and incorporated into a thorough management plan. The bulk of the data on radiation therapy for hepatocellular carcinoma (HCC) mainly comes from patients with Child-Pugh A liver disease,[81] and there is a scarcity of safety data for those with Child-Pugh B or worse liver functions. While treatment can safely be administered to individuals with Child-Pugh B cirrhosis, alterations in dosage might be needed, and scrupulous obedience to dosage limitations is paramount. However, the safety of using radiation to treat HCC on the liver in patients with Child-Pugh C cirrhosis is still ambiguous.[82]

In some cases, proton beam therapy (PBT) could be seen as a suitable choice. Symptom control and hindering the complications from metastatic HCC lesions like those affecting the bone or brain, or those creating a significant tumor load in the liver, can be achieved through palliative external beam radiation therapy (EBRT).[76]

A decision on the regimen and technique for dose-fractionation is dependent on several factors like disease extent, tumor location, liver functions, available technologies at the healthcare centre, and dose constraints. Stereotactic body radiotherapy (SBRT) with the escalation of dosage or moderately hypo-fractionated EBRT could be an option for HCC restricted to the liver. In cases where macrovascular invasion is present, moderately hypo-fractionated EBRT may be used in combination with other catheter-based therapies. Utilization of respiratory movement management and daily image-guided radiation therapy is encouraged for HCC patients undergoing SBRT or moderately hypo-fractionated EBRT. A change to the number of fractions and reduction in dose per fraction should be considered if the tumor is close to any gastrointestinal structure. Preferred dose schedules for SBRT, moderate hypofractionation and conventional radiotherapy are 30–60 Gy in 3–5 fractions, 37.5–72 Gy in 10–15 fractions and 50–66 Gy in 25–33 fractions, respectively.[76]

The recently published NRG/RTOG 1112 study analyzed the effects of sorafenib vs SBRT, followed by sorafenib, in patients with advanced HCC. Most of the subject pool was classified stage Barcelona Clinic Liver Cancer Stage (BCLC) C (82%) and had macrovascular invasion (74%). SBRT was administered at a total dosage of 27.5–50Gy in 5 fractions, with the dose determined by the mean liver dose and other dose limits. After controlling for factors such as Zubrod performance status, M stage, Child Pugh A5 vs A6, and the vascular HCC degree, it was discovered that overall survival improved significantly in the SBRT plus sorafenib arm. Both median progression-free survival and time to progression

saw significant improvement with the SBRT plus sorafenib arm, when compared with only sorafenib, without a notable increase in AEs.[83]

Some data are available on the use of stereotactic body radiotherapy (SBRT) as a bridge to liver transplantation for HCC and SBRT compared with TACE and HIFU. In these studies, SBRT was safe and effective as bridging therapy in waiting-listed patients with HCC. In conclusion, these are considered promising results that SBRT may be a more powerful bridging treatment option.[84,85]

Furthermore, while no difference was noted between PBT and photon-based RT in general treatment outcomes, a single-center retrospective study suggested that proton therapy was associated with an increased OS and reduced risk of non-traditional radiation-induced liver disease. This encouraging retrospective study evaluated patients with nonmetastatic and inoperable HCC who had not been previously treated with liver-directed RT and did not receive additional liver-directed RT within 12 months post-treatment, and the findings of which ought to be evaluated in prospective trials.[85] The NRG GI003 study is designed to compare these techniques, and the results are anticipated to provide conclusive findings.

Sequential or concomitant locoregional treatment and systemic treatment for patient with HCC

The most common treatment for patients with HCC limited to the liver is local-regional treatments, but an answer to an important question is sought regarding these patients' treatment approaches. The question is whether adding systemic therapy to local-regional treatments improves outcomes compared to local-regional treatment alone. In two randomized controlled Phase 3 studies that evaluated sorafenib after TACE, the contribution of sorafenib to PFS and OS could not be demonstrated.[86,87] However, the only positive study with sorafenib in this regard is TACTICS, a Phase 2 study. This study used TACE alone or 400 mg sorafenib once daily before TACE followed by 800 mg sorafenib twice daily after TACE was initiated. In the final analysis, the primary endpoint, median PFS, was significantly higher in combined therapy (22.8 vs 13.5 months, HR: 0.66), but there was no significant difference in mOS.[72] A phase 3 study of adding lenvatinib to locoregional therapy has been evaluated. In the trial results, adding lenvatinib to TACE improved clinical outcomes (PFS and mOS).[88] Its use in the form of sequential transarterial chemoembolization and stereotactic body radiotherapy followed by immunotherapy in patients with no possibility of resection was evaluated in a phase 2 study. In this study, which included 34 patients, 12% of the patients continued with the curative treatment option (surgical resection, radiofrequency ablation), and a radiological complete response was achieved in 42% of the patients.[89] Finally, the results of the study conducted with local regional treatment in combination with immunotherapy and anti-VEGF were reported. Here, in a randomized controlled trial combining TACE, durvalumab (D), and bevacizumab (B), PFS was significantly improved with TACE compared with D+B+TACE, PFS 15.0 versus 8.2 months. (HR: 0.77; $p = 0.032$). PFS for D+TACE and TACE was not statistically significant (mPFS 10.0 vs 8.2 months; HR: 0.94; $p = 0.638$). However, in terms of response, it was more pronounced in the combined treatment arm. Objective response rates were 43.6%, 41.0%, and 29.6% for D+B+TACE, D+TACE, and TACE, respectively (reference 23). Positive results regarding combining local-regional treatments and systemic treatments are promising, and they can be made a standard approach with long-term results.

Neoadjuvant or adjuvant treatment for patients with resected HCC

Considering the high local recurrence rates after hepatic resection, neoadjuvant therapy before resection has been evaluated with different treatment options. Since most studies have not yet shown a survival advantage, it has not become standard. Therefore, neoadjuvant therapy before hepatic resection is not recommended except in a clinical trial.[90–92]

As like rationale for neoadjuvant therapy, adjuvant studies have been conducted on the high recurrence rate after curative resection for HCC, and the application of effective postoperative (adjuvant) treatment options that reduce the risk of recurrence. Sorafenib, which is effective in the metastatic stage, was used as adjuvant treatment, but the benefit of adjuvant sorafenib could not be demonstrated in the international phase III STORM study.[66] After the negative study

with sorafenib, atezolizumab and bevacizumab, which were shown to be more effective than sorafenib in the metastatic stage, were studied as an adjuvant combination treatment. Adjuvant atezolizumab plus bevacizumab was compared with observation in non-metastatic patients with hepatocellular carcinoma who were at high risk for recurrence after curative-intent resection or ablation. According to the pathological findings of the patients, high-risk parameters were determined as tumor larger than 5 cm, more than three tumor foci, microvascular invasion, minor microvascular invasion, or poor-grade pathology. Adjuvant combination therapy improved RFS relative to active surveillance (HR 0.72, 95% CI 0.53–0.98), and overall health-related quality of life and functioning were similar between arms.[93] However, grade ≥3 toxicities were higher for adjuvant therapy versus surveillance, and the overall survival data were immature at the first interim analysis. Therefore, the use of adjuvant therapies following potentially curative resection of HCC is not established and remains investigational.

Development of Systemic Treatment Options for Advanced Stage (BCLC Stage C) HCC Patients

Until 2007, there was no established medical treatment for HCC. Despite the lack of phase III randomized trials and high-level clinical evidence for efficacy, cytotoxic agents alone or in combination were defined in guidelines and frequently used by clinicians.[94]

Sorafenib is a multi-targeted tyrosine kinase inhibitor (TKI), which inhibits the tyrosine kinase activity of receptors like RAF, VEGF receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR). Its use as a systemic agent was the first to demonstrate an overall survival (OS) benefit in a phase 3 clinical trial, hence becoming a standard treatment internationally for advanced hepatocellular carcinoma in 2007. A phase 3 clinical study, SHARP, showed an impressive median OS of 10.7 months compared to 7.9 months with a placebo, a statistically significant difference.[95] Similarly, the OS benefit of Sorafenib was shown in a phase 3 study mainly involving HBV-affected Asian patients.[96] Consequently, the primary treatment for advanced HCC remained primarily Sorafenib for over a decade, but its application was constrained to Child-Pugh A, and some BCLC B7 patients. Most patients with advanced-stage HCC were ineligible to receive sorafenib.

From 2017 to 2019, three other multi-TKIs (lenvatinib, regorafenib, and cabozantinib) alongside ramucirumab, a VEGFR-2 monoclonal antibody, were discovered to be effective in the treatment of advanced-stage HCC. In patients whose HCC continued to progress despite Sorafenib treatment, or those intolerant to it, regorafenib, cabozantinib, and ramucirumab were proven to extend OS compared to a placebo.[97,98] The primary OS benefit of regorafenib was evident in patients intolerant to a daily dose of 400 mg of Sorafenib. However, the survival advantage was limited only to patients with serum alpha-fetoprotein (AFP) levels ≥400 ng/mL for ramucirumab, according to the REACH-2 study. The median OS was 8.5 months versus 7.3 months, and progression-free survival was 2.8 months versus 1.6 months. Both OS and PFS improved significantly in the ramucirumab group compared to the placebo group at the second-line setting.[99,100]

Recently, immune checkpoint inhibitors (ICIs) were started to be investigated in the treatment of HCC. These immune checkpoint inhibitors include anti-programmed death receptor-1 (PD-1), anti-programmed death ligand-1 (PD-L1), and anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4). These agents and their combinations have been tested in both treatment-experienced and treatment-naïve patients. Additionally, treatment combination strategies such as anti-PD-1/PD-L1 treatment agents plus anti-VEGF agents or TKIs have been evaluated and are still being tested. The use of anti-VEGF and TKIs carries risks, especially due to the increased bleeding risk in patients with cirrhosis and esophageal varicose veins. Therefore, immunotherapy and immunotherapy combinations are preferred in these patients.

Recent findings are suggesting newer treatments for initial and subsequent stages of HCC, either as solo treatments or in various combinations. In particular, in the IMBRAVE 150 study, the combination of atezolizumab and bevacizumab[101] or durvalumab and tremelimumab (HIMALAYA study) has been demonstrated to be of a higher standard to sorafenib for the primary line of treatment.[102]

Lenvatinib, an anti-VEGFR1–3, FGFR1–4, PDGF, RET, and KIT TKI,[103] was evaluated against sorafenib in a phase 3 trial including predominantly Asian patients in the REFLECT study. The lenvatinib group's median Overall Survival (OS) was 13.6 months, slightly longer than the 12.3 months of the sorafenib group. While this discrepancy was not

statistically significant, the lenvatinib group demonstrated superior median Progression-Free Survival (PFS) and overall response rate (ORR) according to secondary endpoints of the study.[104] Owing to these results and additional supporting data, lenvatinib could be contemplated as an initial or even secondary treatment option for progressive hepatocellular carcinoma.

After the successful REFLECT study with Lenvatinib, different agents were assessed in clinical trials, becoming a benchmark treatment selection for advanced HCC. These include Bevacizumab, an antiVEGF-A antibody, and Atezolizumab, an anti PD-L1 antibody.[105] IMbrave150, a phase 3 study, showed notable survival benefits of the "atezolizumab-bevacizumab" combination as compared to sorafenib - 19.2 months in the combined group versus 13.4 months in the sorafenib group. Median PFS was also outstanding relative to sorafenib (6.9 months vs 4.3 months). The sorafenib group's ORR was 11%, compared to a 30% rate in the combination group. In addition, 8% of patients in the combination group achieved a complete response (CR), compared to just 1% in the sorafenib group.[101]

Different clinical trials have experimented with combination treatments involving immunotherapy drugs. One such drug, cabozantinib, is a multikinase inhibitor with possible antiangiogenic and immunomodulatory benefits. The COSMIC-312 study[106] set up a comparison of the combo of cabozantinib and atezolizumab versus sorafenib. Although there was an advantage in progression-free survival (PFS) with the combination (6.8 months as opposed to 4.2 months with sorafenib), there was no noteworthy difference in overall survival (OS), the primary objective of this trial. The median, or middle value, OS was 15.4 months in the combined treatment group against 15.5 months in the sorafenib group. In certain patients with HBV infection, the observed median OS was 18.2 months (cabozantinib/atezolizumab) compared to 14.9 months (sorafenib). The overall response rate (ORR) reported in the combined treatment was 11% versus 4% in the control.

The HIMALAYA trial, a three-arm comparative study, which juxtaposed a combination of durvalumab and tremelimumab or standalone durvalumab against sorafenib as an initial line of treatment for patients with advanced hepatocellular carcinoma.[102] In this combination therapy, which included regular periodic durvalumab doses and one dose of tremelimumab, as defined by the STRIDE regimen, evidence of a significant difference was found for OS in the combined treatment group as compared to the sorafenib treatment. Durvalumab, when used alone, was similarly effective as sorafenib in patients with HCC. Furthermore, both the durvalumab–tremelimumab combination and durvalumab alone had higher ORRs than sorafenib, at 20%, 17%, and 4%, respectively. Yet, no marked difference was identified in PFS among the treatment groups (3.78 months for the combination versus 4.07 months for sorafenib).[107]

The potential effectiveness of lenvatinib, as indicated by the REFLECT study (80), led to an investigation of a combination therapy consisting of lenvatinib and pembrolizumab. This combination treatment was tested against lenvatinib alone in the LEAP-002 phase III study. A significant improvement was observed in the combination arm's ORR (26%) versus the control arm's (17%). However, the study did not favor the combination treatment outcomes. The median PFS and OS showed comparably closer rates.[108]

When used as the initial treatment for advanced HCC, nivolumab was also measured against sorafenib in the phase III CheckMate 459 study. While nivolumab resulted in a higher ORR (15% vs 7%), there was no enhanced improvement over sorafenib alone, rendering the study negative.[109]

A different combination treatment investigated for the primary treatment of patients suffering from advanced HCC was a combination of camrelizumab, a PD-1 inhibitor, and rivoceranib, a selective VEGFR-2 TKI. Compared to sorafenib in the phase 3 CARES 310 trial, the median survival rate was measured as 22.1 months with camrelizumab and rivoceranib, and 15.2 months with sorafenib. The median time for disease progression was 5.6 months with camrelizumab and rivoceranib, in contrast to 3.7 months with sorafenib. The proportion of patients who were presented with an antitumor response improved by 25.4% with the combined method as opposed to 5.9% with sorafenib, signifying the combination method's superior efficacy.[110,111] This study reported that the dual primary endpoints, OS and PFS, were met with camrelizumab plus rivoceranib, increasing both rates: a benefit of 6.9 months for median OS and 1.9 months for median PFS.

Tislelizumab, an anti-PD-1 monoclonal antibody, was evaluated against sorafenib in the phase-3 RATIONALE-301 study,[112] as a first line of treatment for inoperable HCC. Key results were centred around median OS non-inferiority, which for tislelizumab was 15.9 months, proving its worth compared to sorafenib's 14.1 months. Also, median PFS in the

tislelizumab branch was 2.2 months versus 3.6 months in the sorafenib group. A notable increase in ORR was experienced in the tislelizumab group, coupled with a considerably longer response duration.

Numerous alternative treatments and combinations have been investigated as second- and third-line treatments for advanced HCC. A phase-3 RESORCE study[113] has shown positive results with regorafenib compared to a placebo in treating patients, with progressive disease following sorafenib treatment, or who could not tolerate sorafenib. The median OS was 10.6 months with regorafenib vs 7.8 months of placebo. Following these findings, in 2017, regorafenib was accepted as an option for second-line treatment of HCC.

In the RELIVE study, following sorafenib's failure, an attempted treatment with doxorubicin-loaded nanoparticles did not yield an increase in overall survival.[114]

Cabozantinib was evaluated as a second-line treatment for HCC in the CELESTIAL trial.[115] The trial compared cabozantinib with a placebo for second- or third-line treatment of advanced HCC, and the results showed a 10.2-month overall survival rate in the cabozantinib group compared to 8.0 months for the placebo group Despite a low overall response rate, cabozantinib showed higher median PFS and improved patient's quality of life. Consequently, this drug was approved as an option for second and third-line treatment of advanced HCC, aligning with the study's findings.

The REACH research concluded that ramucirumab did not enhance the average OS survival in the entire HCC patient population who had previously undergone treatment with sorafenib. However, a subgroup review of the trial highlighted an OS advantage in patients with baseline serum AFP levels ≥400 ng/mL. The same benefit was noted in the REACH-2 random study, resulting in the acknowledgement of ramucirumab as second-line treatment in this specific patient group.[98,99]

The Phase I/II CheckMate 040 research included a group of 148 patients who were previously treated with sorafenib.[116] The trial evaluated the effectiveness of combined ipilimumab and nivolumab as a second-line treatment. It tested three dosage schedules, ie, nivolumab 1 mg/kg, and ipilimumab 3 mg/kg every three weeks, followed by 240 mg nivolumab every two weeks. The highest ORR at 32%, along with an 8% CR occurred in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg regimen every three weeks. The median patient OS was 22.5 months.

In the advanced HCC second-line treatment, Pembrolizumab was compared to a placebo in the phase III KEYNOTE-240 research. The trial showed an OS of 14 months with pembrolizumab treatment against an OS of 11 months with a placebo. PFS was three months with pembrolizumab and 2.8 months with placebo; however, it did not hit the pre-set efficacy thresholds.[117,118]

The Phase 1/2 study CheckMate 040 also assessed Nivolumab as a solo therapy for second-line treatment.[116] The exploration included patients from both Child-Pugh class B (with a total score of 7 or less) and class A. The Objective Response (OR) accounted for 15% of the dose-escalation group and 20% of the expansion group, with six patients demonstrating a Complete Response (CR). The Overall Survival (OS) was 15 months in the dose escalation sector, while the median OS of the expansion sector was not disclosed. Following these outcomes, the Food and Drug Administration (FDA) initially endorsed the use of nivolumab as a sped-up treatment alternative for patients who had earlier received sorafenib. However, this approval was later revoked due to unfavourable outcomes in the first-line comparison between nivolumab and sorafenib.

Table 3 and 4 provides an overview of pivotal clinical research that has significantly influenced the present approach to primary and secondary/tertiary systemic HCC therapies.

Treatment Choice in Specific Populations, Which Treatment to Whom

Choosing treatment options should consider the initial causes of liver cancer. Both viral and non-viral causes can impact the immune response to HCC, resulting in different treatment outcomes including those involving immune checkpoint inhibitor combinations and TKI treatments. In the future, it is possible HCC treatments could be tailored to the specific cause, whether viral or non-viral. This would include diseases like steatotic liver disease (NAFLD) and steatohepatitis (NASH), which are often linked to conditions like metabolic syndrome, obesity, dyslipidemia, and type 2 diabetes.[119]

In line with the current knowledge, the debate is ongoing over whether treatment should be strictly chosen based on the primary cause. The evidence currently available is conflicting and insufficient for making treatment decisions. One particular study indicated that HCC cases originating from NASH had a more favourable prognosis. The study suggested

Table 3 A Summary of Practice-Changing Clinical Studies That Shaped Our Current First-Line Treatments for Advanced/Metastatic Hepatocellular Cancer

Trial	Line	Agent	Phase	Patient Number	ORR (RECIST 1.1)	mPFS Months	mOS Months	Reference
Sharp	First-line	Sorafenib vs Placebo	III	299 vs 303	2% vs 1%	5,5 vs 2.8	10,7 vs 7.9	[95]
Asia-Pacific	First-line	Sorafenib vs Placebo	III	150 vs 76	???	2,8 vs 1.4	6,5 vs 4.2	[96]
REFLECT	First-line	Lenvatinib vs Sorafenib	III	478 vs 476	19% vs 7%	7,3 vs 3.6	13,6 vs 12.3	[97]
HIMALAYA	First-line	STRIDE vs Durvalumab Vs Sorafenib	III	393 vs 389 vs 389	20% vs 17% vs 5%	3,8 vs 3.7 vs 4.1	16,4 vs 16.6 vs 13.8	[102]
IMbrave150	First-line	Atezolizumab plus Bevacizumab vs Sorafenib	III	336 vs 165	30% vs 11%	6,9 vs 4.3	19,2 vs 13.4	[105]
COSMIC-312	First-line	Atezolizumab plus Cabozantinib vs Sorafenib	III	432 vs 217	11% vs 4%	6,8 vs 4.2	15,4 vs 15.5	[106]
LEAP-002	First-line	Lenvatinib plus pembrolizumab vs Lenvatinib	III	395 vs 399	26,1% vs 17.5%	8,2 vs 8.0	21,2 vs 19.0	[108]
CheckMate 459	First-line	Nivolumab vs Sorafenib	III	371 vs 372	15% vs 7%	3,7 vs 3.8	16,4 vs 14.7	[109]
NCT03764293	First-line	Camrelizumab plus rivoceranib vs Sorafenib	III	272 vs 271	25,4% vs 5.9%	5,5 vs 3.7	22,1 vs 15.2	[110]

Abbreviations: N.A, not applicable; ORR, objective response rate; mOS, mean overall survival; mPFS, mean progression free survival.

Table 4 A Summary of Practice-Changing Clinical Studies That Shaped Our Current Second-Line Treatments for Advanced/Metastatic Hepatocellular Cancer

Trial	Line	Agent	Phase	Patient Number	ORR (RECIST 1.1)	mPFS Months	mOS Months	Reference
REACH	Second line	Ramucirumab vs Placebo	III	283 vs 282	7% vs <1%	2,8 vs 2.1	9,2 vs 7.6	[98]
REACH-2	Second line	Ramucirumab vs Placebo	III	197 vs 95	5% vs 1%	2,8 vs 1.5	8,1 vs 5.3	[99]
RESORCE	Second line	Regorafenib vs Placebo	III	379 vs 194	7% vs 3%	3,1 vs 1.5	10,6 vs 7.8	[113]
CELESTIAL	Second line	Cabozantinib vs Placebo	III	470 vs 237	4% vs <1%	5,2 vs 1.9	10,2 vs 8.0	[115]
CheckMate 040	Second line	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	I/II	50	32%	NA	22,5	[116]
CheckMate 040	Second line	Nivolumab 3mg/kg, dose expansion cohort	I/II	214	20%	NA	NA	[116]
KEYNOTE-240	Second line	Pembrolizumab vs Placebo	III	178 vs 135	18,3% vs 6.4%	3,0 vs 2.8	13,9 vs 10.6	[118]

Abbreviations: N.A, not applicable; ORR, objective response rate; mOS, mean overall survival; mPFS, mean progression free survival.

that the cause of HCC might serve as an indicator for overall survival (OS). Furthermore, the results indicated that lenvatinib treatments correlated with an extended OS and progression-free survival (PFS) in patients with non-viral HCC, particularly those with NAFLD/NASH-induced HCC.

If the patient has significant comorbidities such as uncontrolled hypertension/varicose veins/ coronary artery disease/ stroke/ emboli, the patient should be evaluated in a multidisciplinary manner and treated individually

The other specific situations to be considered are pulmonary embolism, level of thrombocytopenia, presence of significant splenomegaly and portal hypertension.

The criteria for selection of patients who are not eligible for systemic treatments are not precise and not evidence based

The use of tumor markers i.e alpha fetoprotein are still far from being optimal. No consensus is present on the management of patients with an increase in serum alpha fetoprotein level

There can be individual differences efficacy and toxicity between different type of antiPD-1 and PD-L1 type of immune checkpoints inhibitors ant their combinations

Combinations with IO plus anti VEGF agents, IO plus multi-targeted TKI'ies and IO/IO combinations have shown relevant clinical activity

In the presence of major vascular invasion systemic treatment should be initiated without delay

Besides, cabozantinib in combination with atezolizumab in COSMIC 312 trial showed a very good overall survival benefit in a subgroup analysis in patients hepatitis b positive HCC patients. These findings need confirmation and further trials and data maturation. Issues still need to be addressed in clinical trials such that biological biomarkers are still absent for patient selection for specific TKI and immune checkpoint inhibitors, or their combinations. Other clinical issues such as the presence of hypertension/varicose veins/coronary artery disease/stroke/pulmonary embolism, level of thrombocytopenia, and splenomegaly are still very important. They may affect individual outcomes in patients treated with currently available treatment options. We also need markers for patient follow-up such as AFP. It is currently unclear what the exact role of alpha-fetoprotein is in patient surveillance, and appropriate action is uncertain in case of an increase in AFP levels. In conclusion, advancements in systemic therapy for HCC are continuously emerging; therefore, the recommendations and comments must be regularly updated based on ongoing scientific investigations.

Conclusions

The treatment plan for hepatocellular carcinoma (HCC) should be determined based on the patient's liver function, overall health status, and tumor characteristics, including size, number of lesions, macrovascular invasion, and metastasis. These patient and tumor factors designate the disease stage, each having varied prognoses and clinical outcomes.[120] In accordance with accepted guidelines for very early and early-stage HCC, measures intended for cure such as local ablative treatments, surgery, and liver transplantation should be contemplated. In instances where patients have maintained liver function and are in an intermediate phase of HCC past Milan criteria, hepatic arterial therapies such as TACE are suggested. Regrettably, a significant percentage of patients are diagnosed with an advanced stage of the disease. Advanced-stage HCC is untreatable, and during this phase, for patients with satisfactory liver function, systemic treatment is the sole treatment choice. Also, systemic treatment is proposed for patients in earlier stages, but present contraindications or progression during or after local treatments are also proposed. Furthermore, even with patients initially receiving potentially curative local treatments like surgery and ablation, recurrence rates remain high, reaching up to 70% within 5 years.

The HCC management guidelines from BCLC were revamped in 2022.[45] As per these new guidelines, the treatment recommendations for intermediate-stage HCC (BCLC-B) have been adjusted and are now contingent on both the tumor load and liver function. The patients are now further divided into three sub-categories based on these criteria. The group 1 patients may be eligible for liver transplantation, according to the local extended criteria for transplantation that considers tumor size and serum AFP level. There are also patients, the second group, who are not suitable for LT, but can benefit from TACE due to proper portal flow and distinct lesions that provide selective access to the tumor's blood vessels. The third and last group is represented by patients with pervasive, invasive and extensive dual lobular liver involvement, for whom system-wide treatment is suggested. Among the patients in the BCLC-B HCC category, transplantation is a viable consideration for those who meet the expansionary LT criteria or for those who demonstrate the possibility of improvement beyond transplantation criteria postsuccessful TACE downstaging.

The current guidelines advocate that patients with progressive infiltrative tumors, instances of vascular invasion, dissemination of cancer cells, or no significant response after two TACE treatments should be evaluated for systemic treatment. The decision to switch from TACE to systemic treatment due to TACE failure is not consistent around the world, with many scores having been suggested to aid in the decision-making process. Nevertheless, the validity of some of these treatment options in populations strictly treated according to BCLC guidelines still requires further validation.

The importance of transitioning from TACE to systemic treatment becomes more pronounced in cases where superior systemic agents are available in the treatment of HCC. It is crucial to start these treatments before the liver function or patient's health status reaches a point of irreparable decline.

In patients new to systemic therapy, sorafenib extends overall survival (OS) when compared to a placebo, with atezolizumab-bevacizumab extending OS in comparison to sorafenib. Furthermore, the IMbrave 150 trial verified that atezolizumab and bevacizumab combined outperform sorafenib in prolonging both OS (hazard ratio [HR] of 0.58) and progression-free survival (PFS) (HR of 0.59).[105]

Moving forward, the incorporation of systemic treatment at early stages, either stand alone or in conjunction with local treatments, is anticipated. Currently, combining locoregional intervention with systemic therapy is becoming increasingly common, as evidenced in a recent study by Kudo and colleagues demonstrating improved PFS in intermediate-stage HCC patients who received both endovascular locoregional and systemic treatment, which included sorafenib in tandem with on-demand TACE, compared to those receiving only TACE. As clinical trials investigating the combination of locoregional and systemic therapies, such as TKIs, checkpoint inhibitors, and anti-vascular agents in the treatment of advanced-stage HCC continue to enrol patients, the results will clarify the most effective and prudent use of these strategies in this patient demographic. Moreover, the typical progression of treatment from curative to locoregional to systemic, as seen in the early to advanced HCC spectrum, may be adjusted based on the findings from these studies.[121] At present, combining multi-kinase inhibitors (MKI) and TACE is supported by some evidence as a standard procedure, and there is an expanding body of clinical research endorsing the usage of immunotherapy in this context.[109] Besides their biological action mechanism, systemic treatments (combined with locoregional treatments) for earlier-stage patients could offer benefits for those showing clinical decline or liver function deterioration during TACE and seen as unable to tolerate further systemic therapy.[122]

It is crucial to note that none of the available local therapies have shown superior results to sorafenib in any clinical study in advanced stage. Moreover, the newer systemic treatments are superior than sorafenib. Therefore, it is imperative to classify the disease as "advanced stage" and consider systemic treatment if the patient has macro-vascular involvement and extrahepatic disease.

The presence of disease outside the liver tissue, such as in adrenal glands, bones, lungs, omentum, peritoneum, or regional lymph nodes, indicates an unfavourable prognosis. Although non-malignant swelling of abdominal lymph nodes can occur in HCC patients with cirrhosis, the possibility of lymphatic metastasis should be always considered. Thus, any HCC patient should have any enlargement of the abdominal lymph nodes meticulously assessed through Multi-Disciplinary Team Boards. (MDTBs)

In the case of documented extrahepatic disease, systemic therapies are the mainstay of the HCC mangement. In case of limited regional lymph node enlargement, and no other extrahepatic disease, liver-directed transarterial therapies may be recommended by MDTBs, in addition to systemic therapies, as, these patients may potentially be cured or down-staged by LT.

During TACE or TARE, interventional radiologists may choose highly selective techniques to maintain the maximum amount of healthy liver tissue. It's important to carefully select the right lobar treatment for left lobe hypertrophy. Although combining TACE/TARE with sorafenib has been unsuccessful, there are innovative approaches being explored. In certain situations, TACE +sorafenib has shown promising results. Additionally, there is a growing trend towards the early implementation of systemic therapies. However, it's crucial to consider the potential drug-specific toxicities that may compromise the effectiveness of liver-directed arterial therapies during later stages of treatment.

Intraarterial hepatic treatments are a series of procedures that utilize catheters to deliver therapeutic elements such as chemical or radionuclide substances, and/or embolic materials, directly into the artery to focus on liver tumors. These agents are often incorporated as part of single-drug therapy, chemotherapy, or radiotherapy treatments. This category

encompasses embolotherapy alone (plain embolization (TAE)) or embolization with chemotherapy infusions (TACE), transcatheter arterial chemo-infusion (TACI), and chemoembolization with drug-eluting beads (DEB-TACE). Radiotherapy treatments include radioembolization with yttrium-90 and injection of iodine-131 (131I) tagged lipiodol. For around two decades, these therapies have been used for the palliative treatment of primary and metastatic liver cancer and have shown to yield clinical advantages in chosen patient groups.[123]

According to the most recent update of BCLC, the role of TACE has been limited compared to the previous updates. On the other hand, the role of TARE is now recognized at very early and early stages (up to 8 cm in tumour size). The role of hepatic arterial therapies for downstaging and bridging is widely recognized among the surgical and radiological societies with respect to several prospective studies. Also, BCLC's recent update includes TARE as an option in the clinical decision-making section.

Due to the technical and logistical differences, there is a high degree of awareness in understanding the difficulties of designing multicenter prospective randomized studies with hepatic arterial therapies.

There is also cumulating data on the role of TARE for early-stage BCLC as a curative approach. Radiation segmentectomy is may be used in some selected patients depending on the multidisciplinary tumor board discussion.

Disclosure

The authors report no conflicts of interest in this work.

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