2023 Update of Indian National Association for Study of the Liver Consensus on Management of Intermediate and Advanced Hepatocellular Carcinoma: The Puri III Recommendations

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Abbreviations: BCLC: Barcelona Clinic Liver Cancer; CECT: Contrast-Enhanced Computed Tomography; CNI: Calcineurin Inhibitor; CT: Computed Tomography; DDLT: Deceased Donor Liver Transplantation; DM: Diabetes Mellitus; DWI: Diffusion-weighted imaging; ECOG: Eastern Cooperative Oncology Group; EASL: European Association for the Study of the Liver; FDG PET-CT: Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography; GRADE: Grading of Recommendations Assessment Development and Evaluation; HCC: Hepatocellular carcinoma; INASL: Indian National Association for the Study of Liver; INASL-BCLC: Indian National Association for Study of the Liver-Barcelona Clinic Liver Cancer; LDLT: Living Donor Liver Transplantation; LRT: Locoregional Therapy; MC: Milan Criteria; MRI: Magnetic Resonance Imaging; MRE: Magnetic Resonance Elastography; MVI: Microvascular Invasion; ORR: Objective Response Rate; OS: Overall Survival; PFS: Progression-Free Survival; PIVKA-II: Protein Induced by Vitamin K Absence or Antagonist-II; PVTT: Portal vein tumor thrombosis; RETREAT: Risk Estimation of Tumor Recurrence After Transplant; SBRT: Stereotactic Body Radiotherapy; TACE: Transarterial Chemoembolization; TARE: Transarterial Radioembolization; TKI: Tyrosine Kinase Inhibitor; UCSF: University of California San Francisco; VEGF: Vascular Endothelial Growth Factor

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Hepatocellular carcinoma (HCC) presents significant treatment challenges despite considerable advancements in its management. The Indian National Association for the Study of the Liver (INASL) first published its guidelines to aid healthcare professionals in the diagnosis and treatment of HCC in 2014. These guidelines were subsequently updated in 2019. However, INASL has recognized the need to revise its guidelines in 2023 due to recent rapid advancements in the diagnosis and management of HCC, particularly for intermediate and advanced stages. The aim is to provide healthcare professionals with evidence-based recommendations tailored to the Indian context. To accomplish this, a task force was formed, and a two-day round table discussion was held in Puri, Odisha. During this event, experts in their respective fields deliberated and finalized consensus statements to develop these updated guidelines. The 2023 INASL guidelines offer a comprehensive framework for the diagnosis, staging, and management of intermediate and advanced HCC in India. They represent a significant step forward in standardizing clinical practices nationwide, with the primary objective of ensuring that patients with HCC receive the best possible care based on the latest evidence. The guidelines cover various topics related to intermediate and advanced HCC, including biomarkers of aggressive behavior, staging, treatment options, and follow-up care. (J Clin Exp Hepatol 2024;14:101269)

Hepatocellular carcinoma (HCC), also known as primary liver cancer, continues to present significant treatment challenges despite notable advancements in its management. In 2014, the Indian National Association for the Study of the Liver (INASL) published the initial set of guidelines on HCC,[1] followed by an update in 2019,[2] to offer healthcare professionals guidance for diagnosis and management. Since then, significant developments have occurred in the field, particularly in the diagnosis and management of intermediate and advanced HCC. Consequently, INASL has decided to revise its guidelines, providing evidence-based recommendations tailored to the Indian context. The updated guidelines cover various topics, including risk factors, screening and diagnosis, staging, treatment options, and follow-up care, with a focus on intermediate and advanced HCC. By incorporating the latest advancements in the field, these guidelines have the potential to improve patient outcomes and enhance the quality of care provided by healthcare professionals in India.

METHODS

To formulate the updated guidelines, a task force was established to review the previous guidelines and integrate recent advancements in treatments relating to intermediate and advanced HCC. The task force organized a two-day round table discussion on May 14th and 15th, 2022, in Puri, Odisha. The discussion involved thorough debates and deliberations among the task force members, who were experts in their respective fields, to finalize the consensus statements for the revised guidelines. Each issue was meticulously addressed, taking into account the most relevant data available in the literature. The final consensus statements were developed based on scientific evidence and the clinical expertise and experience of the participating physicians. Only those statements that obtained approval from the majority (>50%) of the task force members were accepted.

To ensure the accuracy and reliability of the guidelines, each statement was graded according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, with minor modifications.[3,4] The GRADE system assesses the quality of the underlying evidence as high, moderate, or low for each recommendation. The strength of the recommendations, either strong or weak, reflects the quality of the underlying evidence, as outlined in Table 1. Overall, the task force adopted a rigorous approach in developing the updated guidelines, incorporating the latest scientific evidence along with the clinical expertise and experience of the members. By adhering to a stringent grading system, the guidelines provide healthcare professionals with evidence-based recommendations tailored to the Indian context, offering the potential to enhance outcomes for patients with HCC.

Indicators of Aggressive Tumor Biology

This section discusses indicators of aggressive tumor biology in HCC. Clinical indicators include gender differences, age, symptoms at presentation, hepatitis status, liver dysfunction, and diabetes. Radiological indicators encompass tumor size, number, encapsulation, differentiation, and vascular invasion. Biochemical markers such as alpha fetoprotein (AFP), des-gamma-carboxy-prothrombin (DCP) (also known as protein induced by vitamin K absence or antagonist II (PIVKA-II)), and *Lens culinaris agglutinin A-reactive fraction of alpha-fetoprotein* (AFP-L3) as well as nuclear medicine techniques like ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography-computed tomography (PET-CT), provide additional

Table 1 Level of Evidence and Grade of Recommendations (Adapted From Grading of Recommendations, Assessment, Development and Evaluations [GRADE] System[3,4] With Minor Modifications[a]).

Level of evidence[b]		Confidence in the evidence
High	Information obtained from meta-analyses or systematic reviews, or from numerous randomized trials that have high quality data.	It is improbable that additional research will significantly alter our level of confidence in the assessment of potential benefits and risks.
Moderate	Information obtained from either a singular randomized controlled trial (RCT) or various non-randomized studies.	Additional research, if conducted, may potentially alter our estimation of the benefit and risk and have an impact on our level of confidence in the estimate.
Low	Studies of limited sample size, observational studies conducted retrospectively, and registries.	There is a degree of uncertainty associated with any estimate of the effect.
Recommendations – Grade[c]		**Wording associated with the grade of recommendation**
Strong	The strength of the recommendation was influenced by several factors, such as the quality of the evidence, the presumed outcomes that are important for the patient, and the cost implications.	"must", "should", or "we recommend"
Weak	The recommendation may be made with less certainty and may result in higher costs or resource consumption due to variability in preferences and values, or increased uncertainty.	"can", "may", or "we suggest"

[a]To make the GRADE system more objective, the type of studies from which the evidences are derived have been mentioned in the Level of Evidence section.
[b]Level was graded down if there was a poor quality, strong bias or inconsistence between studies; level was graded up if there was a large effect size.
[c]Recommendations reached by consensus of the members and included the quality of evidence, presumed patient-important outcomes and costs.

insights. Understanding these indicators aids in prognosis prediction and personalized treatment planning for HCC patients.

Clinical Indicators of Aggressiveness

Gender differences in HCC morbidity and survival outcomes are well-documented.[5–7] Women have a lower risk of developing HCC compared to men, with an approximate incidence ratio of 1:4.[5,8] Women also tend to present with less-advanced HCC and have a greater overall survival.[9] The gender disparity in HCC may stem from various factors, including hormonal, genetic, anatomic, metabolic, behavioral risk factors, tumor biology, and treatments received.[10]

While it is generally believed that younger patients with HCC often have more invasive tumors, higher metastatic potential, and worse survival and prognosis compared to older patients,[11,12] some subsequent studies have refuted this finding.[13]

HCC detected at the asymptomatic stage generally has a better prognosis. The appearance of symptoms such as lethargy, pain, jaundice, anasarca, ascites, encephalopathy, variceal bleeding, diarrhea, and paraneoplastic symptoms indicates the development of severe and aggressive disease.[14,15] These symptoms may indicate either an aggressively growing tumor leading to decompensation or advanced liver disease, which may preclude effective curative treatment.

A Japanese study identified independent risk factors for length of disease-free survival after curative resection of HCC. The study found that younger age, lower indocyanine green (ICG) retention rate, presence of solitary HCC with expansive growth, absence of microscopic portal invasion, and lower activity of co-existing hepatitis were favorable factors for longer disease-free survival, highlighting the importance of not only early detection, but also suppression of co-existing hepatitis, in achieving better disease-free survival.[16]

Type 2 diabetes mellitus not only increases the risk of developing HCC[17,18] but is also associated with worse survival.[19] A meta-analysis of 21 studies comprising 9767 HCC patients found that diabetes in HCC patients was independently associated with poorer overall and disease-free survival.[20] Hyperinsulinemia, hyperglycemia, increased oxidative stress, and chronic inflammation in diabetic patients contribute to a poor prognosis.

Numerous reports indicate that perioperative blood transfusion enhances the risk of intrahepatic recurrence of HCC and is a significant independent factor influencing the cumulative survival rate of patients.[21–24]

Consensus statement	Level of evidence	Strength of recommendation
1. In HCC, male gender, symptoms at presentation, co-existing hepatitis status, underlying liver dysfunction, perioperative blood transfusion, and the presence of diabetes mellitus are clinical indicators associated with a poor prognosis.	Moderate	Strong

Morphological and Radiological Indicators of Aggressiveness

Tumor size serves as a crucial prognostic factor in HCC. Zhou *et al.* conducted a comparative study involving 1000 patients with small HCC (≤5 cm) and 1366 patients with large HCC (>5 cm) during the same period. They observed that larger HCC tumors were associated with a lower curative resection rate, higher operative mortality rate, increased incidence of tumor emboli in the portal vein, and lower overall survival.[25] The presence of multiple nodules in HCC (multi-nodular HCC) indicates a much poorer prognosis compared to single nodules.[26,27] Poorly encapsulated HCC tumors are also linked to worse prognosis compared to well-encapsulated tumors.[28] The features listed, including tumor size and number, washout rate, intracellular fat accumulation, invasive growth, absence of a capsule, bile duct invasion, and tumor thrombosis of the portal and/or hepatic vein, are indeed indicators associated with poor prognosis in HCC. These characteristics can suggest both aggressive tumor behavior and late detection. More aggressive tumors tend to grow and spread more rapidly, leading to these concerning features, while late detection can mean that these features have had more time to develop, reflecting a more advanced stage of disease and subsequently poorer prognosis. It is important to note that the boundary between aggressive behavior and late detection can be blurred, as late detection might be the consequence of rapid and aggressive tumor growth that advances before symptoms prompt medical attention.

Functional imaging techniques like diffusion-weighted imaging (DWI), chemical-shift magnetic resonance imaging (MRI), magnetic resonance elastography (MRE), and MRI with liver-specific contrast have revolutionized the management of HCC. These techniques provide valuable insights into cellular and metabolic activities, aiding in the effective grading and staging of HCC. DWI assesses the cellularity and integrity of cell membranes,[29] while chemical-shift MRI exploits differences in resonance frequencies of water and fat protons for contrast generation.[30] MRE quantifies tissue stiffness to detect fibrosis or cirrhosis.[31] MRI with liver-specific contrast helps in better lesion characterization.[32] These advancements contribute to a holistic approach to HCC management, from diagnosis to treatment planning. Thus these techniques can provide valuable cellular and metabolic information for HCC grading and staging.[33,34]

Consensus statement	Level of evidence	Strength of recommendation
2. Tumor size and number, intracellular fat accumulation, invasive growth, absence of capsule, bile duct invasion, and tumor thrombosis of the portal and/or hepatic vein are all indicators associated with a poor prognosis in HCC.	Moderate	Strong
3. Functional imaging techniques such as diffusion-weighted imaging (DWI), chemical-shift MRI, magnetic resonance elastography (MRE), and MRI with liver-specific contrast play a valuable role in providing cellular and metabolic information for the grading and staging of HCC.	Moderate	Weak

Biochemical Indicators of Aggressiveness

Tumor markers, including alpha-fetoprotein (AFP), des-gamma-carboxy prothrombin (DCP) (also known as protein induced by vitamin K absence or antagonist II (PIVKA-II)), and *Lens culinaris* agglutinin A-reactive fraction of alpha-fetoprotein (AFP-L3), are extensively studied biomarkers for assessing the aggressiveness of HCC. Elevated levels of these tumor markers indicate tumor stage progression and are associated with a worse prognosis, higher recurrence rate, and poorer survival compared to individuals with normal marker levels.[35] In 2006, researchers from Japan developed the BALAD score, which incorporates AFP >400 ng/mL, AFP-L3 >15%, DCP >100 mAU/mL, as well as serum bilirubin and albumin values, to predict HCC patient survival.[36] Although initial validation studies did not demonstrate the superiority of this score over other systems without biomarkers, the combined use of biomarkers may still have predictive value for prognosis. Based on a review of Indian studies, it is evident that both elevated levels of AFP and PIVKA-II are associated with aggressive HCC. However, specific cut-off values for AFP and PIVKA-II to predict the aggressiveness of HCC cannot be conclusively determined from the current Indian studies.[37–41]

Post-transplant recurrence affects up to 15% of HCC patients transplanted within the Milan criteria,[42] highlighting the role of factors beyond tumor morphology in post-liver transplantation (LT) prognosis. AFP is correlated with tumor differentiation and vascular invasiveness,

consistently predicting poor outcomes after LT for HCC. The French Liver Transplantation Study Group proposed a prognostic model in 2012 that combined AFP with tumor size and number, demonstrating its superiority over the Milan criteria alone in predicting HCC recurrence and overall survival after LT. Additionally, an AFP level >1000 ng/mL was associated with significantly higher HCC recurrence risk and worse post transplant survival among patients within the Milan criteria.[43] This cutoff level has been validated in subsequent studies, with AFP >1000 ng/dL currently being used as an exclusion criterion for LT.

Positive AFP at baseline and relapse, or a change from negative to positive, imply shorter survival rates. Conversely, a complete AFP response to locoregional therapies (LRT) suggests the lowest recurrence rates, while a partial response, marked by over a 15% decline post-LRT, yields outcomes similar to the control group.[44,45] Serum AFP estimation further helps monitor responses to locoregional and systemic HCC therapies.[46–48]

Statement	Level of evidence	Strength of recommendation
4. Elevated levels of commonly used HCC tumor markers (AFP, PIVKA-II, AFP-L3) are associated with a poorer prognosis and an increased risk of recurrence.	High	Strong
5. The combined use of these biomarkers may offer benefits in predicting prognosis.	High	Strong
6. Currently, an AFP level exceeding 1000 ng/dL is utilized as an exclusion criterion for liver transplantation (LT).	Moderate	Strong
7. Serum AFP estimation can also be valuable in monitoring the response to therapy, particularly with the emergence of more effective locoregional and systemic treatments.	High	Strong

Nuclear Medicine Indicators of Prognosis/ Aggressiveness

The clinical value of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) in diagnosing HCC has been limited due to its low sensitivity (between 36% and 70%) for detecting intrahepatic HCC lesions. Nevertheless, the use of positron emission tomography-computed tomography (PET-CT) for prognosticating HCC has shown significant progress in recent years.[49,50] A study from a non-transplant center in India suggested that ^{18}F-FDG PET/CT can be valuable in the initial work-up of newly diagnosed HCC patients, especially when there are high levels of AFP (>93.7 ng/mL) or a large tumor (>5 cm).[41] FDG uptake is closely related to therapeutic response in HCC and can provide additional information on the risk of HCC recurrence after surgery or liver transplantation (LT). Another study from India utilized FDG avidity to predict post-transplant survival, as poorly differentiated HCC showed higher FDG avidity compared to well-differentiated HCC.[51] FDG PET avidity was associated with higher levels of alpha fetoprotein (AFP) and a higher incidence of microvascular invasion on explant histology.[40] If FDG-PET demonstrates uptake in the tumor, it is suggestive of high possibility of microvascular invasion.[52] However, absence of PET uptake does not rule out microvascular invasion.

Dynamic CT with FDG-PET is a convenient modality for detecting portal vein tumor thrombosis (PVTT), characterized by intraluminal filling defects, expansion of the portal vein, contrast enhancement, and linear increased FDG uptake by the thrombus.[53]

Since extrahepatic metastasis is commonly observed in HCC with poor differentiation, FDG-PET has demonstrated higher sensitivity and specificity compared to other modalities such as bone scans for the detection of extrahepatic metastasis.[54]

^{18}F-FDG PET-CT has shown efficiency in assessing the viability of HCC after TACE and superiority to CECT even in low-grade HCC.[55] It can effectively differentiate between HCC recurrence and false-positive tracer uptake due to lipiodol (ethiodized oil) deposition. Metabolic tumor volume (MTV), which represents the extent of abnormally increased FDG uptake by tumor tissue, has the potential to predict progression-free survival (PFS) and overall survival (OS) after transarterial chemoembolization (TACE).[56] One study showed that using FDG-PET can help predict the effectiveness of palliative radiotherapy in controlling bone metastasis. Essentially, better results were seen when patients had a higher initial reading (SUV-ratio) on the scan, a significant drop in the SUV-ratio after radiotherapy, and when a higher dose of radiation was used.[57] PET-derived tumor-to-normal liver ratio (TLR), calculated as SUV-max of the tumor divided by SUV-mean of the normal liver, is a valuable parameter for determining HCC aggressiveness. Several reports indicate that TLR ≥2 indicates high malignant potential. High TLR significantly affects overall survival (OS) on lenvatinib, while delta-TLR serves as a predictor of response.[58] It also plays a role in assessing response to treatment by highlighting residual tumor tissue after TACE.[59]

Statement	Level of evidence	Strength of recommendation
8. ^{18}F-FDG PET-CT is capable of detecting lymph node metastasis, and extrahepatic metastatic lesions, particularly in bone and other tissues that have an impact on treatment decisions. INASL recommends the use of an ^{18}F-FDG PET scan to evaluate extrahepatic spread.	Moderate	Strong
9. A tumor-to-normal liver ratio (TLR) greater than 2 indicates an aggressive tumor with poor overall survival. TLR also plays a role in assessing the response to treatment after TACE.	Low	Weak
10. Tumor biopsy is not necessary for the routine diagnosis of HCC, but it may be needed prior to treatment planning if the imaging results show atypical features.	Moderate	Strong
11. Despite the progress made in comprehending the molecular pathogenesis of HCC and identifying various molecular/genetic signatures, the routine testing of these biomarkers in blood or liver cannot currently be recommended for clinical practice.	Moderate	Strong

Histological and Molecular Indicators of Aggressiveness

Histological indicators of aggressive tumors include poor differentiation, intracellular fat accumulation, microvascular invasion, invasive growth, and bile duct invasion.[33] Even though tumor biopsy is not routinely necessary for the diagnosis of HCC, but it may be required in cases where the imaging results are atypical. Explant histology can help identify patients with unfavorable prognoses due to poorly differentiated HCC or microvascular invasion. However, some centers have started using preoperative liver biopsy to guide liver transplantation (LT). The extended Toronto criteria allow LT for patients with tumors of any size or number, provided they do not exhibit systemic cancer-related symptoms, extrahepatic disease, vascular invasion, or poorly differentiated tumors on preoperative liver biopsy.[60]

The development of HCC involves the gradual accumulation of molecular changes that contribute to various molecular and cellular events. Next-generation sequencing (NGS) techniques have made it easier to examine the molecular landscapes of HCC. Recent research highlights the significance of the tumor microenvironment and cancer metabolism in HCC development.[61] Despite advancements in understanding HCC's molecular pathogenesis and identification of potential biomarkers, their translation into clinical practice is challenging. The main issues are variability in biomarker expression, lack of large-scale validation studies, difficulty in obtaining liver biopsy samples, and challenges in correlating these markers with clinical outcomes.[62] Furthermore, standardized, cost-effective techniques for biomarker assessment in the clinical setting are lacking.[63] Therefore, the routine testing of molecular/genetic signatures for HCC in blood or liver cannot currently be recommended for clinical practice.

INASL-BCLC Staging: The Recommended HCC Staging for India

Staging is crucial in the management of all cancers as it enables the assessment and description of the tumor burden within the primary organ and its spread throughout the body. An ideal staging system should provide an accurate prognostic stratification and guide the selection of the most appropriate therapeutic approach based on the stage. Additionally, the staging system should facilitate the homogeneous grouping of patients in clinical trials and facilitate scientific research.

The Barcelona Clinic Liver Cancer (BCLC) staging system[64] is widely recognized as a prognostic tool for HCC. It effectively categorizes the severity of HCC and offers a reliable assessment of a patient's prognosis and suitable treatment options. Numerous studies have demonstrated the strong predictive value of BCLC staging for survival outcomes, highlighting its importance in the evaluation and management of HCC patients.

The 2022 BCLC guidelines have undergone further updates specifically targeting intermediate-stage HCC (BCLC-B) and systemic therapy options for advanced-stage HCC (BCLC-C).[65] The guidelines recommend systemic therapy for patients with diffuse, infiltrative, and extensive bilobar liver involvement. A novel concept called treatment stage migration (TSM) has been introduced in these guidelines, allowing for personalized treatment decisions based on clinical judgment when first-line treatment is not feasible due to patient characteristics. These updates emphasize the importance of individualized treatment approaches tailored to each patient's specific needs.[66]

Despite the updates, the 2022 BCLC staging system has several limitations that need to be addressed.[66–70] The INASL taskforce has modified the existing BCLC staging system and recommends the use of the 'INASL modification of the BCLC staging system (INASL-BCLC

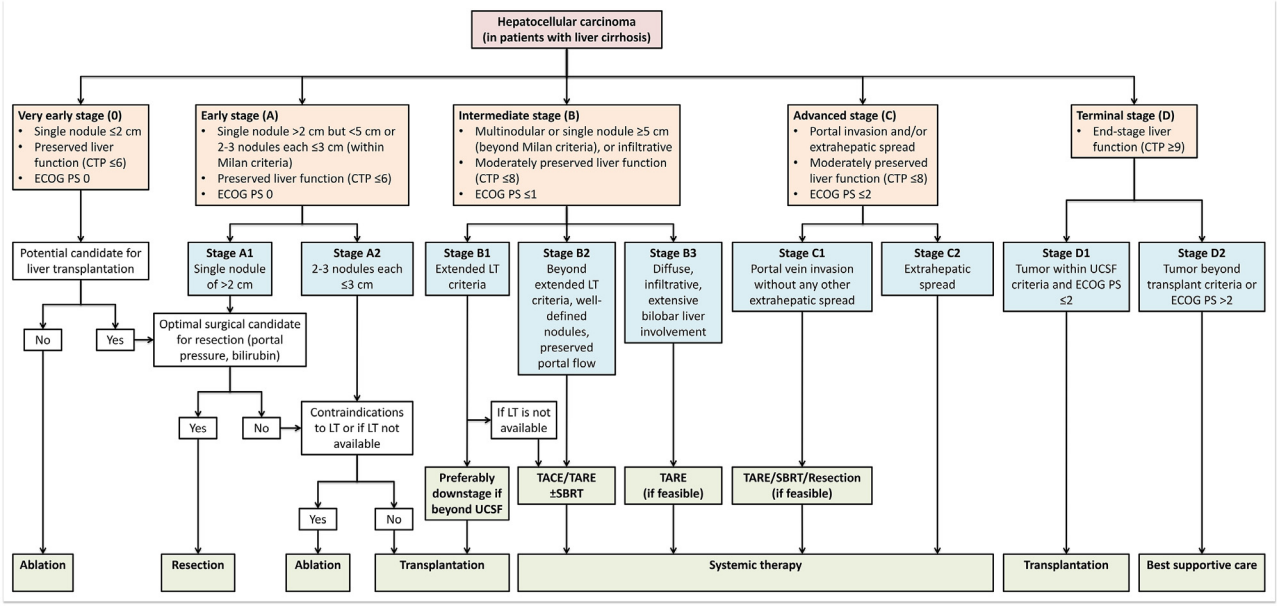


Figure 1 The 'INASL modification of BCLC staging' (INASL-BCLC) for prognosis prediction and treatment of HCC. BCLC, Barcelona Clinic Liver Cancer; HCC, Hepatocellular carcinoma; INASL-BCLC, Indian National Association for the Study of the Liver modification of BCLC

Staging)' for improved prognosis prediction and treatment of HCC (Figure 1). One shortcoming of the BCLC system is its ambiguity regarding the presence of underlying liver disease, merely mentioning HCC at the outset. The INASL-BCLC system provides clarity by specifically stating that the staging system applies to HCC patients with liver cirrhosis. The BCLC system lacks subdivisions in the advanced stage (BCLC-C) and terminal stage (BCLC-D). In contrast, the INASL-BCLC staging subdivides these stages to cater to the diverse patient population better. The stage C subdivision (C1 and C2) acknowledges the role of locoregional therapy in stage C1 patients. The subdivision of stage D into D1 and D2 allows for potential liver transplantation in patients with advanced liver disease but whose tumors still fit transplantation criteria (stage D1).[71,72] Additionally, the BCLC staging system does not account for the role of combination or adjuvant therapies. The revised INASL-BCLC staging recognizes the emerging importance of these therapies,[73] expanding the indication of systemic therapy to patients receiving locoregional therapy. The BCLC system also does not consider downstaging. However, the INASL-BCLC system indicates downstaging for tumors beyond the University of California, San Francisco (UCSF) criteria in patients with stage B1. Finally, the BCLC staging does not include the role of Transarterial Radioembolization (TARE) and Stereotactic Body Radiation Therapy (SBRT), both of which have been incorporated in the INASL-BCLC staging in light of strong supporting evidence. Thus, the revised INASL-BCLC staging system addresses several limitations of the BCLC staging system, offering a more comprehensive and nuanced approach to HCC management (Table 2).

Treatment Stage Migration

Treatment stage migration (TSM), also known as treatment sequence or pattern of therapy, refers to the transition of a patient from one treatment modality to another due to disease progression or treatment failure. TSM occurs when a patient's profile prompts a shift in the recommended treatment to a modality that is typically prioritized for a more advanced stage of the disease. In the context of HCC, TSM usually involves the shift from curative treatment options (resection, ablation, liver transplantation [LT]) to palliative treatment options (transarterial chemoembolization [TACE], transarterial radioembolization [TARE], stereotactic body radiotherapy [SBRT]), or from locoregional therapies to systemic therapy options.

The concept of TSM can also be applied in reverse, where a change in patient condition, often due to therapeutic intervention, makes them eligible for treatments that were previously not feasible. For example, if a patient initially presents with poor liver function and advanced HCC, they might be treated initially with best supportive care (such as treatment for hepatic encephalopathy, ascites, low albumin etc.). If these treatments lead to improved liver function, and potentially an improvement in liver function, the patient could then `migrate´ to an earlier treatment stage, such as systemic treatment or locoregional therapy.

Table 2 Comparison of BCLC Staging and INASL Modification of BCLC Staging.

Criteria for Comparison	BCLC Staging	INASL-BCLC Staging
Consideration of Underlying Liver Disease	Initial condition only mentions HCC.	Initial condition explicitly mentions HCC in patients with liver cirrhosis.
Division of Stage C	No subdivision of advanced stage BCLC-C (PVTT and EHM).	INASL-BCLC stage C is subdivided into stages C1 and C2 to allow for the role of locoregional therapy in stage C1.
Division of Stage D	Terminal stage is a single, undivided stage; only offers best supportive care.	INASL-BCLC stage D is subdivided into stages D1 and D2. Stage D1 includes patients with advanced liver disease whose tumors still fit liver transplantation criteria, offering potential for LT.
Inclusion of Combination/Adjuvant Therapy	No mention of combination/ adjuvant therapy.	Recognizes the emerging role of combination therapy, particularly the combination of locoregional with systemic therapy; expands indication of systemic therapy to patients receiving LRT.
Provision for Downstaging	The algorithm does not consider downstaging.	In patients with INASL-BCLC stage B1, if the tumor is beyond UCSF criteria, downstaging is indicated.
Role of TARE and SBRT	These treatment modalities are not included.	With robust evidence supporting TARE and SBRT, both modalities are included at appropriate stages.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; INASL-BCLC, Indian National Association for the Study of the Liver modification of BCLC; PVTT, Portal Vein Tumor Thrombus; EHM, Extrahepatic Metastasis; LRT, Locoregional Therapy; UCSF, University of California, San Francisco; TARE, Transarterial Radioembolization; SBRT, Stereotactic Body Radiation Therapy.

The proposed treatment options for each INASL-BCLC stage are described below, but it is important to note that expert evaluation of all the clinical and sociocultural information may lead to TSM.[65] On the other hand, untreatable progression represents treatment failure or disease progression that occurs within the patient's initial BCLC stage, despite the selected treatment strategy.

Multidisciplinary Tumor Board

Multidisciplinary tumor board discussions involve key disciplines like hepatology/gastroenterology, oncology, radiation oncology, surgery, diagnostic radiology, interventional radiology, and palliative care.[74,75] These discussions not only help determine optimal treatment for HCC patients, they also assess outcomes. Many studies have showed that implementation of these discussions have significantly improved treatment timeliness and survival rates.[76–78] These findings highlight the critical role of multidisciplinary discussions in improving HCC patient outcomes.

Statement	Level of evidence	Strength of recommendation
12. INASL recommends the use of the 'INASL modification of BCLC staging (INASL-BCLC Staging)' for prognosis prediction and treatment of HCC.	Moderate	Strong
13. The concept of Treatment Stage Migration (TSM) should be used when offering treatment as it allows for the transition to more appropriate treatment modalities based on disease progression or improvement.	Moderate	Strong
14. Multidisciplinary tumor board discussions should be conducted to identify the most suitable treatment modality for each individual HCC case. The response and outcomes of each modality should be reassessed in the tumor board to guide the selection of subsequent treatment approaches based on the patient's response.	Moderate	Strong

Stagewise Management of Intermediate and Advanced HCC (INASL-BCLC stage B and C)

This section is dedicated to discussing the stagewise management of intermediate and advanced HCC. The management of HCC is contingent upon the disease stage, and thus, we will delve into the various treatment approaches and strategies employed for intermediate and advanced

stages of HCC (INASL-BCLC stage B and C), considering factors such as tumor size, liver function, and overall patient health. Additionally, these approaches will be tailored to the specific context of the Indian setting.

Management of Patients of INASL-BCLC Stage B1: Role of Liver Transplantation

Stage B1, according to the INASL-BCLC staging system, is characterized by multifocal HCC that surpasses the INASL-BCLC-A criteria. Patients in this stage exhibit moderately preserved liver function (Child–Turcotte–Pugh score [CTP] ≤8), an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1, and no signs of vascular invasion or extrahepatic spread. Within this group, there are patients with well-defined HCC nodules who may be eligible for liver transplantation if they fulfil various `Extended Liver Transplant criteria´, such as University of California, San Francisco (UCSF) criteria,[79] Up-to-Seven criteria,[80] Metroticket 2.0 criteria,[81] Kyoto criteria,[82] Toronto criteria,[83] and Pittsburgh criteria[84] etc (Table 3). These extended criteria may be applied in association with downstaging (see below). If however, LT is not available, these patients should undergo TACE/TARE (with or without SBRT).

Patients within the UCSF criteria: While the Milan criteria[42] have traditionally served as the standard for patient selection in liver transplantation, they can be overly stringent in the context of living donor liver transplantation (LDLT). Studies have shown that a slight deviation from the Milan criteria in terms of tumor size or number can still yield comparable survival rates.[85] The University of California, San Francisco (UCSF) criteria have emerged as the most validated expanded criteria, allowing for broader selection without compromising outcomes.[86] Therefore, INASL recommends the use of UCSF criteria for patient selection for LT, and patients who meet these criteria should be considered as candidates for upfront LT.

Numerous retrospective and prospective studies, randomized controlled trials, and meta-analyses consistently demonstrate the superiority of mammalian target of rapamycin inhibitors (mTORi)-based immunosuppression compared to mTORi-free immunosuppression following LT for HCC. The primary benefit of these agents is their association with enhanced post-LT survival and decreased tumor recurrence in HCC patients.[87] It's typically advised to avoid starting mTOR inhibitors within the first 30 days following transplant due to an elevated risk of complications such as hepatic artery thrombosis, issues with wound healing, proteinuria, and interstitial pneumonitis during the postoperative period.

Table 3 The Milan Criteria and the Extended Liver Transplant Criteria.

Criteria	Tumor Characteristics
Milan Criteria[42]	Single tumor ≤5 cm OR up to three tumors each ≤3 cm
UCSF Criteria[79]	Single tumor ≤6.5 cm OR up to three tumors with the largest being ≤4.5 cm, total tumor diameter ≤8 cm
Up-to-Seven Criteria[80]	Sum of the size of the largest tumor (in cm) and the number of tumors ≤7
Metroticket 2.0 Criteria[81]	Total tumor diameter ≤9 cm, regardless of the number of nodules, without macrovascular invasion or extrahepatic spread
Kyoto Criteria[82]	10 or fewer tumors each ≤5 cm, serum des-γ-carboxy prothrombin level ≤400 mAU/mL
Toronto Criteria[83]	No macrovascular invasion, sum of the size of the largest tumor and the number of tumors ≤18
Pittsburgh Criteria[84]	Single tumor ≤5 cm OR 2–3 tumors each ≤3 cm, and no vascular invasion or distant metastases, along with a low level of proliferative activity of the tumor (based on Ki67 labeling index)

Statement	Level of evidence	Strength of recommendation
15. INASL recommends the use of the UCSF criteria for patient selection for LT, and patients who meet these criteria should be considered for upfront LT.	Moderate	Strong
16. INASL recommends the use of mTORi-based immunosuppression rather than mTORi-free immunosuppression after LT for HCC.	High	Strong

Patients beyond the UCSF criteria: role of downstaging and tumor biology: Patients classified as INASL-BCLC stage B1 who are beyond the UCSF criteria but fulfill other expanded criteria for LT, with no extrahepatic disease or vascular invasion, should preferably undergo downstaging before considering living donor liver transplantation (LDLT). While some studies have shown that upfront LDLT in these patients may yield acceptable outcomes, there is evidence of poorer recurrence-free survival.[88] Therefore, selecting these patients for upfront LDLT should be considered only if they exhibit favorable tumor biology, as indicated by surrogate markers such as tumor morphology (size and number), alpha fetoprotein (AFP) or protein induced by vitamin K absence or antagonist-II (PIVKA-II) levels, and ^{18}Fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET CT) avidity. If the patient does not meet the criteria for favorable tumor biology, downstaging

prior to LDLT is recommended and response to neoadjuvant or downstaging therapies such as TACE, TARE, or focused radiotherapy should be assessed prior to LT.[40]

Downstaging HCC before transplantation has demonstrated improvements in patient outcomes and a reduction in recurrence risk following transplantation. The most recent guidelines from the European Association for the Study of the Liver (EASL),[62] the American Association for the Study of Liver Diseases (AASLD),[89,90] and International Liver Transplantation Society (ILTS)[91] recommend that patients who exceed the Milan or UCSF criteria or are in T3 stage should only undergo liver transplantation after successful downstaging to meet the Milan criteria. According to a retrospective analysis patients beyond UCSF criteria who underwent downstaging had a high 1-, 3-, and 5-year survival rates (80%, 79%, and 75%, respectively), suggesting the effectiveness of this approach.[92] In another LDLT study patients who were successfully downstaged to fit UCSF criteria the overall 1- and 5-year survival rates were comparable; 94.1% versus 92.7% and 83.7% versus 78.9% of downstaged (beyond UCSF) versus non-downstaged (within UCSF), respectively.[93]

The University of California San Francisco (UCSF) downstaging protocol, introduced by Yao *et al.* in 2005, required that both the total tumor diameter and the size of a single lesion be less than 8 cm for enrollment. Patients with HCC who were successfully downstaged to meet the Milan criteria demonstrated comparable 5-year post-LT survival and intention-to-treat survival rates to the T2 HCC control group.[94] Additionally, excellent 10-year post-LT results in a large, multicenter cohort of patients who were successfully downstaged to meet the Milan criteria validated the downstaging strategies employed in the USA.[95] INASL recommends that patients who exceed the UCSF criteria but have good liver function, no vascular invasion, and no distant spread may be considered for transplantation if defined morphological and biological endpoints of successful downstaging are achieved. After downstaging, these patients should at least meet the UCSF criteria.

Among the various downstaging strategies, transarterial chemoembolization (TACE) is the most widely utilized, while transarterial radioembolization (TARE) has shown promise in downstaging patients with larger tumors and portal vein tumor thrombosis (PVTT). Ablative therapies, such as radiofrequency ablation (RFA), have also demonstrated favorable downstaging outcomes.[96,97] Identifying a single superior downstaging modality proves challenging, as it depends on the individual case. Generally, an aggressive approach to locoregional therapies (LRTs) combined with appropriate patient selection offers the most effective downstaging results.[98]

Elevated levels of AFP are associated with reduced survival probability and an increased risk of HCC recurrence. Patients with tumors exceeding the Milan criteria but having an AFP level below 100 ng/mL exhibited a lower 5-year recurrence risk compared to those with AFP levels exceeding 1000 ng/mL.[43] Consequently, several centers have established a cut-off value of 1000 ng/dL, beyond which patients are typically excluded from LT. Although downstaging therapy can lead to a decline in AFP levels, there is currently no reliable data specifying the extent or duration of the decrease required before considering LT.

Statement	Level of evidence	Strength of recommendation
17. Patients who are beyond the UCSF criteria but have good liver function, lack vascular invasion, and show no distant spread may undergo transplantation following successful downstaging, provided that the specified downstaging endpoints (both morphological and biological) are achieved.	Moderate	Strong
18. In patients with multifocal HCC beyond UCSF criteria, with no extrahepatic disease or vascular invasion; LDLT may be considered in carefully selected patients who exhibit favorable tumor biology. Favorable tumor biology can be indicated by surrogate markers such as tumor morphology (size and number), levels of AFP or PIVKA-II, ^{18}F-FDG PET CT avidity, and/or response to neoadjuvant or downstaging therapies such as TACE, TARE, or focused radiotherapy.	Moderate	Weak
19. No specific form of locoregional therapy can be recommended one over the other for neoadjuvant therapy or downstaging therapy for HCC.	Moderate	Weak

Management of Patients of INASL-BCLC Stage B2 (and Patients of Stage B1 Who Don't Have LT Prospect)

Patients classified as INASL-BCLC stage B2 represent individuals who exceed the extended criteria for transplantation but still have well-defined tumor nodules and preserved portal flow, indicating the potential for selective arterial access to the tumor's feeding arteries for intra-arterial therapies like TACE or TARE. This suggests that these patients may benefit from the targeted delivery of therapies directly to the tumor site while preserving portal flow.

Role of TACE/TARE in patients with INASL-BCLC stage B2 or B1 not undergoing LT: Patients with large or multinodular HCC in the intermediate stage (INASL-BCLC

stage B2) and without available curative treatment options, such as ablation, resection, or transplantation, should be considered for TACE.[99] TACE is suitable for patients with moderately preserved liver function (Child-Turcotte-Pugh score [CTP] ≤8) and a good performance status (Eastern Cooperative Oncology Group [ECOG] ≤1). TACE can also be utilized as a bridging or downstaging therapy prior to liver transplantation, aiming to achieve or maintain a limited intrahepatic tumor burden defined by the Milan/UCSF criteria. However, extensive extrahepatic metastases and tumor infiltration of the main portal vein are contraindications for TACE.

TACE should be performed in a selective manner, aiming to achieve complete devascularization of the tumor tissue.[99] Both conventional TACE, which involves cytotoxic drugs, iodized oil, and embolic particles, and drug-eluting bead TACE (DEB-TACE) have demonstrated similar efficacy. However, DEB-TACE allows for higher concentrations of drugs within the target tumor while maintaining lower systemic concentrations.[100,101] In a prospective single-center study from India, administration of N-acetyl cysteine to patients exhibiting post-TACE syndrome significantly reduced their transaminase levels, demonstrating a potential treatment for this common complication following TACE.[102]

Evidence has consistently shown that TACE can lead to a reduction in tumor size and improved survival outcomes for HCC patients, whether they have solitary or multiple lesions.[103] Randomized controlled trials have further substantiated the efficacy of TACE by demonstrating long-term progression-free survival (PFS), improved overall survival (OS), and enhanced quality of life due to its ability to provide local control of the tumor.[99] Therefore, INASL recommends that HCC patients in INASL-BCLC stage B2, with preserved portal flow and a defined tumor burden, should be considered for intra-arterial locoregional therapies. Specifically, TACE should be recommended for these patients.

Recent findings highlight that TARE utilizing Y^{90} provides a significantly longer time to progression (TTP) compared to TACE, although OS does not significantly differ between the two treatments.[104] Therefore, the decision to employ Y^{90}-TARE in patients with INASL-BCLC stage B2 should be tailored to each individual, taking into account factors such as cost and availability.

Recent studies have demonstrated that in patients with early- and intermediate-stage HCCs larger than 5 cm, the combination of TACE with ablation resulted in a higher therapeutic response rate and longer OS compared to TACE alone.[105–108] Among the ablative modalities used in conjunction with TACE, microwave ablation (MWA) showed superior response rates compared to radiofrequency ablation (RFA) for tumors ranging between 3 and 5 cm, while survival rates did not significantly differ between the two.[109] Furthermore, the addition of TACE to stereotactic body radiotherapy (SBRT) has exhibited higher response rates, local control rates, and survival rates in comparison to SBRT alone.[110]

The use of systemic therapy as adjuvant therapy with TACE is discussed subsequently.

Statement	Level of evidence	Strength of recommendation
20. TACE is indicated for HCC patients with well-defined nodules and preserved portal flow in the following scenarios: • INASL-BCLC stage B2 • INASL-BCLC stage B1 patients who do not have the prospect of LT.	High	Strong
21. The use of Y^{90}-TARE for INASL-BCLC Stage B1/B2 should be individualized.	Moderate	Weak
22. When combining TACE with ablation for tumors larger than 5 cm, it may be preferable to combine TACE with microwave ablation (MWA) rather than radiofrequency ablation (RFA).	Low	Weak

Role of resection in highly selected patients of INASL-BCLC stages B1 and B2: Multiple observational studies[111–115] and one randomized controlled trial[116] have consistently demonstrated a survival advantage of liver resection (LR) over TACE for individuals with intermediate-stage HCC (BCLC-B). A recent meta-analysis revealed a 5-year OS rate of 54% for LR in patients with HCC beyond the Milan criteria.[117] Another meta-analysis showed that patients with BCLC stage B who underwent LR had a longer OS than those who underwent TACE.[118] Another systematic review revealed a 5-year OS of 33.5% for resection of HCC >10 cm, 41.7% for BCLC B, 23.3% for BCLC C, and 36.6% for multinodular HCC. Perioperative mortality ranged from 0 to 6.9%.[119] Furthermore, a large observational study specifically focusing on multinodular tumors (up to three lesions) indicated that LR provided improved 5-year OS compared to TACE, particularly for tumors larger than 3 cm.[115] In cases where patients meet the UCSF criteria but have no prospects for transplantation, hepatic resection with ablation has been attempted with acceptable results.[120] Patients with BCLC-B HCC may experience higher long-term survival rates with LR compared to TACE; however, careful selection of suitable candidates is crucial for minimizing perioperative morbidity rates. In a comprehensive study conducted in Taiwan, which involved 428 patients with BCLC stage B HCC, 140 patients (which is 33% of the total)

were deemed suitable for resection. According to the propensity score analysis, OS was substantially greater in the group that underwent resection, compared to the TACE group, with a hazard ratio of 3.17.[121]

Before performing a major hepatectomy in patients with cirrhotic liver, it is important to ensure a remnant liver volume of approximately 40%.[122] Clinically significant portal hypertension (CSPH), characterized by a hepatic venous pressure gradient (HVPG) exceeding 10 mmHg, is associated with an increased risk of liver decompensation and mortality following liver resection.[123] INASL suggests that the feasibility of liver resection should be evaluated in intermediate-stage HCC patients who do not have CSPH, possess potentially resectable tumors, and have moderate residual liver function with a volume reserve of at least 40%.

Major guidelines for HCC do not recommend the use of adjuvant or neoadjuvant systemic therapy as there is limited evidence to support their efficacy in reducing the risk of recurrence following resection. However, neoadjuvant therapy utilizing locoregional therapies (LRTs) has shown promising results in improving prognosis compared to hepatectomy alone for patients with operable HCC.[124,125] One retrospective study found that preoperative TACE improved RFS and OS in patients with large HCC (≥10 cm), but not in those with smaller tumors (5.0–9.9 cm).[126]

Statement	Level of evidence	Strength of recommendation
23. In patients with intermediate-stage HCC (INASL-BCLC stage B), the feasibility of liver resection should be evaluated in those without clinically significant portal hypertension (CSPH). Specifically, consideration should be given to patients with potentially resectable tumors, moderate residual liver function, and an adequate volume reserve (future liver remnant - FLR - of at least 40%).	Moderate	Weak
24. Neoadjuvant therapy is not generally recommended as a routine approach prior to liver resection. However, in cases where resection is technically challenging, neoadjuvant therapy utilizing locoregional therapies (LRTs) may be considered to facilitate the resection process.	Moderate	Weak

Management of INASL-BCLC Stage B3 and Stage C1

The third subgroup of stage B in the INASL-BCLC classification, known as stage B3, encompasses patients with diffuse, infiltrative, or extensive liver involvement from HCC. In these cases, TACE is not recommended, and instead, systemic therapy with or without TARE should be considered as the recommended treatment approach.

The INASL-BCLC stage C1 comprises patients who exhibit vascular invasion, yet remain relatively fit with an Eastern Cooperative Oncology Group Eastern Cooperative Oncology Group performance status (PS) of ≤2 and moderately preserved liver function (Child-Turcotte-Pugh score [CTP] ≤8). In the majority of these patients, vascular invasion manifests as portal vein tumor thrombosis (PVTT). In India, PVTT is reported in 40–46% of HCC patients.[127,128] PVTT can be classified into various categories based on specific criteria. The Liver Cancer Study Group of Japan's categorization[129] is among the more well-known ones, which categorized portal vein tumor thrombosis (PVTT) into five grades (Figure 2): (1) Vp0, no PVTT; (2) Vp1, subsistence of PVTT not in, but distal to, the 2nd order branches of the portal vein; (3) Vp2, subsistence of PVTT in the 2nd order branches of the portal vein; (4) Vp3, subsistence of PVTT in the 1st order branches of the portal vein; and (5) Vp4, subsistence of PVTT in the main trunk of the portal vein or a portal vein branch contralateral to the mainly involved lobe (or both).[130] In addition to systemic therapy, patients with PVTT may benefit from transarterial radioembolization (TARE), stereotactic body radiotherapy (SBRT), or resection depending on case-to-case basis.

Role of TARE in patients with INASL-BCLC stages B3 and C1: While the general consensus deems TACE to be relatively contraindicated for patients with portal vein tumor thrombosis (PVTT), certain studies suggest otherwise. Some research findings propose that TACE can indeed demonstrate effective disease control and enhanced survival rates in HCC patients presenting with portal vein invasion, regardless of it typically being a relative contraindication.[131,132] Notwithstanding these findings, transarterial radioembolization (TARE) remains the generally preferred option for locoregional therapy in patients with PVTT.

TARE using Yttrium-90 has gained increasing prominence as a treatment option for advanced or intermediate HCC.[133] TARE aims to induce microembolic effects, promoting radiation injury while preserving blood flow to the targeted liver segments. Radioembolic microspheres containing Yttrium-90 (Y^{90}) are delivered through the hepatic artery in TARE, where they lodge at the arteriolar level and emit radiation through beta decay.[133] TARE using iodine-131 has also been used with good results.[134]

Initially developed as a palliative care option for advanced HCC, TARE offers significant advantages as the

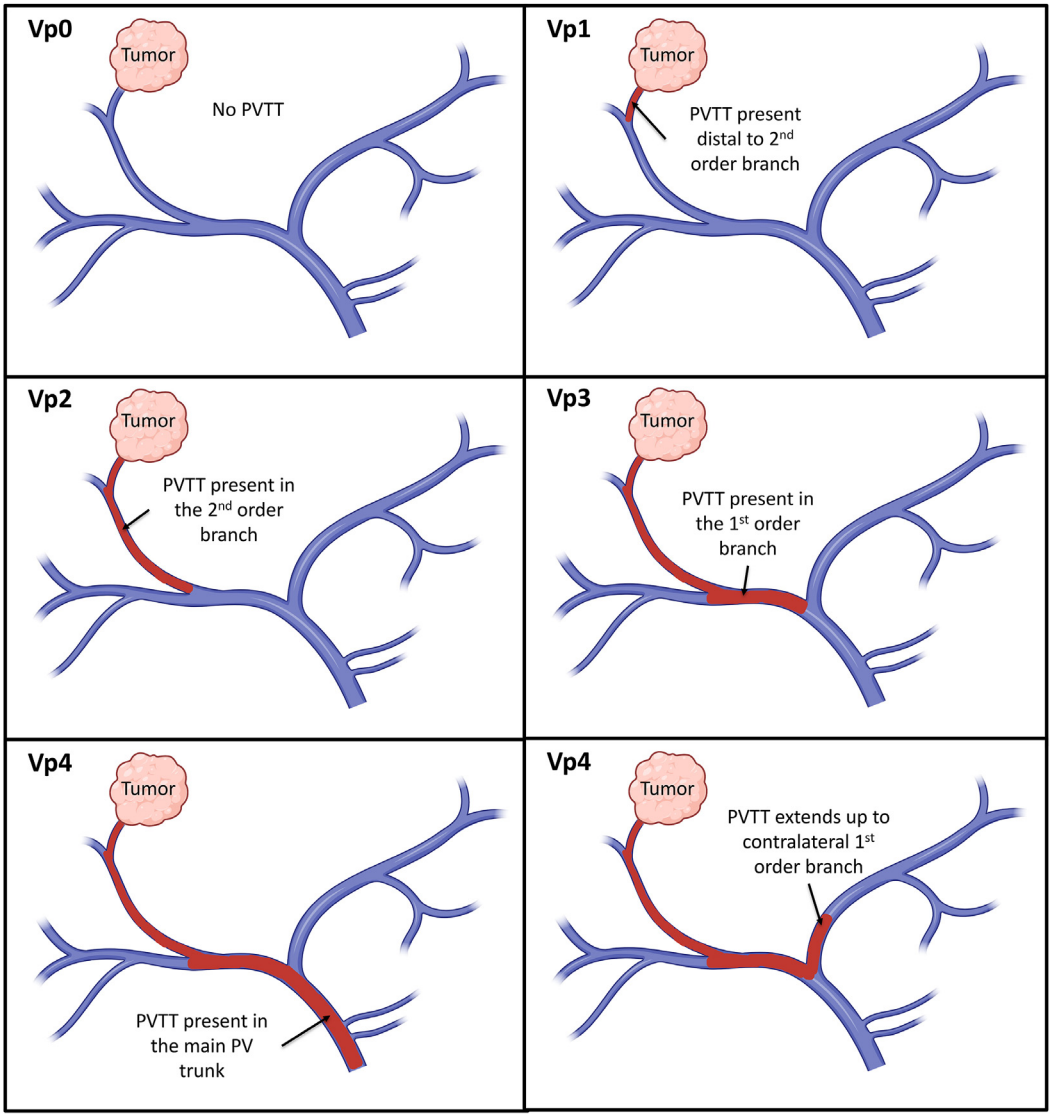


Figure 2 The Liver Cancer Study Group of Japan's classification for PVTT, which categorized PVTT into five grades: (1) Vp0, no PVTT; (2) Vp1, presence of PVTT not in, but distal to, the 2nd order branches of the portal vein; (3) Vp2, presence of PVTT in the 2nd order branches of the portal vein; (4) Vp3, presence of PVTT in the 1st order branches of the portal vein; and (5) Vp4, presence of PVTT in the main trunk of the portal vein or a portal vein branch contralateral to the mainly involved lobe (or both). PVTT, Portal Vein Tumor Thrombus

primary treatment option for PVTT, apart from sorafenib.[135,136] In patients with unresectable HCC limited to the liver in intermediate and advanced stages, numerous retrospective studies and large cohort studies have demonstrated the acceptable safety profile of TARE, its efficacy in local disease control, and favorable long-term survival outcomes.[135,136] Two phase III randomized controlled trials (RCTs), namely SIRveNIB[135] and SARAH,[136] showed no significant difference in overall survival between the TARE group and the sorafenib group. However, the tumor response rates were notably higher in the TARE arm, while there were no differences in progression-free survival (PFS). Fewer patients in the TARE group experienced significant side-effects compared to the sorafenib group. These trials were the first to establish the safety and efficacy of TARE in treating patients with locally advanced HCC, demonstrating its superior tolerability and greater tumor response compared to sorafenib.[135,136] In patients with inoperable multilobar HCC undergoing TARE, high lung shunt fraction, metabolic tumor volume, and total lesion glycolysis were identified as independent predictors of poor overall survival (OS), according to a retrospective analysis from India.[137] Total lesion glycolysis is a parameter that incorporates both the degree of ^{18}F-FDG uptake and the amount of metabolically active tumor volume on pretreatment ^{18}F-FDG PET/CT.

Moreover, Y^{90}-TARE can be employed as a downstaging therapy for patients with advanced HCC whose disease

burden initially exceeds transplant criteria. Radiation lobectomy (RL) has been described as a treatment modality with the goal of treating the HCC-affected liver on the same side while also promoting compensatory hypertrophy in the remaining liver.[133]

For patients with diffuse infiltrative HCC (INASL-BCLC stage B3), systemic therapy is the recommended treatment approach.[65,138] However, TARE has also demonstrated good disease control and improved survival outcomes in this patient population.[139,140]

The use of systemic therapy as adjuvant therapy with TARE in patients with INASL-BCLC stage B and C1 is discussed later.

Statement	Level of evidence	Strength of recommendation
25. Systemic therapy is the recommended treatment for patients classified as INASL-BCLC stage B3. However, Y^{90}-TARE has also shown promising results in terms of providing effective disease control and improved survival outcomes.	Moderate	Strong
26. Patients with PVTT (INASL-BCLC stage C1) without extra-hepatic disease may be considered for Y^{90}-TARE.	Moderate	Strong

Role of liver transplantation in selected patients of INASL-BCLC stage C1: Performing upfront liver transplantation (LT) in patients with HCC and major vascular invasion is considered an absolute contraindication.[141] However, for patients treated with TARE who achieve a complete response in thrombosis with a corresponding biochemical response, positive oncological outcomes have been observed after LT.[142,143] In a recent trial, stereotactic body radiation therapy (SBRT), which delivers high-dose radiation from multiple angles to the tumor, was also explored for downstaging advanced HCC prior to living donor liver transplantation (LDLT).[144] Therefore, in selected patients with segmental/sectoral HCC and vascular invasion, in the absence of extrahepatic metastases and with favorable tumor biology as indicated by tumor markers and ^{18}F Fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) scan, LDLT may be considered after adequate downstaging using TARE/SBRT/TACE, complete resolution of macrovascular invasion, and an appropriate waiting period.[145] Soin *et al.* recently divulged their experiences with LDLT in treating HCC patients with PVTT. They found that patients who successfully underwent downstaging prior to LDLT exhibited improved 1-, 3-, and 5-year disease-free survival (DFS) rates of 77%, 77%, and 51% respectively, compared to 63%, 48%, and 40% in patients who did not undergo downstaging. However, the difference was not statistically significant.[144] In another multicenter study examining LT in HCC patients after successful treatment of macrovascular invasion, researchers found that selected HCC patients showing signs of vascular invasion could be transplant candidates if the macrovascular invasion is successfully treated, leading to a pre-transplant alpha fetoprotein (AFP) level of less than 10 ng/mL, with an expected post-transplant HCC recurrence risk of 11%.[146]

Statement	Level of evidence	Strength of recommendation
27. HCC with major vascular invasion is considered an absolute contraindication for upfront liver transplantation (LT).	High	Strong
28. In carefully selected patients with segmental/sectoral HCC and vascular invasion, in the absence of extrahepatic metastases, and with favorable tumor biology as determined by tumor markers and ^{18}F-FDG PET scan, LDLT may be considered. However, this should only occur following successful downstaging using TARE, SBRT, or TACE. Furthermore, the tumor viability in the portal vein should disappear, and an appropriate waiting period should be observed before proceeding with LDLT.	Low	Weak

Role of resection in selected patients of INASL-BCLC stage C1: In certain cases of HCC patients with PVTT, studies have shown that surgical resection involving hepatectomy combined with thrombectomy can yield improved clinical outcomes.[147,148] However, liver resection in patients with advanced cirrhosis poses technical challenges and difficulties. A nationwide survey conducted by the Liver Cancer Study Group of Japan reported survival benefits associated with liver resection in HCC patients with PVTT.[147] A systematic analysis encompassing 29 trials from East Asia, Europe, and the USA further revealed an overall survival benefit for liver resection in advanced-stage HCC patients with PVTT.[148] A nationwide Chinese study involving 1590 patients with PVTT who underwent resection reported a 3-year actuarial survival rate of 17%. To enhance long-term survival outcomes, the authors recommended extensive hepatectomy, effective management of intraoperative blood loss, achievement of R0 resection, adjuvant TACE, and comprehensive treatment for early recurrence.[149] Therefore, INASL recommends that for patients in INASL-BCLC stage C1 resection may be considered for carefully selected patients with ipsilateral PVTT (Type I and II according to the Cheng

classification or Type Vp1-Vp3 according to the Japanese classification), provided that the primary HCC is resectable and there is moderate residual liver function reserve. The use of neoadjuvant therapy prior to resection can be considered on a case-by-case basis, particularly for patients with intrahepatic metastasis, recurrent HCC, PVTT, and similar factors.[125]

Statement	Level of evidence	Strength of recommendation
29. Liver resection may be considered in carefully selected INASL-BCLC stage C1 patients (Childs Pugh A, ECOG 0–2, no CSPH, confirmed resectable primary HCC and moderate residual liver function reserve), with ipsilateral PVTT involving the first-order branch or higher of the main portal vein (Type I and II according to the Cheng classification or Type Vp1-Vp3 according to the Japanese VP classification).	Moderate	Weak
30. Neoadjuvant therapy prior to resection in these patients may be considered on a case-to-case basis like intrahepatic metastasis, recurrent HCC, PVTT etc.	Moderate	Strong

Role of SBRT in patients with INASL-BCLC stages B and C1: Stereotactic body radiotherapy (SBRT) is a viable treatment option for HCC patients with large tumors, multiple nodules, or oligometastatic disease. According to studies, it has shown acceptable local control and 2-year overall survival rates ranging from 40% to 80%.[150] The specific dose of SBRT administered varies based on factors such as tumor location, size, liver function, and planning constraints. It is crucial to carefully select patients for SBRT, as individuals with poor liver function (Child-Pugh class B8 or higher) may be at risk of experiencing toxicity and are generally not suitable candidates for this treatment. While most studies have utilized a 5–6 fraction schedule, recent trials have explored the use of 3 fraction schedules, which have demonstrated similar rates of local control. However, the impact of higher doses on treatment outcomes remains unknown.[150]

Studies have indicated that SBRT achieves superior 2-year local control rates compared to transarterial chemoembolization [TACE] (91% vs. 23%),[151] while demonstrating similar survival rates.[151,152] Ongoing studies are currently evaluating the efficacy of combination of TACE plus SBRT for unresectable HCC. Consequently, INASL recommends SBRT as an option for patients with INASL-BCLC stage B who are ineligible for surgery, unable to undergo TACE/ transarterial radioembolization [TARE], or have residual/recurrent disease following TACE/TARE, aiming to achieve local disease control.

SBRT has been proven to deliver long-lasting local control in patients with portal vein tumor thrombosis (PVTT).[150,153–155] In a randomized trial comparing the combination of TACE and SBRT to sorafenib in individuals with HCC and PVTT, TACE plus SBRT exhibited superior progression-free survival, longer time to progression, and improved overall survival (OS).[156] Another study investigated the long-term effects of SBRT in patients with HCC and PVT, revealing a one-year local control rate of 87.4% and a median OS of 18.3 months when a dosage of 27–54 Gy was administered in 5 fractions.[157] One Indian study revealed that SBRT significantly reduced the volume, enhancement, and major axis length of PVTT in HCC patients, and no case of radiation-induced liver disease was observed after the treatment.[158] In another Indian study, the rates of local control, PFS, and OS after one year were found to be 95%, 53.4%, and 60%, respectively. The total incidence of grade III toxicity was observed to be less than 5%, with lymphocytopenia emerging as the most frequently occurring adverse effect.[155] Therefore, INASL recommends that SBRT be considered as an option for patients with advanced-stage HCC and PVTT, as it can potentially offer a survival advantage when used in conjunction with systemic therapies or TARE as deemed appropriate.

The use of systemic therapy as adjuvant therapy with SBRT is discussed later.

Statement	Level of evidence	Strength of recommendation
31. SBRT is a viable option for achieving local control in patients with intermediate stage HCC (INASL-BCLC stage B) who are not eligible for surgery, unable to undergo TACE/TARE, or experiencing residual/recurrent disease following TACE/TARE.	Moderate	Weak
32. SBRT is a viable option for patients diagnosed with advanced-stage HCC with PVTT (INASL-BCLC stage C1) and has been shown to offer a survival advantage for these individuals. SBRT may be combined with systemic therapy or TARE, as indicated.	Moderate	Strong

Management of Patients of INASL-BCLC Stage C2 (and Patients of Stages B and C1 not Amenable or Refractory to Locoregional Therapy): Role of Systemic Therapy

INASL-BCLC stage C2 represents an advanced stage of HCC characterized by extrahepatic spread, moderately

preserved liver function (CTP ≤8), and reasonable performance status (ECOG ≤2). Extrahepatic metastasis (EHM) is reported to be present in approximately 25% of patients.[159] Patients in this stage are candidates for systemic therapies, such as targeted therapies or immunotherapy, depending on individual patient characteristics and available treatment options.[65] The role of systemic therapy in the overall management of HCC is further described in the subsequent sections.

Stagewise indications of systemic therapy (in intermediate and advanced HCC setting): Patients with advanced-stage HCC can potentially benefit from systemic therapies, which involve the administration of drugs orally or intravenously to target cancer cells throughout the body. Systemic therapies for HCC include molecular targeted therapy, which aims to disrupt intracellular signals involved in cancer cell growth and metastasis, as well as immunotherapy, which enhances the body's immune system to fight against cancer cells.[160] Cytotoxic chemotherapy is rarely used for HCC. Currently, systemic therapies such as molecular targeted agents and immune checkpoint inhibitors, a type of immunotherapy, are employed in the treatment of HCC. The primary objective of systemic therapy is typically to improve OS and PFS in select cases.

Systemic therapy plays an important role in the treatment of HCC based on the stage and eligibility criteria outlined by INASL. The current indications for systemic therapy as the sole therapy for HCC include INASL-BCLC stage C2 and INASL-BCLC stage B3/C1 patients who are not undergoing transarterial radioembolization (TARE), as well as INASL-BCLC stage B1/B2 patients who are refractory to or ineligible for locoregional or surgical therapy. Systemic therapy can also be considered as a potential treatment option for patients who have experienced progression after receiving locoregional therapy, SBRT, or a combination of systemic and locoregional therapy/SBRT. This approach may provide an alternative treatment strategy for these patients.

Increasing evidence indicates that immunotherapy, particularly the use of immune checkpoint inhibitors, may serve as a pivotal shift in the management of HCC. By integrating these therapies with locoregional treatment, there is potential to enhance the rates of recurrence and overall survival for HCC patients.[161] Thus, INASL suggests the use of systemic therapy as adjuvant therapy with TACE, TARE, or SBRT in patients with INASL-BCLC stage B, and with TARE, SBRT, or resection in patients with INASL-BCLC stage C1[161]. Systemic therapy can also be combined with locoregional therapy for downstaging prior to liver transplantation. However, there is no indication for the use of systemic therapy as adjuvant therapy with liver transplantation. It is important to note that systemic therapy is not recommended for patients with advanced liver disease (Child-Turcotte-Pugh scores [CTP] ≥9).

A meta-analysis of 13 mainly retrospective studies found that adjuvant sorafenib therapy after resection in patients with HCC was associated with improved overall survival, recurrence-free survival, and reduced recurrence rates compared to control.[162] However, an RCT involving 1114 patients who underwent surgical resection or local ablation showed no significant difference in median recurrence-free survival between the sorafenib and placebo groups. The study concluded that sorafenib is ineffective as an adjuvant therapy following resection or ablation for HCC.[163]

The TACTICS trial compared TACE plus sorafenib with TACE alone in patients with unresectable HCC. It demonstrated that the combination therapy significantly improved median PFS compared to TACE alone. However, there was no significant difference in median overall survival between the two groups. The trial suggested that TACE plus sorafenib could be considered as a treatment option for intermediate-stage HCC, particularly in patients with high tumor burden.[164,165] An Indian study found that combining TACE with sorafenib significantly improved disease control, time to progression, and OS in patients with advanced-stage HCC compared to TACE alone, without significantly increasing adverse reactions.[166] A meta-analysis of 30 studies found that TACE combined with tyrosine kinase inhibitors (TKIs) was superior to TACE alone in terms of prolonging time to progression (TTP), OS, and objective response rate (ORR) in patients with unresectable HCC, although it was associated with a higher incidence of adverse events such as hand-foot skin reactions, diarrhea, and hypertension.[167]

A meta-analysis of 9 studies evaluated the efficacy and safety of adding sorafenib to TARE for HCC treatment. The analysis found no significant difference in overall survival and progression-free survival between the combined therapy and TARE alone. The authors concluded that the addition of sorafenib to radioembolization does not appear to improve survival or delay disease progression in patients with hepatocellular carcinoma.[168]

According to current evidence, genetic and serum biomarkers for predicting the response of HCC to systemic therapy are not recommended for routine clinical use due to insufficient data. More research and data are needed to establish their utility and reliability in predicting treatment response. However, in some individual cases, simple serum markers such as alpha-fetoprotein (AFP) and C-reactive protein (CRP) may be used to assess the response to immunotherapy.[169,170] These markers can provide additional information and assist in evaluating the treatment response in specific patients. Nonetheless, further research

is required to establish their broader applicability and effectiveness as predictive biomarkers.

Statement	Level of evidence	Strength of recommendation
33. In the intermediate and advanced HCC setting the current indications for systemic therapy as the sole treatment are as follows:		
• INASL-BCLC stage C2	High	Strong
• INASL-BCLC stage C1, if not undergoing TARE	High	Strong
• INASL-BCLC stage B3, if not undergoing TARE	Moderate	Strong
• INASL-BCLC stage B2, if refractory to or ineligible for locoregional or surgical therapy	Moderate	Strong
• INASL-BCLC stage B1, if refractory to or ineligible for surgical or locoregional therapy.	Moderate	Strong
34. INASL suggests the use of systemic therapy as adjuvant therapy with TACE, TARE, or SBRT in patients with INASL-BCLC stage B, and with TARE, SBRT, or resection in patients with INASL-BCLC stage C1.	Moderate	Weak
35. In patients undergoing downstaging prior to liver transplantation, systemic therapy may be used in conjunction with locoregional therapy.	Low	Weak
36. There is no indication of systemic therapy as an adjuvant therapy with liver transplantation.	Moderate	Strong
37. INASL does not recommend the use of systemic therapy in patients with advanced liver disease (CTP ≥9).	Moderate	Strong

Choice of systemic therapy: first and second line agents: Since 2008, Sorafenib, a tyrosine kinase inhibitor that inhibits tumor cell proliferation and angiogenesis, has been the standard of care for patients with advanced HCC (INASL-BCLC stage C), demonstrating significant improvements in median overall survival and time to progression compared to placebo, as shown in the SHARP trial and the Asia–Pacific trial.[171,172] However, common adverse events like hand-foot skin reaction, diarrhea, and hypertension have been associated with Sorafenib. On the other hand, lenvatinib, an oral multikinase inhibitor with a unique inhibitory profile against fibroblast growth factor receptors (FGFR) 1–4, along with other targets like vascular epithelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), RET, and KIT, has been shown to be non-inferior in terms of overall survival (OS) while offering significantly longer progression-free survival (PFS) and time to progression (TTP) compared to Sorafenib in advanced HCC patients. The REFLECT trial (a Phase 3 non-inferiority trial) demonstrated these findings and reported that Lenvatinib is generally well-tolerated, with manageable side-effects such as hypertension, diarrhea, decreased appetite, and weight loss, though it also carries common adverse events like hypertension and proteinuria.[173] However, it's important to note that while both drugs' individual benefits have been demonstrated the choice between Lenvatinib and Sorafenib could be influenced by factors like the patient's overall health status, potential drug interactions, side-effect profiles, and cost.

Since 2008, sorafenib has been the only approved treatment for advanced HCC (INASL-BCLC stage C), showing improved survival compared to placebo.[171,172] Lenvatinib, an oral multikinase inhibitor, has been shown to have non-inferior OS and significantly longer PFS and time to progression (TTP) compared to sorafenib in advanced HCC patients.[173] However, lenvatinib is associated with common adverse events such as hypertension and proteinuria, highlighting the importance of appropriate management to ensure continued systemic therapy.

The treatment algorithm has been redefined due to advancements in systemic therapies, offering novel agents for advanced and intermediate-stage HCC (Table 4). Atezolizumab is a completely humanized, engineered IgG1 isotype monoclonal antibody that specifically binds to PD-L1.[174] Atezolizumab plus bevacizumab demonstrated significant improvements in OS and PFS in advanced HCC patients in the IMbrave 150 study.[175] However, this combination therapy was associated with adverse events such as hypertension and upper gastrointestinal bleeding. A real-world study indicated that adherence to the IMbrave150 trial

Table 4 Summary of Recent Trials on First Line Systemic Therapy Drugs for HCC.

Study	Treatment groups	n	BCLC stage A/B/C (%)	Child-Pugh A5/A6/B7 (%)	ECOG 0/1/2 (%)	Median OS (months)	Median PFS/TTP (months)	ORR (mRECIST)	Grade ≥3 AEs (%)
IMbrave150[175]	Atez/Bev	336	2/15/82	72/28/0	62/38/0	NE	6.8	27.3	56.5
	Sorafenib	165	4/16/81	73/27/0	62/38/0	13.2	4.3	11.9	55.1
HIMALAYA[178]	Dur/Tre	393	0/19.6/80.4	75.1/23.4/1.0	62.1/37.7/0.3	16.43	3.78	20.1	50.1
	Sorafenib	389	0/17.0/83.0	71.2/26.2/2.6	62.0/37.8/0.3	13.77	4.07	5.1	39.5
COSMIC-312[180]	CAB/Atez	432	0/32/68	100 (CP-A)	64/36/<1	15.4	6.8	11	76
	Sorafenib	217	0/35/65	100 (CP-A)	66/34/0	15.5	4.2	6	57
Checkmate 459[181]	Nivolumab	371	4/14/82	98 (CP-A)	73/27/0	16.4	3.7	15	22.3
	Sorafenib	372	5/17/78	96 (CP-A)	70/30/0	14.7	3.8	7	49.6

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PFS, progression-free survival; TTP, time to progression; ORR, objective response rate; mRECIST, modified Response Evaluation Criteria in Solid Tumors; AEs, adverse events.

inclusion criteria positively impacted patient outcomes, and even patients not meeting the criteria may benefit from treatment.[176] In a retrospective study from two centers in India, the atezolizumab-bevacizumab combination was found to be safe and effective as a first-line systemic therapy for unresectable HCC, with overall survival and progression-free survival notably lower in patients with worse CTP scores. However, the study concludes that careful candidate selection is crucial, especially limiting the use of this combination therapy in patients with CTP C, to optimize patient outcomes and ensure treatment safety.[177] Tremelimumab plus durvalumab showed promising efficacy in a phase 3 trial (HIMALAYA), with significant improvement in OS over sorafenib, while durvalumab monotherapy was non-inferior to sorafenib.[178] The choice between atezolizumab plus bevacizumab (Atez/Bev) and tremelimumab plus durvalumab (Dur/Tre) as first-line treatment for advanced HCC depends on factors such as tolerability of anti-VEGF therapy, tumor burden, WNT/β-catenin mutation status, and HCC etiology.[179] However, tremelimumab is currently unavailable in India, and the high cost of immune checkpoint inhibitors poses a significant financial burden for Indian patients. The COSMIC-312 trial did not demonstrate an improvement in OS with cabozantinib plus atezolizumab compared to sorafenib for first-line treatment of advanced HCC.[180] Similarly, the Checkmate 459 trial showed a trend towards improved OS with nivolumab monotherapy compared to sorafenib in treatment-naõve patients, although the difference did not reach statistical significance.[181]

However, it is crucial to consider that the use of Bevacizumab or other anti-angiogenic drugs should be avoided in patients with cardiovascular disorders, recent bleeding, or untreated high-risk esophageal varices. In cases where these treatment regimens are required for patients with large esophageal varices, primary endoscopic variceal ligation should be performed for variceal eradication. While immunotherapy has emerged as an important treatment option for HCC, meta-analyses have shown that patients with HCC related to non-alcoholic fatty liver disease (NAFLD) are less likely to benefit from ICIs alone, and the addition of angiogenesis inhibitors may be necessary to enhance their response to ICIs.[182] A recent meta-analysis demonstrated that treatments containing ICIs were more effective in improving OS in males, patients with macrovascular invasion and/or extrahepatic spread, and those with viral-related HCC.[183] Notably, cytotoxic chemotherapy, either as monotherapy or in combination, did not show significant improvement in overall survival for advanced HCC patients.

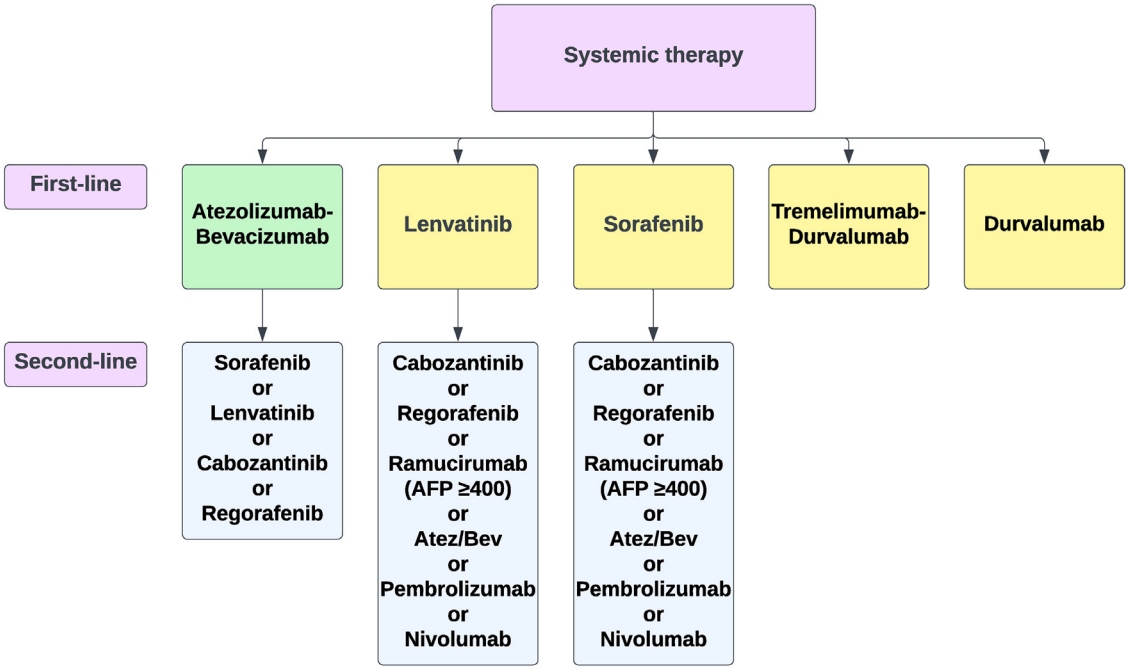
The choice of second-line systemic therapy in HCC depends on the type of first-line treatment. If Atezolizumab-Bevacizumab is unsuccessful as the first-line therapy, a TKI such as sorafenib, lenvatinib, cabozantinib, or regorafenib may be recommended as second-line therapy.[90] However, if sorafenib or lenvatinib fails as the first-line treatment, second-line therapy with cabozantinib, regorafenib, ramucirumab (for patients with AFP ≥400 ng/mL), or atezolizumab-bevacizumab may be considered for eligible patients. Additionally, pembrolizumab or nivolumab are reasonable second-line options for suitable candidates.[90] The KEYNOTE-

240 trial demonstrated that pembrolizumab improved OS and PFS compared to best supportive care in patients previously treated with sorafenib, although the results did not reach statistical significance based on the specified criteria.[184]

The algorithmic approach to systemic therapy is shown in Figure 3.

Statement	Level of evidence	Strength of recommendation
38. INASL recommends the use of atezolizumab-bevacizumab as first-line therapy for patients in whom systemic therapy is indicated.	High	Strong
39. INASL recommends the use of lenvatinib or sorafenib as first-line therapy if the use of Atezolizumab-Bevacizumab is not feasible.	High	Strong
40. Tremelimumab plus durvalumab and durvalumab monotherapy are other reasonable options for first-line therapy, pending their approval in India.	High	Strong
41. Failure of first-line systemic therapy is determined by the progressive disease (PD) according to the modified response evaluation criterial in solid tumors (mRECIST) criteria, typically observed 6–8 weeks post-initiation of the initial therapy or at any subsequent point.	High	Strong
42. Second-line therapy with a tyrosine kinase inhibitor [TKI] (i.e., sorafenib, lenvatinib, cabozantinib, or regorafenib) may be considered following the failure of first-line treatment with atezolizumab-bevacizumab.	Low	Weak
43. Second-line therapy with cabozantinib, regorafenib, ramucirumab (AFP ≥400 ng/mL), or atezolizumab-bevacizumab may be recommended for eligible candidates following the failure of first-line treatment with sorafenib or lenvatinib.	Moderate	Weak
44. Following the failure of first-line treatment with sorafenib or lenvatinib, pembrolizumab or nivolumab is also a reasonable option.	Low	Weak
45. INASL recommends that bevacizumab or other anti-angiogenic drugs should not be used in patients with: • Cardiovascular disorders (such as cerebrovascular accident, acute myocardial infarction or unstable angina, congestive heart failure with New York Heart Association class ≥2, accelerated hypertension, peripheral arterial thrombosis, significant arrhythmias) • Recent bleeding (such as gastrointestinal bleeding, hemoptysis, etc.) • Untreated high-risk esophageal varices.	High	Strong
46. INASL suggests that patients with large esophageal varices who require immunotherapy should be considered for primary endoscopic variceal ligation (EVL) for eradication of varices prior to initiation of immunotherapy.	Low	Weak
47. Cytotoxic chemotherapy, either as a single agent or in combination, did not improve overall survival in advanced HCC and is therefore not recommended.	High	Strong
48. Genetic and serum biomarkers cannot be recommended for routine clinical use to predict the response of HCC to systemic therapy until more data are available.	Low	Strong

Adverse events of systemic therapy: prevention and management: Adverse events (AEs) related to systemic therapy are classified according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, which consists of 5 grades (Table 5).[185] Tyrosine kinase inhibitors (TKIs) are known to cause AEs in more than 15% of patients, with severity ranging from grade 1 to grade 4[186]. Patients experiencing grade 1–2 AEs should not have their medication changed, while those with grade 3 AEs should have the TKI withheld until symptoms improve and liver function tests indicate grade 1 or less before reintroducing the medication. In cases of grade 4 toxicity, the TKI should be discontinued. It is important to implement preventive and specific management strategies tailored to different adverse events.[186]



Notes:

1. *Immunotherapy is contraindicated post liver transplantation or in patients with autoimmune disorders.*
2. *Avoid Bevacizumab in patients with cardiovascular disorders (such as cerebrovascular accident, acute myocardial infarction or unstable angina, congestive heart failure with New York Heart Association class ≥2, accelerated hypertension, peripheral arterial thrombosis, significant arrhythmias), recent bleeding (such as gastrointestinal bleeding, hemoptysis, etc.); and untreated high-risk esophageal varices.*

Figure 3 Algorithmic approach to systemic therapy.

Table 5 Adverse Events (AEs) Related to Systemic Therapy are Classified According to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.[185]

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b].
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Abbreviations: ADL, Activities of Daily Living; AE, adverse event.
[a]Instrumental ADLs include chores and activities necessary to manage and maintain a household and lifestyle, such as shopping and managing finances.
[b]Self-care ADLs include basic tasks like eating, bathing, and dressing.

INASL recommends using the term immune-mediated liver injury caused by immune checkpoint inhibitors (ILICIs) to describe immune-related liver injury.[187,188] Severe grade ILICI is uncommon, occurring in approximately 0–2.5% of cases. In cases of grade 2 ILICI, the immune checkpoint inhibitor (ICI) should be temporarily withheld until symptoms improve and liver function tests indicate grade 1 or less. If symptoms persist for more than 7 days, low-dose steroids should be administered. Grade 3 or 4 ILICI requires discontinuation of the ICI, and high-dose steroids should be used until symptoms and liver function tests (LFTs) normalize to grade 1 or less, followed by a gradual tapering over 4 weeks. If there is no improvement with steroids, other immunosuppressive agents should be considered.[189] It is worth noting that the development of ILICI or other immune-related adverse events may be associated with improved efficacy of immunotherapy, resulting in favorable response rates and prolonged survival. Resuming ICI therapy after the resolution of adverse events does not appear to impact the efficacy of ICI therapy in controlling HCC.[190]

In an Indian study that assessed the safety and efficacy of atezolizumab-bevacizumab as a first-line systemic therapy for unresectable HCC, it was found that while the

therapy was effective across all Child-Turcotte-Pugh (CTP) classes, there was significant variation in survival rates and adverse events. A total of 64.2% of patients experienced adverse events, most commonly fatigue and an increase in serum bilirubin levels, which led to drug discontinuation in 15% of the patients. These adverse events were particularly prevalent in CTP class C, underscoring the necessity of careful patient selection and advising against the use of this combination therapy in class C patients due to a higher incidence of severe adverse events.[177]

Statement	Level of evidence	Strength of recommendation
49. Adverse events are reported in more than 15% of patients using TKIs, with 50–75% of these events classified as grade 3 or 4 in severity.	High	Strong
50. If adverse events are observed with TKIs: • No changes in medication should be made in patients with Grade 1–2 AEs. • TKI should be withheld following Grade 3 AEs until symptoms or LFT improve to Grade 1 or less, and then reintroduced. • In cases of Grade 4 toxicity, TKI should be discontinued.	Moderate	Strong
51. INASL suggests that the standard terminology used for immune-related liver injury should be Immune-Mediated Liver Injury caused by Immune Checkpoint Inhibitors (ILICI).	Moderate	Weak
52. If ILICI is observed with immune checkpoint inhibitors: • For grade 2 immune-mediated liver injury caused by immune checkpoint inhibitors (ILICI), withhold immune checkpoint inhibitors (ICIs) till symptoms and liver function tests (LFTs) improve to grade 1 or less, then reintroduce. Low dose steroids if symptoms persist for more than 7 days. • For grade 3 or 4 ILICI, discontinue ICI. Give high-dose steroids till symptoms and LFT derangement improve to grade 1 or less, then taper over 4 weeks. Other immunosuppressive agents can be given if no improvement is seen on steroids.	Moderate	Strong
53. The development of ILICI or other immune-related AEs may be associated with improved efficacy of immunotherapy, including favorable response rates and prolonged survival.	Moderate	Strong
54. The efficacy of ICI therapy may not be impaired in patients who resume ICI therapy after the resolution of immune-related AEs.	Low	Weak

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Treatment Response Assessment and Repeat Therapies

Treatment Response Evaluation

Objective response (OR) has emerged as an important imaging biomarker for further prognostic assessment.[191] INASL recommends using modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria to measure viable tumor and classify response into complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) (Table 6).[2,192,193] The first imaging after ablation should be conducted at 4 weeks; after transarterial chemoembolization (TACE) or systemic therapy should be conducted within 4–8 weeks; while for transarterial radioembolization (TARE) and stereotactic body radiotherapy

Table 6 mRECIST (Modified Response Evaluation Criteria in Solid Tumors) Criteria for Hepatocellular Carcinoma.

mRECIST Categories	Criteria
Complete Response (CR)	Disappearance of any intratumoral arterial enhancement in all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
Stable Disease (SD)	Any cases that do not qualify for either partial response or progressive disease
Progressive Disease (PD)	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since the treatment started

(SBRT), it can be done at 8–12 weeks. In cases with high tumor burden, the first imaging after TACE should be performed after the post-treatment phase.[192,194] Follow-up imaging for local response assessment should be conducted at 3-month intervals during the 1st year using multiphasic computed tomography (CT)/ magnetic resonance imaging (MRI) with contrast. INASL does not recommend using contrast enhanced ultrasound (CE-US) or positron emission tomography-computed tomography (PET-CT) for evaluating treatment response.

Statement	Level of evidence	Strength of recommendation
55. INASL recommends using multiphasic CT/MRI with contrast and the modified response evaluation criteria in solid tumors (mRECIST) criteria to assess the local response following locoregional therapy, systemic chemotherapy, or immunotherapy.	High	Strong
56. INASL recommends the first follow-up imaging to be conducted: • At 4 weeks after ablation. • At 4–8 weeks after TACE. • At 6–8 weeks after systemic therapy initiation. • At 8–12 weeks after TARE or SBRT.	Moderate	Strong
57. In case of high tumor burden, the first imaging after TACE be performed soon after the TACE procedure to assess any residual tumor.	High	Strong
58. INASL recommends that further follow-up imaging should be done at 3-month intervals during the first year.	High	Strong
59. Failure of therapy or progressive disease is defined as an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since the treatment started.	High	Strong

Post-LT Recurrence

Prevention, Surveillance, and Early Diagnosis of Post-LT Recurrence of HCC

The recurrence of HCC following LT is a grave complication that can considerably affect patient survival. This recurrence often hinges on pre-transplant tumor attributes like size, number, and vascular involvement. For a reliable prediction of HCC recurrence risk post-liver transplantation, both pre- and post-transplant variables should be considered. The use of predictive models that include these variables can help evaluate the probability of HCC recurrence and support the formulation of post-transplant management plans.[195]

The Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score has been developed as a tool to estimate the risk of tumor recurrence after LT for HCC. The RETREAT score incorporates factors such as AFP levels, presence of microvascular invasion, and the sum of the largest viable tumor size and number of tumors on the explanted liver. By considering these factors, the RETREAT score provides valuable information to assess the likelihood of HCC recurrence after LT.[196]

To minimize the risk of HCC recurrence, it is important to maintain an optimally low level of calcineurin inhibitors (CNIs), which are commonly used immunosuppressive medications in LT. Studies have shown that mammalian target of rapamycin (mTOR) inhibitors can help reduce the risk of HCC recurrence post-LT.[197] Therefore, in HCC patients with a high risk of recurrence following LT, a combination therapy of low-dose CNIs and mTOR inhibitors should be considered. This approach may contribute to improved outcomes by minimizing the risk of HCC recurrence.

Post-transplant surveillance plays a crucial role in the early detection of recurrent HCC following LT.[198] To effectively monitor for recurrence, a combination of AFP and either contrast-enhanced CT (CECT) of the abdomen and chest or FDG PET imaging is recommended. It is important to note that patients who were transplanted within the Milan criteria do not require routine surveillance.[62] However, for patients who were transplanted beyond the Milan criteria or those with other high-risk features identified during explant evaluation, close surveillance is highly recommended.[42]

The frequency of post-transplant surveillance should be every 3–6 months during the first two years and then every 6 months for the subsequent five years.[62] This regular monitoring allows for timely detection of any recurrent HCC, enabling prompt intervention and treatment.

Statement	Level of evidence	Strength of recommendation
60. A combination of pre- and post-transplant variables should be used to estimate the risk of HCC recurrence.	Moderate	Strong
61. The RETREAT score, which incorporates tumor characteristics assessed through explant pathology, can be included in the criteria for predicting post-LT recurrence.	Moderate	Strong
62. The level of calcineurin inhibitor (CNI) should be kept optimally low to minimize the risk of HCC recurrence.	Moderate	Strong

(*Continued*)

Statement	Level of evidence	Strength of recommendation
63. mTOR inhibitors have been shown to reduce the risk of HCC recurrence post-LT, and are recommended.	Moderate	Strong
64. Close surveillance after LT is highly recommended for patients who fall beyond the Milan criteria or exhibit other high-risk features in the explant.	Moderate	Strong
65. A combination of AFP, either with CECT of the abdomen and chest or FDG PET, is recommended for post-LT surveillance to enable early diagnosis of recurrent HCC.	Moderate	Strong
66. The recommended frequency of surveillance is every 3–6 months during the first 2 years and then every 6 months for a total of 5 years.	Low	Weak

Management of Post-LT Recurrence

Multimodality treatment, incorporating Surgery, ablative therapies, or medical therapies (TKI and mTOR inhibitors), is recommended to manage post-LT recurrence.[199] Surgical management plays a critical role in addressing post- LT recurrence of HCC. Ablation, either as a standalone therapy or as part of a multimodality approach, has demonstrated better survival outcomes compared to locoregional therapies without ablation. For patients with resectable oligo recurrences in one or two organs, surgical resection should be considered as the first-line treatment, particularly when achieving an R0 resection is feasible.[200] This treatment approach, combined with the use of TKIs, has shown potential for improving survival, especially in cases of recurrence after 12 months, in patients receiving mTOR inhibitors, with an AFP level below 100, and with a single site of recurrence. TACE may be employed as a monotherapy for recurrence, but outcomes can vary. However, due to limited data availability, there is currently no established algorithmic approach for the treatment of post-LT HCC recurrence.[201]

Statement	Level of evidence	Strength of recommendation
67. INASL recommends the use of multimodality treatment, incorporating medical therapies (TKI and mTOR inhibitors), ablative therapies, or surgery, to treat post-LT HCC recurrence.	Moderate	Strong

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Statement	Level of evidence	Strength of recommendation
68. First-line treatment for patients with resectable oligo recurrences in one or two organs (such as liver, lung, abdominal wall, omentum, adrenals, and other sites) should include surgical resection, particularly when R0 resection is feasible. Additionally, adjuvant tyrosine kinase inhibitors (TKI) therapy should be administered.	Low	Weak
69. Ablation alone or as part of multimodality treatment should be used to improve survival compared to locoregional therapies without ablation.	Low	Weak

Concepts of Futility of Specific Treatments and Untreatable Progression in HCC

Futility of a particular treatment in the context of HCC refers to the point at which further treatment using the same modality is unlikely to provide significant benefits in terms of overall survival, disease control, or quality of life. This concept is particularly relevant in cases of advanced HCC, where factors such as tumor burden and underlying liver dysfunction strongly influence treatment response and patient outcomes. Untreatable progression represents treatment failure or disease progression that occurs within the patient's initial BCLC stage, despite the selected treatment strategy.

A comprehensive evaluation involving a multidisciplinary team of healthcare professionals, including medical oncologists, hepatologists, radiologists, and palliative care specialists, is essential in determining the futility of treatment. The team should consider a range of factors, including tumor burden, extent of liver dysfunction, overall patient health, and care objectives. This collective assessment helps guide clinical decision-making regarding the appropriateness and potential benefits of continued treatment for patients with advanced HCC.

Criteria of Futility of Specific Treatments

LT is considered a potential curative option for patients with early-stage HCC or selected cases of intermediate-stage HCC. However, the success of LT in HCC patients can be limited by several factors.[202] Advanced HCC, characterized by large tumor size, multiple tumors, vascular invasion, and extrahepatic metastasis, is associated with a high rate of tumor recurrence and poor survival outcomes,

making these patients less likely to benefit from LT. Patients with high-risk features for tumor recurrence, such as AFP levels or poorly differentiated tumors, may not be suitable candidates for LT.[203] Furthermore, patients with underlying medical conditions or comorbidities may have an increased risk of post-transplant complications, which can limit the feasibility of LT.[202,204]

There are certain criteria and contraindications for LT in HCC. Elderly patients over 70, those with significant non-liver morbidities, extrahepatic disease, or main portal vein or hepatic vein tumor thrombus are generally not recommended for LT. LT outside of the established criteria may not be effective unless successful downstaging is achieved. A five-year survival rate of less than 60% is typically considered a threshold indicating that LT may not be a worthwhile intervention. However, exceptions to these guidelines may be considered on a case-by-case basis, especially for patients with HCC and advanced cirrhosis, as LT can potentially improve survival rates. It is important to note that LT is a costly and resource-intensive procedure that requires prolonged hospital care. Therefore, careful patient selection and evaluation are essential to determine which HCC patients are most likely to benefit from LT. From an oncologist's perspective, LT may be justified in cases of advanced cirrhosis with HCC, but it is important to consider expected cure rates exceeding 60% in terms of five-year survival when recommending LT.[202,203]

In addition to LT, locoregional therapies (LRT) is a commonly used treatment modality for advanced liver disease. However, there are certain situations where LRT may be considered futile. For instance, patients with decompensated liver disease, indicated by a Child-Turcotte-Pugh (CTP) score of 9 or higher, may not be suitable candidates for LRT. Similarly, if a patient shows no response or experiences disease progression following a specific LRT procedure such as TACE, further attempts at the same procedure may be deemed futile.[205] If LRT is expected to result in persistent decompensation of liver disease, it is considered futile. Likewise, any worsening of liver decompensation following an LRT procedure should be regarded as an indication of futility for subsequent procedures. Additionally, systemic therapies may not be effective in patients with poor liver function, specifically those classified as Child B or C with a CTP score of ≥9, or in patients with a poor performance status (Eastern Cooperative Oncology Group [ECOG] score of 3–4).

Statement	Level of evidence	Strength of recommendation
70. LT may be considered futile in the following situations: • Elderly (>70) • Significant non-liver morbidity • Extrahepatic disease • Main Portal vein or hepatic vein tumor thrombus • Deceased donor liver transplantation (DDLT) outside UCSF criteria • Expected five-year survival rate of <60%. However, exceptions can be made on a case-by-case basis.	Moderate	Strong
71.It is important to preserve liver function when selecting candidates for locoregional therapies (LRT). LRT is considered futile if it is likely to result in persistent decompensation of liver disease.	Moderate	Strong
72. Any persistent decompensation (not transient) after an LRT procedure should be considered a futility of care for subsequent LRT procedures.	Moderate	Strong
73. LRT is considered futile and therefore contraindicated in patients with decompensated liver disease (CTP ≥9).	High	Strong
74. The absence of objective response (OR) at 6 months, progression at any time, or rising AFP levels after TACE procedures should be considered as futility for further TACE.	High	Strong
75. LRT may not provide any survival benefit in patients with extrahepatic spread; therefore, it can be considered futile.	Low	Weak

(*Continued*)

Statement	Level of evidence	Strength of recommendation
76. The available systemic therapies may not be of benefit and hence considered futile in: • Patients with end stage liver function (Child B9 or CTP C). • ECOG performance status 3–4.	Moderate	Strong

Role of Best Supportive Care in Patients in Whom all other Treatments are Futile

When futility is determined, the focus of care may shift towards symptom management and palliative care to enhance the patient's quality of life. This may involve implementing supportive measures to address pain, nausea, fatigue, and other symptoms associated with advanced HCC, as well as providing emotional and spiritual support to the patient and their family.

The optimal management of pain is crucial, and the World Health Organization (WHO) ladder should be utilized as necessary, while avoiding the use of hepatotoxic drugs.[206] Palliative radiotherapy is recommended for patients experiencing painful bone metastases. In addition to pain control, appropriate nutritional intervention should be provided to all patients. Psychological support should also be made available, but the use of psychoactive drugs and benzodiazepines should be avoided due to increased adverse effects. Timely counseling for the family and effective communication about outcomes are also essential. These measures collectively contribute to a comprehensive approach to palliative care.[207]

Statement	Level of evidence	Strength of recommendation
77. Optimal pain control should be achieved by utilizing the WHO ladder when necessary and avoiding the use of hepatotoxic drugs.	Low	Weak
78. Palliative radiotherapy maybe recommended for the management of painful bone metastases.	Moderate	Weak
79. Appropriate nutritional intervention should be provided to all patients.	Moderate	Strong

(*Continued on next page*)

(*Continued*)

Statement	Level of evidence	Strength of recommendation
80. Psychological support should be provided while avoiding the use of psychoactive drugs and benzodiazepines due to their increased adverse effects.	Low	Weak
81. Timely counseling of the family and effective communication about outcomes should be provided.	Low	Weak

Contextualizing the Guidelines: Addressing Accessibility, Availability, and Cost Factors in India

While we have outlined comprehensive guidelines for the management of HCC, it's crucial to consider the unique challenges of implementing these guidelines within the context of India. As a developing country with diverse economic and geographic conditions, India faces particular hurdles concerning the availability, accessibility, and cost of diagnostic tools and treatments for HCC. The reality is that many of the therapeutic modalities, while proven to be effective, are not accessible or affordable for a significant portion of the patient population. Moreover, advanced diagnostic tools may be out of reach for many healthcare facilities, particularly in rural areas. Therefore, while these guidelines provide an ideal framework for managing HCC, they must be applied with consideration for these practical constraints.

It is essential that physicians adapt these guidelines to align with the resources at their disposal, without compromising on the quality of patient care. For instance, prioritizing treatments that offer the best balance of cost-effectiveness and clinical benefit may be a necessary strategy. Furthermore, enhancing local capacities for HCC management, through measures such as improved training and infrastructure development, can help widen access to quality care.

These 2023 INASL guidelines for the management of intermediate and advanced HCC in India represent a significant advancement in enhancing patient care and establishing standardized practices nationwide. While our guidelines present the best practices for managing HCC, it is important to acknowledge that their implementation across India will need to navigate the challenges of clinical efficacy and practical feasibility. These guidelines should be seen as a flexible roadmap that can be adapted to individual patient circumstances and local resource availability.

Based on current evidence, the primary goal of these guidelines is to establish a consistent approach to HCC management, ensuring patients receive optimal care. They provide a comprehensive framework for diagnosis, staging, and treatment of HCC, striving to promote uniformity throughout the country. This is crucial in a diverse nation like India, where clinical practices may vary across regions. Standardizing approaches can help guarantee that all patients receive equitable care, irrespective of their geographical location.

These guidelines also serve as a foundation for future research on HCC in India. Although much of the current evidence is drawn from Western studies, these guidelines will be regularly updated and revised to incorporate new findings, especially those emerging from India. This iterative process ensures the ongoing relevance of the guidelines, enabling patients to benefit from the most up-to-date, evidence-based care available, thereby enhancing treatment outcomes and improving their quality of life.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

The authors contributed to this manuscript as follows:

SKA, AK, AD, SPS, PNR, KM: Conceptualization, Methodology.

AK: Original draft preparation.

SKA, SPS, MS: Supervision, Project administration.

AD, PP: Funding acquisition.

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CONFLICTS OF INTEREST

All authors have none to declare.

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