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Review Article

Evaluation and Management of Unresectable Hepatocellular Carcinoma: Multidisciplinary Indian Consensus Statements from a Delphi Panel

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Abstract

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Background India, like many parts of Asia, likely faces a high burden of hepatocellular carcinoma (HCC), though large-scale data on etiology, presentation, and outcomes are lacking. There appears to be a predominance of unresectable, advanced-stage HCC at presentation in India with variable level of expertise in India to manage these scenarios. This publication summarizes the latest evidence with cognizance of the unique challenges faced in India by treating clinicians.

Methods A multidisciplinary panel of medical oncologists, gastroenterologists, hepatologists, interventional radiologists, and hepatobiliary surgical oncologists held a meeting in June 2022 and reviewed the evidence available for management of HCC. The meeting concentrated on the recognition and management of HCC not amenable to surgical approaches in the Indian context. A literature review of these aspects of management was conducted and consensus statements with level of evidence and grades of recommendation were prepared by individual specialists in each field. Statements were evaluated by the modified Delphi method.

Key Content and Findings The panel comprising 22 experts formulated 40 consensus statements with regard to defining unresectable HCC, optimization of underlying conditions prior to management, rationale use of various liver-directed therapies (LDTs) in unresectable HCC, and systemic therapeutic options in this group of patients.

Conclusion Our consensus statements offer practical, yet evidence-based management guidelines for treating unresectable HCC in the Indian context. There is an emphasis on the crucial need for combining available approaches for LDT, even if less well studied though possibly effective, with standard systemic therapy.

Keywords

- HCC
- hepatocellular carcinoma
- Indian consensus
- MDT
- multidisciplinary tumor board

Introduction

Data from GLOBOCAN 2020 suggest that hepatocellular carcinoma (HCC) is the 10th most common cancer in India by incidence, though constituting the 8th most common cause of cancer-related deaths in the country.[1] As cancer is not a reportable disease in India and most of the registries are urban, there is a significant risk of ascertainment bias and underestimation for the true prevalence of HCC in India. Because of the same reasons, there are also contrasting data regarding the common etiologies associated with HCC in India. While older data suggested that hepatitis B-related HCC was most common, individual hospital data suggests an increased proportion of metabolic dysfunction-associated steatotic liver disease-related HCC and this is now the most common cause of HCC in India. As in other parts of the world, hepatitis C is also one of the common causes of HCC in India.[2]

While recommendations for surgical approaches to HCC have moved beyond the Milan criteria in recent years, there has been an even greater explosion in the systemic therapeutic options for advanced HCC.[3] The introduction of atezolizumab plus bevacizumab, durvalumab, and tremelimumab, and lenvatinib, as well as effective second-line options of therapy have improved survival in advanced HCC from less than 12 months to beyond 18 months in well-selected patients.[4–6] Between the two extremes of resectable and advanced HCC, lie a large proportion of "gray zone" HCCs which are usually classified as intermediate stage B HCC as per the Barcelona Clinic Liver Cancer (BCLC) classification or stage IIIa/IIIb by the Hong Kong Liver Cancer (HKLC) classification.[7,8] While previous treatment guidelines concentrated on transcatheter arterial chemoembolization (TACE) as the primary treatment option in this group of tumors, there is growing evidence that this group is heterogeneous and a "one-size-fits-all" approach is not necessarily correct. A combination of non-TACE liver-directed therapies (LDTs) like transarterial radioembolization (TARE) and radiotherapy along with systemic therapeutic options are being increasingly used in intermediate stage HCC in clinical practice, with growing supporting evidence.[9,10] Additionally, a proportion of patients with initially unresectable HCC can get downstaged to surgery or transplant and this is a growing paradigm of treatment in HCC.

While there are Indian retrospective data with regard to practices and outcomes in patients with transplanted and resected HCC, there are very limited studies in patients with "unresectable" HCC from India.[11,12] While most treatment options used in such unresectable patients are routinely available in India, there are limited data with regard to rationale of use and whether there is a standardized treatment approach in place for these patients. Additionally, there is marked variance in the availability of different modalities of treatment across various parts of India. For example, access to TARE may not be available or feasible in some regions. In such situations, there are possibilities of using lesser studied modalities like radiotherapy (or stereotactic body radiotherapy (SBRT). Similarly, while immunotherapy (IO) might show greater survival benefits than lenvatinib in

advanced HCC, the financial constraints associated with IO imply a markedly greater real-world use of lenvatinib than IO. While some of these issues might be similar to other countries, they have been well unaddressed in India. Though the ideal solution to some of these underaddressed issues would be the conduct of clinical trials in India, expert guidance can provide a practical approach to the management of these cancers in the interim. With this background, the aim of this publication was to report the first Indian consensus statements from a multidisciplinary panel for the management of unresectable HCC.

Methods

In June 2022, a multidisciplinary group of 22 Indian clinicians comprising medical oncologists, hepatobiliary surgeons, hepatologists, interventional radiologists, and radiation oncologists met to discuss and define consensus statements on the evaluation and management of unresectable HCC. Attempts were made to involve clinicians from governmental and private institutions that were high-volume centers for the management of HCC.

Two members from each specialty in the group were tasked with developing and framing the consensus statements prior to the meeting. The supportive evidence from all disciplines was discussed in depth and the statements were presented to all group members for feedback and anonymous voting. A modified Delphi method was used for the formation of the consensus. A statement was considered as "accepted" if greater than 70% of the group voted to agree with the statement. In cases where a consensus was not met, statements were revised and voted on again until consensus was reached. The group evaluated each statement's level of evidence and grade of recommendation as per the Infectious Diseases Society of America-US Public Health Service Grading System.[13] As per this system, the letters A to E signify the strength of the recommendation for or against a preventive or therapeutic measure, while the Roman numerals I to III indicate the quality of evidence supporting the recommendation.

Consensus Statements

Assessment of Underlying Liver Dysfunction in Unresectable HCC

Statement 1.1: Child–Pugh score is recommended as the primary tool in the assessment of liver dysfunction prior to undertaking liver-directed and systemic therapies for intermediate stage HCC. (IA)

Statement 1.2: ALBI (albumin-bilirubin) score can help in determining liver function prior to liver-directed and systemic therapies in intermediate stage HCC but needs further validation. (IIA)

Statement 1.3: Further research is needed to validate the use of indocyanine green (ICG) clearance, 99Tc-iminodiacetic acid (IDA) scintigraphy, and elastography for the assessment of liver function prior to liver-directed and systemic therapies for HCC. (IIIB)

Individual biochemical tests like serum bilirubin, albumin, or international normalized ratio (INR) are poor predictors of overall liver function.[14] Child-Turcotte-Pugh (CTP) score is the most common score to assess functional status of the liver. CTP score is incorporated as part of the BCLC and HKLC staging system as a measure for functional assessment of liver.[15] The CTP score includes parameters of bilirubin, albumin, INR, ascites, and hepatic encephalopathy. Patients with CTP A cirrhosis are considered fit for HCC-directed therapy, whereas those with significant liver dysfunction (CTP class C cirrhosis) are unfit for HCC-directed therapy due to high competing risk of mortality. Patients with CTP B[7] can be considered on a case-by-case basis for HCC-directed therapy, after careful consideration of what parameters drive the CTP score. Patients with overt hepatic encephalopathy and moderate to severe ascites are unfit for any form of HCC-directed therapy. CTP is easy to calculate but has limitations with floor effects, ceiling effects, and subjectivity of parameters.[16]

Recently, the ALBI score has been used as a prognostic marker in patients with different stages of HCC. It is easy to calculate and objective, providing three subclasses based on the score (ALBI grade 1, 2, and 3). ALBI has been found to be a good prognosticator in patients undergoing both surgery and nonsurgical HCC-directed therapies across all stages.[17–19] However, larger validation studies are needed to include ALBI in the treatment algorithm for HCC.

Other scores for assessment of liver function like ICG clearance (ICGC) (ICG R15), 99Tc-IDA scintigraphy, and elastography are not yet validated for use for liver functional assessment in HCC. ICGC, although known to have predictive value for posthepatectomy liver failure (PHLF) after hepatectomy, needs further studies for evaluating its predictive potential prior to HCC-directed therapies. Also, the test performs poorly in patients with raised bilirubin.[20] Technetium scintigraphy is known to be useful for prediction of liver function in patients undergoing radioembolization.[21,22] However, data on its use to predict functional liver reserve prior to other LDTs is sparse. Transient elastography is known to correlate with portal hypertension.[23,24] While elastography largely correlates with structure, its functional correlation is not yet validated, so its utility as a test for functional assessment prior to LDT remains unclear.

Statement 1.4: Decompensation of underlying chronic liver disease in the form of jaundice (total bilirubin >3 mg/dL), moderate-severe ascites, and overt hepatic encephalopathy, with Child-Pugh class B[8,9]/C are contraindications for any LDTs or systemic therapies of HCC in most cases. (IA)

Statement 1.5: Patients with Child-Pugh class A cirrhosis and no prior history of decompensation should be considered for HCC-directed therapy. (IA)

Statement 1.6: Patients with Child-Pugh class B7 cirrhosis can be considered for HCC-directed therapy on a case-by-case basis. (IIC)

Statement 1.7: LDTs and systemic therapies should be considered on a case-by-case basis after recompensation of previously decompensated chronic liver disease, accounting for tumor burden, potential for worsening liver function, and liver transplant eligibility. (IIC)

Statement 1.8: Early palliative care should be considered for patients with decompensated chronic liver disease with HCC, specifically those who are ineligible for liver transplantation or unlikely to become recompensated to offer any cancer-directed therapy. (IA)

Traditionally, treatment algorithms including both BCLC and HKLC recommend therapeutic options for patients with Child-Pugh A cirrhosis.[25] In patients with decompensation in the form of jaundice (> 3 mg/dL), moderate-severe ascites, and overt hepatic encephalopathy, LDT is typically of minimal benefit, outside of liver transplant eligibility, given high competing risk of mortality and high risk of worse decompensation. In patients undergoing thermoablation, there is a likely increase in CTP score in patients who are CTP A in 3 to 7% and CTP B in 3 to 14%.[26,27] For transarterial therapies, select patients with CTP B are considered fit for LDT.[28] For systemic therapies, retrospective analyses have suggested safety and tolerability in selected patients with CTP B cirrhosis although objective survival benefit in these patients is unknown.[29] Palliative care in patients with HCC aims at management of symptoms, discussion of treatment choices, and psychosocial support for patients and their caregivers.[26] Palliative care has been shown to reduce patient and family suffering, reduce health care utilization, and even improve survival in the context of cancer. Early palliative care should be offered to patients who are planned for therapy with palliative intent.

Statement 1.9: Treatment of underlying chronic liver disease affects outcomes of patients with intermediate stage HCC. (IA)

Statement 1.10: In patients with chronic hepatitis B and HCC, therapy for hepatitis B should be started using antivirals with high barrier to resistance (entecavir or tenofovir) and continued lifelong. (IA)

Statement 1.11: In patients with chronic hepatitis C and HCC, therapy for hepatitis C should be considered using directly acting oral antivirals (DAAs) in those with expected survival exceeding 1 year. Addition of ribavirin should be considered in patients with cirrhosis. In patients with contraindications or intolerance to ribavirin, therapy should be considered with DAAs alone for an extended period of 6 months. (IIA)

Status of underlying liver disease is known to impact therapeutic options for HCC. Hepatitis B and C are two common causes of HCC in India.[30,31] Antivirals (entecavir or tenofovir [TAF/TDF]) improve CTP status and reduce risk of decompensation in patients with hepatitis B virus (HBV)-related cirrhosis. Antivirals are associated with reduced risk of HBV reactivation after surgery, TACE, and SBRT. Choice of antivirals has largely been at the treating hepatologist's discretion. A recent meta-analysis showed that tenofovir is better than entecavir for tertiary prevention after LDT for HCC.[31] However, large-scale randomized trials are needed for further clarification on choice of one antiviral over another.

Therapy for chronic hepatitis C is finite and is usually considered for patients with life expectancy more than 1 year in the background of HCC.[32] Antivirals improve CTP score and reduce the risk of decompensation in compensated hepatitis C virus (HCV)-related cirrhosis. Although there was initial concern about increased risk of recurrence, recent multisite data have demonstrated no increased risk of recurrence. Further, DAA improves overall survival (OS) in patients with a history of HCC, independent of recurrence risk, for both patients undergoing curative or palliative therapies.[33,34] In contrast to HBV antivirals, therapy for HCV does not need to be started prior to HCC-directed therapy given lower concern for acute flares. Notably, patients with HCC have lower rates of sustained virologic response compared to those without HCC.

Defining Criteria of Unresectability in HCC

The assessment of resectability in HCC is based on the presence of liver-related factors (i.e., degree of dysfunction) and tumor-related factors (i.e., tumor burden and presence of extrahepatic disease).

Statement 2.1: An inadequate future liver remnant (FLR) is a factor to define unresectable HCC. Adequate FLR for resection is defined as 25 to 30% for noncirrhotic livers and > 40% for cirrhotic livers. HCC (Category IIA).

Statement 2.2: CTP scoring is an indicator of liver function and predicts outcomes posthepatectomy. CTP score above B7 should be considered unresectable (Category IIA).

Statement 2.3: ICG retention is a marker of functional capacity of liver and a value of > 15% for major hepatectomy can be considered as a criterion for unresectability (Category IIA).

Statement 2.4: Clinically significant portal hypertension (CSPH) in the form of hepatic venous pressure gradient (HVPG) of > 10 mm Hg, varices, and symptomatic splenomegaly is an indicator of postoperative liver decompensation and long-term mortality. CSPH should be considered as a contraindication for surgery, although thresholds for thrombocytopenia are being reassessed for minor resections with increasing use of laparoscopic and robotic techniques (Category IIA).

The FLR determines risk of posthepatectomy liver dysfunction. Cirrhotic livers have a decreased ability to tolerate injury and regenerate. Hence, there is general consensus that a higher FLR for cirrhotic livers is needed to prevent PHLF. Compared to FLR of > 25 to 30% for noncirrhotic livers being considered standard, an FLR of > 40% is required in the setting of cirrhosis. Portal vein embolization can be considered to increase FLR in patients initially considered unresectable with good long-term survival outcomes, and there is now increasing data for use of TARE to induce hypertrophy of contralateral lobe.[35,36] CTP score is an indicator of liver function and CTP score of B8 and above correlates with postoperative mortality as high as > 20% as well as reduced OS; therefore, major liver resection should not be considered for these patients.[37] ICGC is a marker of metabolic function of the liver as the dye gets excreted without enterohepatic circulation. ICGC value of 14% or less is suitable for a major hepatectomy and values > 20% should not be considered for major liver resection.[38] CSPH with HVPG > 10 mm Hg or portal vein pressure of > 20 cm H2O, esophageal varices,

platelet < 100,000/mm^3, and splenomegaly > 12 cm is associated with a higher risk of death at 3 and 5 years as well as an increased risk of clinical decompensation and therefore should be considered a criteria for unresectability.[39] Recent data suggest that lower platelet counts of 90,000 may be tolerated with laparoscopic and robotic techniques when performing a minor resection.

Statement 2.5: Size of tumor should not be considered as a factor determining unresectability (Category IIA).

Statement 2.6: Invasion of second order portal vein is not a contraindication, however, invasion of first order branches or main portal vein should be considered unresectable unless downstaged (Category IIA).

Statement 2.7: Hepatic vein invasion with or without tumor extension into infra- or suprahepatic inferior vena cava (IVC) is not a contraindication to surgery if can be performed safely with extraction of tumor thrombus with or without IVC resection (Category IIC).

Statement 2.8: Tumor compression of bile duct causing jaundice is not unresectable if surgery or drainage feasible. Tumor thrombus of bile duct is not a contraindication to surgery unless invasion of contralateral bile duct system (Category IIC).

Statement 2.9: Multicentric (bilobar) HCC is generally considered unresectable; however, localized multinodular HCC that can be resected with a safe resection margin and preserve adequate FLR is not a contraindication (Category IIC).

Statement 2.10: Presence of extrahepatic disease in HCC is unresectable (Category IIC).

The size of primary HCC tumors even larger than 10 cm have 5-year survival outcomes of 33 to 35% with partial hepatectomy. The previous stress on tumor size as a criteria for consideration of resection does not hold significant validity in the current era, if adequate FLR is possible.[40,41] Liver resection for HCC with branch portal vein thrombus (Vp1 or Vp2) is associated with improvement in survival outcome without major perioperative mortality (< 5%) as compared to other treatment modalities and hence these patients can be offered surgery beyond BCLC criteria.[42] In contrast, patients with Vp3 or Vp4 disease have high risk of metastatic disease and upfront resection is likely of limited benefit. Similarly, patients with hepatic vein invasion have reasonable 5-year outcomes with surgery and should be considered for resection prior to assessment for other treatment modalities.[43] Hepatic vein invasion involving IVC by tumor has a superior survival outcome with surgery compared to nonsurgical approaches and should be offered surgery. In patients with hepatic vein invasion or hepatic vein thrombosis (especially those without portal vein thrombosis [PVT]), surgery possibly offers survival benefits compared to nonsurgical approaches and can be considered as the initial modality of treatment.[44] HCC with bile duct tumor invasion, wherein the thrombus is resected or otherwise, results in 5-year survival outcomes of 28 to 36% with surgical approaches.[45,46] While transplant is the preferred approach in HCC with multinodular disease given high risk of recurrence, resection can be considered safely in such patients, though factors such as tumor number, total tumor diameter, and the presence of microvascular invasion may be associated with decreased survival after resection in cirrhotic patients with multinodular HCC.[47,48]

Though patients with HCC who have been resected or ablated are usually observed, there is emerging data to suggest that adjuvant atezolizumab-bevacizumab may be of benefit in patients with high-risk characteristics. The interim analysis of the IMbrave050 trial has shown that adjuvant atezolizumab-bevacizumab planned for a period of 12 months might improve survival compared to observation in this setting. However, data with a longer follow-up will be required before this can be considered as a treatment option.[49] Presence of extrahepatic disease should be considered as unresectable as a standard. However, isolated adrenal lesions or single lung nodule or single bone lesions can be considered as oligometastatic disease. The definitive management of oligometastatic disease should depend on performance status, disease-free interval, or response to therapy to consider for curative options either in the form of surgery or ablative measures.[50] Although important in all patients, management at high-volume centers and a multidisciplinary approach are particularly critical for these patients.

Liver-Directed Therapy in Unresectable HCC

LDT in the form of TACE forms the backbone of treatment in patients with BCLC B HCC. Some patients in this group are also candidates for a combination of TACE and radiofrequency ablation (RFA), while a certain proportion of patients can also be considered for TARE. Current guidelines deal predominantly with patients with unresectable HCC as opposed to inoperable HCC, wherein surgery has not been considered due to patient-related or logistic factors. In a scenario where anatomic factors preclude resection, the predominant modality of treatment remains TACE with a lesser role for RFA and microwave ablation (MWA).

Statement 3.1: In patients with BCLC B (Intermediate stage), the use of TACE alone is the standard of care treatment option, with systemic therapy to be considered when there is development of liver lesions not addressable by further TACE or extrahepatic disease. (I, A)

Statement 3.2: In patients with BCLC B (Intermediate stage) with tumors larger than 5 cm, TACE can be combined with RFA or MWA. (II B)

TACE is the primary modality of treatment in patients with unresectable HCC with most older studies showing benefits compared to systemic therapeutic options. While there are limited studies in the current era comparing TACE with IO or newer tyrosine kinase inhibitors (TKIs), practice patterns have overwhelmingly used TACE as the primary modality in unresectable HCC and it occupies a central position in both the BCLC and HKLC systems as a treatment of choice in unresectable HCC.[51,52]

However, the frequent development of local tumor recurrence and impaired liver function reserve after TACE leads to unsatisfactory outcomes, especially in larger tumors. Additionally, repeated TACE potentiates the expression of vascular endothelial growth factor, thereby increasing tumor

angiogenesis and possibility of recurrence. There is evidence to suggest that patients with larger tumors (> 5 cm) might benefit from addition of RFA or MWA to TACE in unresectable HCC. While there is no strict single cutoff in terms of tumor size for the additional use of RFA/MWA, the synergism of TACE and RFA/MWA and the available evidence supports their combined use in larger unresectable HCCs.[53,54]

Statement 3.3: Drug-eluting beads (DEBs)-TACE can be considered a preferred option compared to conventional TACE (cTACE) in patients with BCLC B and single large tumors. (II B)

Statement 3.4: TACE is relatively contraindicated in BCLC C patients with main PVT (MPVT); however, it can be considered safely in patients with branch PVT (BPVT). (IIIB)

Statement 3.5: TARE can be considered as an alternative to TACE or in patients with contraindications to TACE in HCC BCLC B tumors as well as select patients with PVT, particularly those in whom downstaging to transplant is intended. (II B)

Section 3.6: Transarterial embolization (TAE) is the treatment of choice in patients with ruptured unresectable HCC. (II A)

cTACE acts by the selective obstruction of tumor-feeding arteries by injection of chemotherapeutic agents (predominantly doxorubicin and rarely, cisplatin) mixed with lipiodol. This leads to ischemic necrosis of the targeted tumors by cytotoxic and ischemic effects. DEB-TACE purports to improve on the effects of cTACE by sustained release of chemotherapeutic agents over a prolonged period of time. This also entails higher concentrations of drugs within the target tumor and lower systemic absorption and concentrations compared with cTACE. While this is appealing conceptually, there is controversy over the actual benefits of DEB-TACE over cTACE.[55] The largest trial comparing the two options, the PRECISION V study showed numerically improved response rates and disease control rates as well as a significant decrease in chemotherapeutic agent-related systemic and liver toxicity with DEB-TACE compared to cTACE. However, the trial did not achieve statistical significance in terms of primary endpoint of tumor response at 6 months.[56] A majority of the studies comparing the two modalities have shown similar results wherein there is some improvement in response rates, but without unequivocal survival benefits.

The presence of PVT entails poor survival outcomes in the current era, irrespective of the treatment modality used in management of this subset of HCC. Traditionally, the use of TACE has been avoided in HCC with PVT due to the potential for embolization to cause hepatic infarction and worsened liver function. However, multiple studies as well as a meta-analysis have shown that TACE can be safely used in patients with PVT, though survival continues to remain poor. As expected, patients with BPVT perform better than patients with MPVT. The development of "super selective" or "ultra selective" catheterization techniques and "microcatheters" has enabled advancement of catheters into smaller vessels of the hepatic vasculature, allowing the safe use of TACE in patients with PVT. This has entailed a very low risk of ischemic necrosis and liver failure with the use of TACE in patients with PVT.[57] However, it is to be emphasized that treating HCC BCLC C patients with PVT with TACE does not lead to significantly improved outcomes and the predominant modality of treatment remains systemic therapy.

Most comparisons between TACE and TARE comprise small retrospective heterogeneous cohort studies where drawing firm conclusions are not feasible. However, the available evidence suggests that the two modalities have similar OS although TARE induces greater progression-free survival (PFS) than TACE in patients with unresectable HCC. A recently published overall and individual patient-level meta-analysis also showed a similar trend with TARE resulting in a longer time to progression (TTP) than TACE (mean TTP 17.5 vs. 9.8 months; mean TTP difference 4.8 months, 95% confidence interval [CI] 1.3–8.3 months). The same meta-analysis also comprised an individual patient analysis of three studies showing no difference in OS between the two modalities including among subgroups stratified by tumor stage and liver function.[10]

One of the major criticisms of studies evaluating TARE has been the lack of adequate dosing in patients and whether a personalized and potentially higher dose would have greater efficacy than techniques using the standard dosimetry. This was the question evaluated in the phase II randomized DOSISPHERE-01 study, comparing standard dosimetry (120 ± 20 Gy) targeted to the perfused lobe or personalized dosimetry (≥ 205 Gy targeted to the index lesion) in patients with locally advanced HCC. The results showed a near doubling of response rates (71% vs. 36%), as well as increased resection rates (36% vs. 4%) and median OS (26.6 vs. 10.7 months) in the personalized dosimetry group. Additionally, there were lesser safety issues, despite the increased dosimetry in the personalized dosimetry group.[58] While this was a phase II study, it does show the potential benefits of personalized dosimetry with TARE as opposed to older studies with standard dosimetry.

Radiotherapy in Unresectable HCC

Radiation-based regimens were historically limited by radiation-induced liver injury, though there is emerging evidence to suggest that newer techniques, such as SBRT, can safely be used in HCC with reasonable efficacy. In regions where access or technical expertise with TARE is difficult or contraindications to TACE exist, SBRT is a reasonable alternative as a standalone option or with systemic therapy.

Statement 4.1: SBRT can be considered an alternative treatment for localized or recurrent HCC especially when accompanied with tumor thrombus. The role of SBRT is limited to patients with preserved liver function (Child A5-B7) and where at least > 700 mL of the normal liver volume can be spared. (Category IIC)

Statement 4.2: The combination of systemic therapy with SBRT can be considered for localized or recurrent HCC especially when accompanied with tumor thrombus. The role of SBRT is limited to patients with preserved liver function (Child A5-B7) and where at least > 700 mL of the normal liver volume can be spared. (Category IIB)

In patients with HCC where TACE is not feasible, SBRT is a good alternative in carefully selected patients with liver

confined disease based on multiple phase I/II prospective and retrospective studies (local control at 2 years $\geq$ 80%). Most patients in these trials had well-compensated baseline liver function (Child-Pugh A5-B7) with single or multiple tumors (up to 5) and technically feasibility of SBRT like a minimum of 700 mL of spared normal liver volume. Bujold et al in a prospective study of 102 patients reported excellent outcomes in patients treated by SBRT with median tumor size of 7.2 cm with maximum up to 23.1 cm.[59] Local control rate at 1-year was 87.5% and median OS of 17 months. Fukuda et al reported the outcomes of 129 patients with Child A/B and median tumor size of 3.9 cm (1–13.5 cm) treated by protons.[60] The 5-year local tumor control (LTC), PFS, and OS rates were 94, 28, and 69% for patients with 0/A stage disease ($n = 9/21$), 87, 23, and 66% for patients with B stage disease ($n = 34$), and 75, 9, and 25% for patients with C stage disease ($n = 65$), respectively. The interim results of a randomized study comparing protons with TACE in the setting of bridge to transplant showed a trend to improved 2-year LTC (88% vs. 45%, $p = 0.06$) and PFS (48% vs. 31%, $p = 0.06$) in favor of protons.[61] The results of other ongoing studies comparing SBRT versus TACE are awaited.

In recurrent unresectable HCC, Kim et al conducted a phase 3 randomized controlled trial comparing protons to RFA and concluded that 2-year local PFS with protons was noninferior to RFA (92.8% for protons vs. 83.2% for RFA) and 4-year survival (75%) was similar between the two arms.[62] While this study included small tumors (size < 3 cm, number ≤ 2), a prospective phase II study by Jang et al reported the SBRT (3 fractions) outcomes in 65 recurrent HCC patients primarily after 1 to 5 sessions of TACE with median tumor size of 2.4 cm (1–9.9 cm). The 3-year LTC rate was 95% and 3-year OS was 76%[63]

In de novo or recurrent HCC with secondary PVT or MPVT, TACE is not feasible and systemic therapies are recommended as first-line treatment. The recently presented phase III randomized controlled trial RTOG-NRG 1112 at ASTRO 2022 compared addition of SBRT to sorafenib versus sorafenib alone and showed a trend toward superiority of SBRT plus sorafenib over sorafenib alone in terms of PFS and OS.[64] This study included patients with large HCC not amenable to TACE or RFA, 84% were BCLC C and 74% had macrovascular invasion.

Statement 4.3: For patients with liver-confined multifocal and/or unresectable HCC, SBRT/proton beam therapy (PBT) alone or sequenced with TACE/RFA is conditionally recommended. (Category IIB)

For unresectable tumors, TACE (especially the superselective TACE) has been the preferred local treatment modality. However, for larger lesions the response rates with TACE are only 40 to 60%. Several retrospective, prospective, and randomized trials have suggested addition of radiation (external beam radiotherapy or SBRT) to improve complete response rates and OS. A prospective phase II study by Buckstein et al evaluated addition of SBRT after 2 TACE in 32 patients with solitary HCC 4 to 7 cm, Child-Pugh A5-B7, and unsuitable for resection/transplant.[65] The overall response rate was 91% with 63% complete response. The median OS was not yet reached and median PFS was 35 months. The 2- and 3-year local control was 85% and 2- and 3-year OS 64 and 60%, respectively. A recent phase III randomized trial by Comito et al comparing SBRT versus further TACE in patients with incomplete response after 1 TAE/TACE showed superior local control with SBRT versus TAE/TACE rechallenge (median not reached vs. 8 months, $p = 0.0002$). The 1-year PFS was 37% with SBRT compared to 13% with TAE/TACE.[66] A randomized trial by Yoon et al compared the combination of TACE and radiation with sorafenib in 90 patients with Child-Pugh A HCC with PVT and showed improved PFS (86.7% vs. 34.3%; $p < 0.001$), TTP (31.0 vs. 11.7 weeks; $p < 0.001$), and OS (55.0 vs. 43.0 weeks; $p = 0.04$) with TACE-RT.[67] It is important to note the potential for additive toxicities when SBRT is used as a single option or in combination with other modalities such as TACE. The most common form of radiation-induced toxicity is radiation-induced liver disease, followed by gastrointestinal toxicities. Available data suggests an incidence of severe toxicities of 3 to 30% and this needs to be kept in mind when combination therapies including SBRT are being considered.

When the tumors are resectable and undergo hepatectomy with removal of portal vein tumor thrombus (PVTT), RT has shown to have improved outcomes in neoadjuvant settings. In a randomized trial by Wei et al, patients were randomly assigned to receive neoadjuvant RT followed by hepatectomy or hepatectomy alone.[68] Neoadjuvant RT significantly reduced HCC-related mortality and HCC recurrence rates compared with surgery alone leading to a superior disease-free survival and OS. The optimal role of SBRT/PBT and patient selection for patients with liver-confined unresectable HCC remain an area of need.

Systemic Therapy in Unresectable HCC

The advent of IO has changed the paradigms of treatment in patients with advanced HCC. Such has been the impact that IO is now being explored in patients postresection as well as in combination with various modalities of LDT to improve survival outcomes. However, TKIs continue to remain a backbone for the management of advanced HCC because of their ease of administration and relatively lower costs when compared with IOs.

Statement 5.1: In patients with BCLC B (Intermediate stage) the use of sorafenib 800 mg per day or lenvatinib (weight-based) can be associated with improved survival when used concurrently with TACE. This should be limited to patients with CTP A-B7 and PS 0-1 only. (II, A)

A majority of older studies have not shown benefit for the use of systemic therapy (predominantly sorafenib) in combination with LDT in terms of increases in survival.[69] However, two well-conducted studies have suggested that a combination of TKIs and LDT might improve outcomes. The TACTICS trial, wherein a combination of sorafenib with TACE improved PFS compared to TACE alone (25.2 vs. 13.5 months; $p = 0.006$), though OS was not statistically improved in the final analysis. Important points to note in this study was the use of a novel primary endpoint as an equivalent of PFS called

time to untreatable (UnTACEable) progression and the selection of an extremely fit cohort of patients in the study.[70,71] The second study is the LAUNCH 3, a phase 3 clinical trial comparing lenvatinib plus TACE with lenvatinib alone in patients with advanced HCC (as defined by the American Association for the Study of Liver Diseases 2018 Guideline on Liver Cancer Diagnosis). The study showed an improvement in PFS (10.6 vs. 6.4 months; hazard ratio [HR], 0.43; 95% CI, 0.34–0.55; $p < 0.001$) and OS (17.8 vs. 11.5 months, HR, 0.45; 95% CI, 0.33–0.61; $p < 0.001$).[72] Both the above studies, while exploring different subsets in the spectrum of HCC, suggest that combining TKIs with TACE may provide some survival benefit in well-selected patients. While there is a greater quantum of data with sorafenib in this setting, the noninferiority of lenvatinib with respect to sorafenib in the advanced setting as well as potentially better tolerability means there will be increased use of lenvatinib with LDT in the aforementioned scenario.

There is limited data to suggest benefits of adding immunotherapeutic agents like durvalumab, tremelimumab, and atezolizumab-bevacizumab to LDT, though they are being evaluated in a similar scenario in clinical trials. It is important to note that BCLC B intermediate stage includes patients with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 only. Patients with ECOG PS 1 are classified as BCLC C and will only be candidates for systemic therapy. In clinical practice patients with ECOG PS 1 are usually included in the same bracket as BCLC B and treated with LDT, with or without systemic therapy.[73]

Statement 5.2: In patients with BCLC B (Intermediate stage) the use of sorafenib 800 mg per day concurrently with TARE can be used on a case-to-case basis. This should be limited to patients with CTP A-B7 and PS 0-1 only. (II, B)

Statement 5.3: In patients with BCLC B (Intermediate stage) the use of lenvatinib (weight-based) concurrently with TARE can be used on a case-to-case basis. This should be limited to patients with CTP A-B7 and PS 0-1 only. (II, C)

Available evidence suggests that TARE in unresectable HCC (BCLC B and BCLC C) has not improved survival compared to sorafenib. This is true in patients who would have been candidates for TACE and have been treated with TARE (BCLC B) or patients who have been candidates for systemic therapy alone (BCLC C).[74,75] Additionally, the addition of TARE to sorafenib in patients with unresectable HCC or HCC with limited extrahepatic disease has also not improved survival compared to sorafenib alone.[76] However, the increasing realization that such patients are at a high risk for the development of distant metastases or disease progression can entail the use of systemic therapy on a case-to-case scenario based on a multidisciplinary assessment.

Statement 5.4: In patients with BCLC C with PVT (VP3/VP4), the primary modality of therapy should be systemic therapy. (I, A)

Statement 5.5: In patients with BCLC C with PVT (VP3/VP4), TARE alone can be considered in select cases. (II, B)

Statement 5.6: In patients with BCLC C with PVT (VP3/VP4), systemic therapy and TARE can be considered in select cases. (II, C)

The presence of PVTT designates advanced disease (BCLC C) and confers a poor prognosis. Out of various classification systems for PVTT, the Vp classification system from the Liver Cancer Study Group of Japan is the most commonly used and the knowledge of the location of PVTT impacts prognosis and therapeutic options.[73] The risk of extrahepatic spread is high in patients with Vp3 and Vp4 disease so use of systemic therapy may be an optimal option with the addition of local therapy in those without evidence of extrahepatic spread on subsequent imaging, particularly in those with evidence of initial response and stable liver function.

The standard of care in such patients should be appropriate systemic therapy as detailed below under systemic therapeutic options used in advanced HCC. It is important to note that not all trials evaluating systemic therapeutic options have included MPVT as an inclusion criterion. For example, the REFLECT study evaluating lenvatinib systematically excluded patients with PVT, whereas these patients were included in IMBrave150 evaluating atezolizumab-bevacizumab.[4,6] However, there is retrospective evidence to suggest that lenvatinib can be used in the setting of PVT.[77,78] Hence, in clinical practice, most systemic therapeutic options can be used in HCC with PVT with the understanding that outcomes may not be commensurate with those seen in clinical trials.

Conceptually, in patients with liver-limited disease, but PVT, there is a propensity to consider LDT and TARE is an attractive option in this scenario. Although initial prospective studies showed promise, three randomized controlled trials have failed to demonstrate superiority of TARE compared to sorafenib, even when TARE was combined with sorafenib.[74–76] Some of the lack of benefit with TARE in older studies can be attributed to lower than effective doses of radiation delivered, though this has been standardized with time. The effectiveness of TARE, with or without systemic therapy, in this patient population is an area of need.

Statement 5.7: In patients with BCLC C (Advanced disease) HCC, the following systemic therapeutic can be considered as first-line therapy;

- Atezolizumab plus bevacizumab (no prior history of transplantation/autoimmune disorders and should have an endoscopic evaluation within prior 6 months with properly treated esophageal varices and no history of major bleeding) (I, A)
- Durvalumab plus a single priming dose of tremelimumab (1A)
- Lenvatinib (I, B)
- Sorafenib (I, A)
- Durvalumab monotherapy (I, B)
- Pembrolizumab or nivolumab (IIC)

Over the last decade several different systemic therapy options have been approved for the management of advanced HCC and these broadly include TKIs, IO, and anti-angiogenic agents. For patients naive to systemic therapy, sorafenib prolongs OS compared to placebo, lenvatinib provides a noninferior OS compared to sorafenib, atezolizumab-bevacizumab prolongs OS compared to sorafenib, and the

STRIDE regimen (tremelimumab 300 mg as a single dose with durvalumab followed by durvalumab every 4 weeks) improved OS compared to sorafenib alone.[4,5,79–82] Additionally, durvalumab alone appears to be noninferior to sorafenib. Limited Indian retrospective data with regard to sorafenib and the use of IO has shown outcomes similar to available data from seminal clinical trials. While most therapeutic treatment options have been compared in trials with sorafenib as the standard arm, there are no large trials comparing individual IO regimens or IO regimens with lenvatinib. While IO has shown numerically longer survival and objective responses when cross-compared to lenvatinib in network meta-analysis, this has not been conclusively borne out from recently published high-volume multi-institutional retrospective data.[83,84] Hence, we recommend both regimens as first-line systemic therapeutic options in advanced HCC. As previously noted, the REFLECT trial showing noninferiority of lenvatinib compared to sorafenib had strict exclusion criteria (main portal vein invasion and > 50% liver involvement excluded). Similarly, the HIMALAYA trial evaluating the STRIDE regimen excluded patients with MPVT. However, this does not necessarily preclude the use of these drugs and regimens in routine clinical practice with the understanding of the relative pros and cons of such an approach. In rare scenarios, nivolumab or pembrolizumab can be considered in advanced HCC, though both drugs did not improve survival compared to sorafenib in first-line and second-line trials, respectively.[85,86]

Statement 5.8: In patients with BCLC C (Advanced disease) HCC and CTB7, the following systemic therapeutic can be considered as first-line therapy:

- Sorafenib (I, A)
- Nivolumab (II, B)

A majority of clinical trials have systematically excluded patients with CTP-B or have only included patients with CTP B7 alone. Real-world data has suggested that certain agents, including lenvatinib and atezolizumab-bevacizumab, can be used safely with caution in this scenario. If atezolizumab-bevacizumab is considered, careful assessment of gastrointestinal bleeding risk and adequate treatment of varices must be performed. Based on the available current evidence, sorafenib and nivolumab are the first-line therapy options with the most robust data for patients with advanced unresectable HCC who are unsuitable for LDT and have CTP score B/7.[87,88]

Statement 5.9: In patients who have disease progression or intolerance to first-line IO, TKIs like sorafenib, lenvatinib, regorafenib, and cabozantinib or ramucirumab can be considered. (IIIC)

Given recency of approvals for IO agents, there are limited data on the use of subsequent therapies post-progression on first-line IO and such decisions need to be individualized. Existing data among small cohorts have suggested similar PFS as use post-sorafenib. Patients with preserved functional status liver functions may be treated with second-line therapeutic options. This is more a reflection on the lack of trials in this scenario as immunotherapeutic options have only recently entered the management paradigm of advanced HCC.

Statement 5.10: In patients who have disease progression or intolerance to first-line sorafenib or lenvatinib, the following options can be considered as further therapy:

- Regorafenib (patients must have previously tolerated sorafenib well) (IB)
- Cabozantinib (1B)
- Ramucirumab (if alpha-fetoprotein > 400 ng/mL) (1B)
- Nivolumab + ipilimumab (IIB)
- Pembrolizumab (IIB)
- Nivolumab (IIB)

The majority of second-line treatment options have been evaluated post-progression or intolerance to sorafenib. Similar indications can be used when lenvatinib has been used as initial therapy, though there are limited prospective data with regard to the same. Most of the second-line treatment options have shown superiority to placebo or best supportive care, with no prospective trials comparing the different treatment options head-to-head.[85,86,89–93]

Conclusion

The current set of guidelines in unresectable HCC represents the first attempt at forming a consensus-based guideline in the Indian scenario. It represents the coming together of clinicians from high-volume centers from various parts of the country to outline treatment guidelines for patients with unresectable HCC in India.

While multiple comprehensive and well-elucidated guidelines exist for the management of HCC across the world, there are certain unique scenarios that exist in India that require evaluation and guidelines are needed to address these aspects. Most of these situations relate to availability of all treatment options in all parts of the country, that is, unavailability of TARE or interventional radiologists well versed with TARE in all parts of the country, unaffordability of IO in many patients with advanced HCC, etc. Additionally, unlike regions like North America and Hong Kong which have extensive published data on etiology, treatment practices, and outcomes with HCC, there is extremely limited data on these aspects from India. This results in a need for reliance on expert views and opinions until the time large-scale data is available from India. We have attempted the same with a majority of clinicians having significant experience of treating HCC in high-volume centers across the country. Once there is prospective or large observational data from India with regard to unresectable HCC guidelines will be on firmer ground with regard to recommendations.

Another aspect of these guidelines is the recognition of gray zones in the management of unresectable HCC and recognizing that an individualized approach is to be considered, as opposed to a strictly guideline-based approach. The concurrent use of systemic therapy with TACE in BCLC B HCC as well as the use of TARE in patients with PVT are two such scenarios where available data from trials and clinical practice likely differ. The guidelines recognize such situations and

have suggested multiple treatment options with varying grades of recommendations for each treatment option.

The advent of IO has revolutionized the management of HCC, and the efficacy of IO in advanced HCCs has prompted multiple trials evaluating their utility in earlier stages of HCC as a downstaging or adjuvant modality. The lack of head-to-head comparison between atezolizumab-bevacizumab and lenvatinib lead the committee to recommend both options for first-line treatment in advanced HCC. There are limited data for treatment post-IO and thus, the guidelines recognize multiple such treatment options based on available clinical trials.

In conclusion, the current set of guidelines in unresectable HCC is the first of its kind in India and can serve as a pragmatic resource for physicians across the country treating HCC. Development of Indian data and conduct of studies in this scenario will further advance the usability and reach of these guidelines to a wider audience in the times to come.

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Conflict of Interest

J.P. has worked on this manuscript in her independent capacity. Roche has no inputs or activity with respect to this manuscript. A.S. has served as a consultant or on advisory boards for Genentech, AztraZeneca, Eisai, Exelixis, Bayer, Boston Scientific, FujiFilm Medical Sciences, Exact Sciences, Roche, Glycotest, Universal Dx, Freenome, and GRAIL. All other authors reported no conflict of interest.

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