# INASL Consensus on Management of HCC: Navigating an Evolving Field

Hepatocellular carcinoma (HCC) is one of the few cancers with a 5-year survival that remains below 20 % and an incidence-to-mortality ratio that approaches one. Poor prognosis is attributable to multiple factors including underuse of surveillance and frequent late-stage diagnosis, underuse of curative treatment, and limited efficacy of palliative treatments.[1,2] However, the field is now on the cusp of a revolution with marked improvements in the safety and efficacy of HCC treatments across all stages of disease. For example, there is increased application of surgical therapies for patients with mild portal hypertension using robotic techniques, broader application of liver transplantation for patients beyond the Milan Criteria after downstaging, and introduction of immunotherapy-based regimens for patients with unresectable HCC.[3] With these advances, we have observed changes in decision-making for the management of patients with HCC, particularly for those detected beyond early stage. Considering this significant evolution in treatment paradigms, the Indian National Association for Study of Liver (INASL) Puri III Recommendations provide updated guidance for the management of patients in India with intermediate and advanced stage HCC.

## INTRODUCTION OF THE INASL-BCLC STAGING SYSTEM

The first step in the management of any patient with HCC is accurate staging, which is important for prognostication and selection of an optimal first-line therapy. Although there is no single universally accepted staging system, there is widespread recognition that HCC prognosis and treatment decisions extend beyond tumor burden and incorporate other elements including liver dysfunction and patient performance status. These factors were included in the Barcelona Clinic Liver Cancer (BCLC) staging system, which has been endorsed by the American Association for the Study of Liver Disease (AASLD) and European Association for the Study of Liver (EASL) guidelines.[4–6] Among recent updates to the BCLC in 2022 was a recommendation to individualize treatment approaches based on specific aspects including nutritional status, comorbidities and frailty, social status, and patient values. However, the BCLC faces criticism that the stages are too heterogeneous regarding prognosis and treatment eligibility.

The INASL Puri III Recommendations proposes the INASL-BCLC staging system, which divides BCLC stages into substages to address this heterogeneity and provide more specific treatment recommendations. For example, stage B includes stages B1 (within transplant criteria), stage B2 (beyond transplant criteria), and stage B3 (diffuse extensive intrahepatic disease); stage C includes stage C1 (vascular invasion alone) and C2 (extrahepatic spread); stage D includes stage D1 (within transplant criteria) and stage D2 (beyond transplant criteria). Prior efforts to refine staging, such as the Hong Kong Liver Cancer and ITA.LI.CA staging systems, have increased prognostic discrimination compared to the BCLC,[7,8] and one would anticipate the same is true for INASL-BCLC staging. However, the extent to which this increased complexity of staging improves clinical care for patients remains to be demonstrated and presents an opportunity for INASL to address.

HCC staging is typically performed using dynamic contrast-enhanced abdominal MRI or multi-phasic CT, as well as chest CT to evaluate for metastatic disease. In contrast to AASLD and EASL, the INASL Puri III Recommendations endorse the use of PET-CT to detect occult extrahepatic metastases. The value of PET-CT in most patients with HCC currently remains unclear, with some studies suggesting increased detection of extrahepatic metastases and others showing a change in staging for only a small minority of patients.[9,10] Further, many of the patients in whom occult extrahepatic disease is discovered are those with diffuse bilobar disease, in whom systemic therapy would already be considered. The potential for detecting extrahepatic metastases using PET-CT should be weighed against costs as well as the risk of false positives, which can increase patient anxiety and psychological distress, require biopsy for resolution, and delay appropriate care. While PET-CT may have a role for staging, which warrants further evaluation, its current role may be best restricted to those in whom there is suspicion of unrecognized extrahepatic disease (e.g., biomarkers discordant with radiographic disease) that would prompt a change in clinical management (e.g., change from locoregional therapy to systemic therapy or determination of transplant eligibility).

## INASL RECOMMENDATIONS FOR THE TREATMENT OF HCC

Two of the INASL Puri III recommendations for treatment also notably differ from those of the AASLD, EASL, and

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BCLC. First, INASL Puri III endorses systemic therapy in combination with local therapies for patients with BCLC stage B disease, and second, they endorse the use of locoregional (transarterial radioembolization (TARE) or stereotactic body radiotherapy (SBRT)) or surgical therapy for selected patients with portal vein invasion.

## COMBINATION OF SYSTEMIC AND LOCOREGIONAL THERAPY FOR BCLC STAGE B HCC

The INASL Puri III Recommendations endorse consideration of systemic therapy in patients with transarterial chemoembolization (TACE)-refractory or TACE-unsuitable disease, which has also been endorsed by other guidelines. There is increasing recognition that patients with large intrahepatic disease are less likely to have responses to locoregional therapy and have increased risk of treatment-related adverse events, including liver dysfunction. A propensity-matched analysis by Kudo *et al.* compared up-front systemic therapy and TACE for patients with HCC exceeding the Up-to-Seven Criteria and found that patients treated with systemic therapy had significantly longer survival, largely related to better preservation of liver function.[11] Although there is no consensus for exact threshold of tumor burden at which a patient becomes TACE-unsuitable, the INASL-BCLC defines TACE-unsuitable disease (stage B3) in a similar manner to the BCLC as diffuse, infiltrative, extensive disease. APASL has endorsed the Up-to-Seven Criteria and some in the United States use UNOS-downstaging as a threshold. Recognition of TACE unsuitable disease is important to reduce the risk of liver dysfunction and permit maximal potential benefit of systemic therapies in these patients.

In contrast to other guidelines, the INASL Puri III Recommendations advocate for the use of adjuvant of combination systemic therapy in patients undergoing TACE, TARE, or SBRT. There is pre-clinical rationale for this combination, specifically as it relates to the effects of locoregional therapy in increasing VEG-F activity and activated CD8+ T cells in the tumor microenvironment; however, existing clinical data (albeit predominantly with TKI-based therapy) have failed to demonstrate a survival benefit. Several phase II and phase III clinical trials failed to show the benefit of adding sorafenib to TACE in overall survival or progression-free survival. Although the TACTICS trial initially showed an improvement in time to unTACEable progression, further follow-up failed to show a difference in overall survival.[12] Notably, there are limited data evaluating the combination of TACE/TARE with immune checkpoint inhibitors. In a phase II single-arm study, 42 patients were treated with TARE and Nivolumab, with ORR of 41.5 % (95%CI 26.3–57.9 %) and median survival 20.9 (95%CI 17.7–24.1) months; treatment-related adverse events occurred in eight (19 %) patients.[13] Although there is optimism surrounding ongoing randomized clinical trials comparing TARE alone versus TARE with immune checkpoint inhibitor combinations, it's currently unknown if any increase in objective response rates would be offset by potential harms including risk of liver dysfunction that could mitigate survival benefit.

Society consensus recommendations must balance the strength of evidence and expert opinion for situations in which there is not sufficient data, which can be difficult in areas or times of quickly emerging science. These decisions are particularly difficult when there is a desire to bring promising therapies to patients sooner and improve outcomes, although there are several recent examples where this optimism is met with disappointment when final clinical trial data is reported. In HCC, this was recently the case with single-agent immunotherapy with nivolumab, where excitement about durable responses observed in Checkmate040 failed to translate into a survival benefit compared to sorafenib in Checkmate459.[14] Early dissemination of these recommendations, without sufficient data, can expose patients to treatment-related adverse events and unnecessary financial toxicity, which is particularly important in a diverse geographically and financially variable healthcare delivery system as in India.[15] While there are occasional cases in which quick succession of therapies may be beneficial, these cases are best determined on an individual basis by a multidisciplinary tumor board. While awaiting these data, an approach of combination or adjuvant therapy is best performed as part of a clinical trial or on a protocol, as this balances increased access to promising therapies for patients, ensuring sufficient provider expertise in HCC management and assessment of adverse events, considerations of the risk-benefit ratio in a systematic manner, and generation of data to evaluate these emerging therapies. Accordingly, it is critical that continued advocacy efforts strive to expand the global availability of clinical trials to historically underrepresented areas, such as India.

## TREATMENT OF PATIENTS WITH PORTAL VEIN INVASION

There is increasing recognition that BCLC stage B and stage C are both heterogeneous groups. This heterogeneity has been incorporated into treatment decisions for BCLC stage B, with downstaging being considered for those with limited tumor burden and systemic therapy recommended for those with large tumor burden. However, the same differentiation of guideline recommendations for patients with BCLC stage C disease has not yet occurred despite data showing differential prognosis and treatment response depending on the presence and degree of vascular invasion, extrahepatic metastases, or both. Currently

available data, primarily from Asia, suggest resection can be effective in select patients with portal vein invasion, although data among non-HBV-infected patients are more limited and less encouraging. It is possible that the availability of (neo)adjuvant therapies may increase the appetite for surgical resection in patients with limited vascular invasion over time.

Although TARE is highly effective and can induce high objective response rates, particularly when delivered in a selective manner to early-stage tumors, studies do not consistently demonstrate that TARE induces similar responses or survival in patients with more advanced tumors. In one of the largest retrospective cohort studies among 1000 patients, Salem *et al.* reported the median survival after TARE was 47.3, 25.0, and 15.0 months for patients with Child Pugh A cirrhosis and BCLC stage A, B, and C HCC, respectively.[16] In multivariable analysis, vascular invasion was an independent negative prognostic factor (HR 0.47, 95%CI 0.39–0.56). Similarly, the prospective CIRT study recently demonstrated that the degree of vascular invasion was independently associated with overall survival after TARE, including 1.5 and 2.5-increased hazards of death with segmental and main portal vein invasion, respectively.[17] However, in the DOSISPHERE study, patients with portal vein tumor invasion achieved a median survival of 22.9 months with personalized dosimetry group, which was significantly higher than the 9·5-month survival observed with standard dosimetry (HR 0.39 [95 % CI 0·17–0·90][18]).

The potential role of TARE and SBRT for patients with advanced-stage HCC is perhaps best informed by several randomized controlled trials comparing these modalities to systemic therapy. The SARAH and SIRveNIB Trials both failed to find a significant difference in overall survival between TARE and sorafenib in patients with locally advanced HCC (HR 1.15, 95%CI 0.19–1.41, and HR 1.12, 95%CI 0.9–1.4, respectively), although TARE appeared to be better tolerated.[19,20] The SORAMIC Trial also failed to show a significant difference in overall survival between patients who received TARE plus sorafenib vs. sorafenib alone (HR 1.01, 95%CI 0.81–1.25).[21] Retrospective data are similarly promising for SBRT achieving local tumor control for patients with vascular invasion, although there is still a need for randomized data showing superiority over systemic therapy.[22] In a randomized controlled trial of SBRT plus sorafenib vs. sorafenib among 177 patients with large intrahepatic or locally advanced HCC, median survival was numerically higher in the SBRT arm although the difference failed to achieve statistical significance (15.8 vs. 12.3 months; $P$ = 0.055). As above, notable advances continue in both the systemic and locoregional arenas - objective responses with TARE are significantly increased with the use of personalized dosimetry, and immune checkpoint inhibitor combinations result in significantly higher objective responses and overall survival than sorafenib.[18,23,24] Therefore, continued data are needed to evaluate the comparative effectiveness of TARE or SBRT versus systemic therapy in patients with portal vein invasion, as well as potentially identify treatment response biomarkers to identify patients who may particularly benefit from one therapy over the other.[25]

One rationale to recommend combination locoregional therapy and systemic therapy in this patient population is the possibility of inducing a greater objective response prior to consideration of living donor liver transplantation. Soin and colleagues have demonstrated that selected patients with vascular invasion who are successfully downstaged using locoregional therapy (e.g., TARE or SBRT) and systemic therapy (e.g., sorafenib) can achieve disease-free survival rates of 77 % and 51 % at 3 and 5 years, respectively.[26] However, successful downstaging is achieved in only a fraction of patients and the chance of success is inversely proportional to tumor burden, including degree of vascular invasion. Further, the use of these therapies must be weighed against the risk of treatment-related adverse events, most notably the risk of liver dysfunction that could preclude eligibility for future therapies and negatively impact overall survival, as well as lower post-transplant survival compared to other indications.[27]

With all of this being considered, the INASL-BCLC staging system and treatment recommendations push the current paradigm of how we should view patients with BCLC stage C disease, although further refinement may be considered in the future. While the authors should be acknowledged in recognizing the important variations within BCLC stage C patients, all patients with vascular invasion remain in a single group instead of referencing the heterogeneity – in terms of tumor burden, liver dysfunction, tumor biology, and goals of care. Compared to patients with Vp1 or Vp2 involvement, those with Vp3 or Vp4 disease have higher risk of micrometastatic disease, lower chance of objective response, and higher risk of treatment toxicity. This is an area that needs to be further defined and clarified in terms of treatment options while specifically accounting for access to healthcare and availability of medical expertise in India.

## FUTURE OF HCC TREATMENT

The authors identify several factors associated with aggressive tumor biology, which reflects increasing data highlighting heterogeneity in HCC biology, including molecular subtypes as well as tumor growth patterns[28] – an area that is often ignored or mentioned superficially in other guidance statements. However, it is currently less clear how these factors should be routinely incorporated into clinical decision-making. Although AFP levels and histology have been incorporated into transplant eligibility consideration, other factors including liver disease etiology, comorbidities, and ancillary imaging features

(e.g., intracellular fat, restricted diffusion) are not routinely considered in treatment decisions. Similarly, there has been marked interest in prognostic and treatment response biomarkers to allow individualized decisions, particularly in situations where there is debate about two potential options.[25] These prognostic factors and biomarkers may also help identify those who would most benefit from combination therapies instead of traditional sequential approaches; however, risk-based treatment paradigms require further testing in controlled trials.

Overall, the INASL Puri III Recommendations incorporate several recent advances in HCC treatment and push the boundaries even further for emerging strategies in other areas; however, similar to BCLC staging, the INASL Puri III Recommendations only offer a starting point for treatment decisions. All treatment algorithm remains bound by arrows connecting a specific stage with treatment recommendations, which cannot fully capture the complexity of HCC treatments, highlighting the importance of being seen at high-volume centers that offer multidisciplinary care. Several studies have shown the association between patient volume and multidisciplinary care with improved clinical outcomes, including receipt of curative treatment and overall survival in patients with HCC.[29,30] Health systems in India should strive to deliver efficient multidisciplinary care for these complex patients; however, we recognize the heterogeneity in resources, access, and delivery of care that exist in a large diverse country such as India. In situations where evaluation in high-volume multidisciplinary settings is not possible, the INASL Puri III Recommendations help offer expert guidance for emerging management of patients with HCC.

Editorial

## CONFLICTS OF INTEREST

Amit Singal has served as a consultant or on advisory boards for Bayer, FujiFilm Medical Sciences, Exact Sciences, Universal Dx, Glycotest, Roche, Freenome, Delfi, GRAIL, Genentech, AstraZeneca, Eisai, Exelixis, Boston Scientific, HistoSonics.

Anjana Pillai serves on the medical advisory board for Exelixis, Genentech, Eisai, AstraZeneca and data safety monitoring board for Replimune.

Neehar Parikh has served as a consultant or on advisory boards for Bayer, FujiFilm Medical Sciences, Exact Sciences, and Freenome.

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**Amit G. Singal,**
Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, USA

**Anjana Pillai,**
Department of Internal Medicine, Division of Gastroenterology, Hepatology and Nutrition, University of Chicago, Chicago, IL, USA

**Neehar D. Parikh,**
Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI, USA

*Address for correspondence*: Amit G. Singal, M.D., M.S. Division of Digestive and Liver Diseases, University of Texas Southwestern, 5959 Harry Hines Blvd, POB 1, Suite 420, Dallas, TX, 75390-8887, USA. Tel.: +1 214 645 6029, fax: +1 214 645 6294.
*E-mail:* amit.singal@utsouthwestern.edu (A. G. Singal)