Intermediate-stage hepatocellular carcinoma: refining substaging or shifting paradigm?

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This review explores the evolution of cancer staging, focusing on intermediate hepatocellular carcinoma (HCC), and the challenges faced by physicians. The Barcelona Clinic Liver Cancer (BCLC) staging system, introduced in 1999, was designed to address the limitations associated with providing accurate prognostic information for HCC and allocating specific treatments, to avoid overtreatment. However, criticism has emerged, particularly regarding the intermediate stage of HCC (BCLC-B) and its heterogeneous patient population. To overcome this limitation, various subclassification systems, such as the Bolondi and Kinki criteria, have been proposed. These systems are aimed at refining categorizations within the intermediate stage and have demonstrated varying degrees of success in predicting outcomes through external validation. This study discusses the shift in treatment paradigms, emphasizing the need for a more personalized approach rather than strictly adhering to cancer stages, without dismissing the relevance of staging systems. It assesses the available treatment options for intermediate-stage HCC, highlighting the importance of considering surgical and nonsurgical options alongside transarterial chemoembolization for optimal outcomes. In conclusion, the text advocates for a paradigm shift in staging systems prioritizing treatment suitability over cancer stage. This reflects the evolving landscape of HCC management, where a multidisciplinary approach is crucial for tailoring treatments to individual patients, ultimately aiming to improve overall survival. (2024 Mar 12 [online ahead of print])

Keywords: Carcinoma, hepatocellular; Intermediate stage, staging system

INTRODUCTION

Cancer staging involves assessing the extent and location of cancer in the body. It aims to delineate the severity of an individual’s cancer by considering the size of the primary tumor and the extent to which the cancer has disseminated throughout the body.

Recognizing the imperative need for effective staging systems for patients affected by cancer has been long-standing. This urgency is rooted in the staging systems’ capacity to provide prognostic information to affected patients and doctors. Moreover, these systems have demonstrated their utility as valuable tools for improving the allocation of patients to diverse treatment modalities.

The TNM staging system is the most widely used tool to define different stages in oncology for a majority of cancer types. The first attempts to create the TNM staging system date back to the 1940s when Pierre Deloix embarked on the development of this classification. However, the formal first edition of the TNM was introduced only in 1968.¹

One would expect the TNM system to be the most utilized for staging hepatocellular carcinoma (HCC). However, in contrast to other types of cancer, HCC represents a unique challenge for treating physicians. Indeed, the prognosis and management of this neoplasm are heavily influenced by the presence of liver dysfunction caused by the underlying cirrhosis, a condition that is often
associated with HCC and represents a significant competitive risk of death.²

Currently, HCC is the third leading cause of cancer-related death worldwide.³ Furthermore, it ranks between the first and second most diagnosed cancers in certain Eastern countries, such as China and Japan. This prevalence is primarily attributed to the high incidence of hepatitis C virus in Japan and hepatitis B virus (HBV) infection in China, the latter being responsible for more than 50% of liver cancers.⁴

Accordingly, the TNM system exhibited a limited prognostic value, particularly for early-stage HCC treated with resection or liver transplantation.⁵,⁶ The Okuda classification⁷ was the first integrated staging system for HCC, taking into account both liver function and tumor burden, albeit with only a rough estimation of these parameters.

Staging systems for HCC, including variables related to tumor burden and the degree of liver function, were defined as integrated staging systems.

These considerations, along with a better understanding of the natural history of HCC, led to the development of the Barcelona Clinic Liver Cancer (BCLC) staging system in 1999.⁸ Notably, the BCLC not only aimed to establish a staging system but also devised a treatment strategy for each stage. According to the BCLC staging system and treatment algorithm, patients were categorized into very early (BCLC-0) and early stage (BCLC-A), deemed eligible for curative treatments, namely liver resection, transplantation, and percutaneous treatments. Patients with intermediate stage (BCLC-B) require trans-arterial procedures, those with an advanced stage (BCLC-C) require systemic therapy, and those with terminal stage (BCLC-D) receive supportive care if liver transplantation is deemed unsuitable, due to end-stage liver dysfunction (Child-Pugh C) or poor performance status.

Since its creation, the BCLC staging system has demonstrated good performance in different clinical settings and has undergone external validation on multiple occasions⁹,¹⁰ establishing itself as the most commonly used staging system for prognosis determination and treatment allocation in Western countries and probably worldwide.

Thanks to the valiant efforts of the authors, the BCLC staging system has been constantly updated following the emergence of evidence between its inception and the present.¹¹⁻¹⁵ These attributes have resulted in the endorsement of this staging section of the BCLC by various international societies, such as American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver, and European Organisation for Research and Treatment of Cancer.¹⁶,¹⁷

Despite its widespread adoption, the BCLC classification system has faced criticisms over the years. The primary concerns revolve around the inaccurate stratification of patients included in subclass BCLC-B and the perceived inflexibility in recommending specific treatments for every stage, particularly transarterial chemoembolization (TACE).

The BCLC-B subgroup comprises approximately 30% of the patients at the time of diagnosis, as indicated by large observational studies.¹⁸,¹⁹ This subgroup includes a heterogeneous population, encompassing patients with significant differences both in terms of tumor burden and liver function. Several studies reported that patients classified within the BCLC-B stage exhibit a diverse range of survival times, highlighting the existence of certain limitations. Therefore, alternative subclassification staging systems were proposed over the years to address these shortcomings.

PROPOSED SUBCLASSIFICATIONS OF THE BCLC-B STAGE

Bolondi et al.²⁰ were among the first to advocate in favor of a subclassification of the BCLC-B class. In a seminal paper published in 2012, an international panel of experts elaborated a subclassification of the BCLC stage B into four different classes (B1-B4), taking into account tumor burden, performance status (PS), and liver function.

The proposed thresholds for the subgroup of patients considered 1) the capacity of the liver functional reserve, and 2) the liver expected functional damage from the selected first-line treatment chosen accordingly to the degree of tumor burden. Consequently, this led to the proposal of not only one but possibly various different therapies for each substage, aligning with the strength of the available evidence. According to the authors, patients initially classified as BCLC stage B should be reclassified as stage B1 if they met the up-to-7 criteria,²⁰ a measure of tumor burden, with a Child-Pugh score between 5 and 7 and a PS stage of 0. Stage B2 included patients surpassing the up-to-7 criteria with a Child-Pugh class A (5 or 6) and a PS stage of 0, while stage B3 included the same patients but with a Child-Pugh score of 7. Lastly, stage B4 included patients exhibiting deteriorated liver function (Child-Pugh score 8 or 9) and/or experiencing a cancer-related compromise of the general conditions (Eastern Cooperative Oncology Group-PS 1).

The primary rationale behind this proposal for restaging was rooted in the wide variety of patients included in class B. The authors explicitly highlighted the fact that patients with varying probabilities of survival and distinct suitability for different treatments were being grouped together under the same class, following the treatment allocation indicated in the standard BCLC
scheme valid at that time.

This substaging system was externally validated on multiple occasions. In a retrospective analysis of 254 European BCLC-B patients, Weinnmann et al.21 demonstrated that the Bolondi staging system effectively distinguished patients with different probabilities of survival, yielding a median overall survival (OS) ranging from 31.9 months in the subgroup B1 to 10.9 months in the subgroup B4 (P=0.01). However, this study revealed that the substaging system failed to show differences between intermediate classes (B2 vs. B3 or B3 vs. B4), and it did not have a significant influence on prognosis in the multivariate analysis, probably due to the limited sample size and the confounding factors associated with different treatments received by the patients.21 Conversely, Giannini et al.22 demonstrated the effectiveness of the substaging system in all subgroups, maintaining statistical significance in the multivariate analysis in a well-characterized cohort of 269 patients from the Italica population. Notably, this study exclusively enrolled untreated patients, thereby eliminating the potential bias stemming from the varying treatments and eliminating any impact on survival outcomes.

Ha et al.23 validated this subclassification in a cohort of 466 Korean patients treated with standard TACE. The Bolondi criteria effectively discriminated among patients with different survival probabilities. In their population, subgroups B3 and B4 exhibited similarity, and the analysis of the same population after merging the B3 and B4 subgroups further improved the performance of this new subclassification.24

Finally, Wang et al.24 conducted an external validation of the Bolondi subclassification in a retrospective study involving 580 patients who underwent transarterial embolization (TAE) as the first HCC treatment. The four subclasses identified by Bolondi et al.20 distinctly identified patients with different overall survival rates. Interestingly, within the same study, the authors proposed a modified subclassification that incorporated the α-fetoprotein (AFP) level, categorized as over/under 200 ng/mL. This modified subclassification also effectively distinguished between different probabilities of survival, demonstrating a slight improvement in the discriminatory ability according to the Akaike information criteria.24

Following this approach, Kudo et al.25 proposed the Kinki criteria. This substaging system was quite similar to that proposed by Bolondi. However, the Kinki staging system included only three subclasses. the first (Kinki B1) and last (Kinki B3) were identical to the Bolondi stages B1 and B4, respectively, while the intermediate stage (Kinki B2) included the Bolondi B2 and B3 stages. Notably, the Kinki criteria were initially validated only by the same group who originally designed them. Arizumi et al.26 conducted a retrospective analysis of 425 BCLC-B patients who underwent TACE. In this study, the Kinki substaging system successfully stratified patients based on their probability of survival. However, a multivariate analysis was not performed. Unfortunately, no solid external validation of these criteria is available, except for the study published by Yamamoto et al.,27 where the Kinki criteria were effective only in a small subgroup of patients who underwent liver resection. However, significant differences were found in the baseline characteristics between patients in different Kinki subgroups, which weakened the results of this study.

Yamakado et al.28 analyzed 325 patients who received TAE as a first-line treatment. Based on the findings of multivariate analysis, which identified Child-Pugh class, size, and number of nodules (four or fewer tumor nodules and within 7 cm of the maximum tumor diameter) as the only independent risk factors, the authors defined a new staging system for intermediate-stage HCC, which was later endorsed by the Japanese Society of Transcatheter Hepatic Arterial Embolization. In this staging system, the patients were divided into four subclasses ranging from Ba to Bd. The first two classes (Ba and Bb) included patients with Child-Pugh class A, both within and beyond the size criteria. Conversely, the latter two subclasses (Bc and Bd) exhibited a similar size distribution but exclusively included patients with a Child-Pugh class B. Notably, only the patients with Ba subclass showed a significantly better survival compared with the other three subgroups.

Lee et al.29 analyzed a large cohort of patients (n=2,740) diagnosed with either intermediate-stage or advanced-stage HCC from two Korean databases. Patients with intermediate-stage HCC (34.3%; n=994) were subclassified according to tumor size and Child-Pugh class, excluding performance status due to its absence in this database. Three different subclasses were identified. B1 was characterized by the presence of a tumor measuring <5 cm in diameter. Patients with a tumor size of ≥5 cm and a Child-Pugh A were assigned to class B2, while those with a tumor size of ≥5 cm and a Child-Pugh B were assigned to class B3. The three subclasses achieved the median OS values of 30.73, 20.60, and 9.23 months, respectively (P<0.001).

More recently, Kim et al.30 proposed a modification of the Bolondi subclassification system using the up-to-11 criteria instead of the up-to-7 criteria for tumor burden definition. This decision stemmed from the analysis of 821 patients with intermediate-stage HCC treated with TACE. In this retrospective analysis, the Bolondi criteria demonstrated effective performance for B1 (51.5 months) vs. B2 (26.0 months) and B2 vs. B3 (14.8 months), with subgroup B4 exhibiting superior OS compared with

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subgroup B3.

Subsequently, they defined three subgroups (nB1, nB2, and nB3) using up to the up-to-11 criteria and Child-Pugh classes. The newly proposed staging system exhibited significantly improved performance, with the subgroup stage being independently associated with survival, showing adjusted hazard ratios of 2.04 for nB2 and 4.46 for nB3.30

Another approach was proposed by Kimura et al.,31 who analyzed 125 patients with newly diagnosed intermediate-stage HCC undergoing TACE. They categorized patients into three subgroups according to the up-to-7 criteria and a combination of serum levels of AFP (categorized at 100 ng/mL) and des-γ-carboxyprothrombin categorized at 150 mAU/mL.

In a recent study, Ielasi et al.32 demonstrated the prognostic capacity of the majority of these substaging systems for patients with intermediate-stage HCC who were candidates for systemic therapy due to multicentric collaboration. In this study, we retrospectively examined six of these staging systems in a cohort of 171 patients with intermediate-stage HCC who received sorafenib as a first-line systemic treatment. Results demonstrated that all subclassification systems showed a significant correlation with OS, except for the one proposed by Yamakado et al.28 Notably, according to this study, the Bolondi and Wang criteria exhibited superior accuracy compared with the other systems.32

Interestingly, when analyzing this subclassification system, a large majority of the data were derived from a retrospectively created dataset of treated patients, most frequently TACE. This introduces a risk of overfitting,33 a factor that is seldom estimated in many of these studies, thereby limiting the generalizability of these results. In fact, deriving a staging system from patients who receive

<table>
<thead>
<tr>
<th>Study</th>
<th>Subclasses</th>
<th>Function</th>
<th>Tumor burden</th>
<th>Performance status</th>
<th>Biomarkers</th>
<th>Extrapolated from a retrospectively treated population</th>
<th>External validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolondi et al.20 (2012)</td>
<td>B B2</td>
<td>CP 5-7</td>
<td>Up-to-7 in</td>
<td>0</td>
<td>NI</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>B3</td>
<td>CP 5 or 6</td>
<td>Up-to-7 out</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B4</td>
<td>CP 7</td>
<td>Up-to-7 out</td>
<td>0</td>
<td>0 or 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ha et al.21 (2014)</td>
<td>B B2</td>
<td>CP 5-7</td>
<td>Up-to-7 in</td>
<td>0</td>
<td>NI</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>B3</td>
<td>CP 7</td>
<td>Up-to-7 out</td>
<td>0</td>
<td>0 or 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al.24 (2015)</td>
<td>B B2</td>
<td>CP 5-7</td>
<td>Up-to-7 in</td>
<td>NI</td>
<td>AFP &lt;200</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>B3</td>
<td>CP 7</td>
<td>Up-to-7 out</td>
<td>0</td>
<td>AFP &gt;200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kudo et al.25 (2015)</td>
<td>B B2</td>
<td>CP 5-7</td>
<td>Up-to-7 in</td>
<td>NI</td>
<td>NI</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>B3</td>
<td>CP 8-9</td>
<td>Up-to-7 out</td>
<td>4-7 cm in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamakado et al.28 (2014)</td>
<td>B B2</td>
<td>CP A</td>
<td>4-7 cm in</td>
<td>4-7 cm in</td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>B3</td>
<td>CP B</td>
<td>4-7 cm out</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al.29 (2016)</td>
<td>B B2</td>
<td>CP any</td>
<td>Within 5 cm</td>
<td>NI</td>
<td>NI</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>B3</td>
<td>CP A</td>
<td>Beyond 5 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CP B</td>
<td>Beyond 5 cm</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Reig et al.12 (2017)</td>
<td>B B2</td>
<td>Ni</td>
<td>Up-to-7 in</td>
<td>NI</td>
<td>DCP &lt;150</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>B3</td>
<td>Ni</td>
<td>If not B1 or B3</td>
<td>Up-to-7 out</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kimura et al.31 (2017)</td>
<td>B B2</td>
<td>Ni</td>
<td>Suitable for LT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B3</td>
<td>Ni</td>
<td>Unsuitable for LT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HCC, hepatocellular carcinoma; BCLC-B, the Barcelona Clinic Liver Cancer class B; CP, Child-Pugh class; NI, not included; AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin; LT, liver transplantation; LRT, local regional therapy.
treatment might only select patients who benefit most from the treatment rather than provide prognostic information about the patients.

Table 1 summarizes the proposed sub-classification staging systems, which display validating evidence when available.

Finally, after several different proposals, the last BCLC update acknowledged the need for subgrouping the BCLC-B stages and endorsed a subclassification of the intermediate class for the first time.

In the recently updated BCLC algorithm, the intermediate class is subclassified into three different classes. Interestingly, the three subgroups within BCLC-B were defined mainly relying on the suitability of the patients to receive treatments rather than considering tumor burden or liver function upfront. In fact, they defined the first subgroup as comprising patients with HCC nodules falling within the extended liver transplant criteria; the second subgroup comprises patients with well-defined nodules, preserved portal flow, and selective (arteria) access but exceeding the transplantation criteria. The last subgroup includes patients with diffuse/infiltrative HCC, who are not expected to benefit from TACE.12

Although it is not difficult to assert the necessity of subgrouping the BCLC-B stage, it is significantly harder to choose between the from various proposed classifications based on the available data, as we have endeavored to present and discuss in the current manuscript. Some of these classifications emerge as particularly relevant. The Bolondi’s criteria stand out as a robust option, having undergone an external validation on multiple occasions and demonstrating prognostic informativeness even in untreated patients. Similarly, the staging system proposed by Wang et al.24 demonstrated optimal prognostic abilities, outperforming the Bolondi’s criteria in the original derivative retrospective study and in a subsequent study.24,32 Lastly, although not yet validated, the BCLC subgrouping also represents a reasonable choice given the flexibility it allows in determining the subgroups, despite the expectation that the substaging may still include a large and heterogeneous group, specifically those with well-defined nodules and preserved portal flow.

DIFFERENT AVAILABLE TREATMENT OPTIONS FOR INTERMEDIATE-STAGE HCC

In addition to providing prognostic information, another appealing characteristic of an effective staging system is the efficient and accurate allocation of patients to the most suitable treatments.

Until the most recent update, the BCLC algorithm offered only TACE as the recommended treatment option for intermediate-stage HCC or systemic therapy in cases of contraindications to TACE in well-compensated patients. However, numerous studies revealed a discrepancy between these recommendations and the actual clinical practice. In contrast to the recommendations, real-life patient treatments varied across different modalities, especially in tertiary centers, where up to 50% of the treatments deviated from the BCLC recommendations.24,35

Such a significant mismatch between recommendations and clinical practice was mainly determined by the heterogeneity of the BCLC-B class but supported by several studies. These studies demonstrated that selected patients with intermediate-stage HCC could benefit from different kinds of treatment, including surgery, either liver resection (LR) or liver transplantation (LT); percutaneous ablation; transarterial radioembolization (TARE); or systemic anticancer treatments,36 whereas the old BCLC recommendations only endorsed the latter as treatment stage migration in addition to TACE.

Table 2 shows the available evidence supporting various treatments in the BCLC-B class.

Liver resection demonstrated a survival benefit in patients with intermediate-stage HCC and well-preserved liver function (Child-Pugh A) in various articles. Most notably, Yin et al.37 published solid evidence from a randomized clinical trial involving 180

Table 2. Published evidence of studies evaluating different available treatments possibilities alternative to TACE across the BCLC-B class and their efficacy against TACE in selected patients with intermediate-stage HCC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study type</th>
<th>Survival benefit vs. TACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver transplantation</td>
<td>Retrospective evidence</td>
<td>Yes</td>
</tr>
<tr>
<td>Liver resection</td>
<td>Prospective and retrospective</td>
<td>Yes</td>
</tr>
<tr>
<td>LRT (RFA, MWA, PEI)</td>
<td>Retrospective evidence</td>
<td>Not tested</td>
</tr>
<tr>
<td>TARE</td>
<td>Prospective and retrospective</td>
<td>No</td>
</tr>
<tr>
<td>Systemic treatment</td>
<td>Ongoing prospective</td>
<td>Not available</td>
</tr>
</tbody>
</table>

TACE, transarterial chemoembolization; BCLC-B, the Barcelona Clinic Liver Cancer class B; HCC, hepatocellular carcinoma; LRT, local regional therapy; RFA, radiofrequency ablation; MWA, microwave ablation; PEI, percutaneous ethanol injection; TARE, transarterial radioembolization.
patients with multinodular HCC outside the Milan criteria but without evidence of extrahepatic disease or vascular invasion. The patients were randomized to receive either TACE, as recommended by the BCLC algorithm, or LR. The primary outcome was OS, the group of patients who underwent LR had a significantly prolonged OS with a 3-year OS rate of 51.5% compared with the 18.1% OS rate in the TACE group. Remarkably, the type of treatment received was independently associated with OS, favoring patients who underwent LR over those who underwent TACE, with a hazard ratio of 0.43.37

Similarly, Pecorelli et al.38 analyzed 485 consecutive patients diagnosed with intermediate-stage HCC who were treatment naive. The 145 patients who were exposed to curative treatments including LR, radiofrequency ablation, and ethanol injection achieved a median OS of 45 months (95% confidence interval [CI], 38.0-59.1), while patients who received TACE only achieved a median OS of 30 months (95% CI, 24.7-35.3). Notably, the survival benefit persisted even after correcting for baseline clinical characteristics using propensity score analysis.38

Several other retrospective studies conducted mainly in Chinese cohorts also proved the benefit of liver resection over TACE in selected patients with intermediate-stage HCC.39-43

Conversely, only two studies reported no difference between these treatments; Ciria et al.44 showed no significant difference in the overall survival between patients with intermediate-stage HCC treated with LR and those treated with TACE in a cohort of 80 patients from Spain. Notably, the survival benefit was more pronounced in the B1-B2 subgroups, according to the Bolondi criteria. Similarly, Luo et al.45 showed no statistical difference in the 1-, 3-, and 5-year OS rates between patients with intermediate-stage HCC treated with LR or TACE only.

Additionally, LT represents a valuable surgical option for selected patients with intermediate-stage HCC, as shown in several studies reporting favorable outcomes in terms of survival and recurrence rates.46 Tsai et al.47 observed a longer OS in BCLC-B patients treated with living donor LT compared with BCLC-B patients not allocated to LT. They delineated how a combination of age, neutrophil to lymphocyte ratio and locoregional treatments before LT were able to stratify the risk of HCC recurrence and mortality in LT patients. However, their data resulted from a retrospective analysis, and LT patients were compared with a population subjected to heterogeneous treatments, including both curative treatments, like radiofrequency ablation (RFA), and palliative treatments, like TACE and systemic therapies.47

In contrast to surgical options, the evidence supporting curative ablative techniques is far less clear. The majority of available evidence supporting ablation is primarily extrapolated from studies that encompass different treatments, such as those by Pecorelli et al.38 and other similar studies.48,49 Notably, the number of patients treated using ablative techniques is limited. Moreover, in these studies, the survival benefit of ablative techniques has never been formally compared against TACE. Therefore, it is not possible to suggest a potential benefit of percutaneous ablation over TACE, given the robust data supporting the use of TACE in patients with intermediate-stage HCC.50,51

TARE is another treatment option commonly used in clinical practice for patients with BCLC-B. After an initial excitement when TARE was thought as the new loco-regional technique suitable for all intermediate HCC and for advanced HCC due to limited portal vein invasion, some shortcomings of this treatment emerged when it failed to demonstrate a survival benefit against TACE in the phase II PREMIERE trial.52 No subsequent prospective study has demonstrated an OS benefit compared with TACE. Despite this limitation, TARE still has a role in clinical practice. Currently, BCLC recommends TARE for unresectable early-stage HCC of less than 8 cm based on the results of the LEGACY trial,53 and it can be considered for intermediate-stage HCC. Interestingly, according to the AASLD, head-to-head comparisons between TARE and TACE have to be addressed in future studies to clarify whether there is a first-line option or if decisions should be made on a patient-by-patient basis. Furthermore, TARE represents an interesting option for downstaging and bridging, particularly considering the prospective evidence showing that TARE achieves a longer time to progression than TACE.54

Lastly, systemic therapy becomes the only viable option in some cases of intermediate-stage HCC. It is usually reserved for patients who are not expected to benefit from TACE despite being within the intermediate class, particularly those with diffuse multinodular liver involvement or an unacceptable tumor burden deemed unsuitable for safe treatment with intra-arterial approaches. With the improvement in the effectiveness of systemic treatments,55 ongoing trials56 are investigating whether, in selected cases of intermediate-stage HCC with a high tumor burden, systemic therapy as a first-line option might be more advantageous than TACE, even when TACE is technically feasible. Notably, situations where both TACE and systemic treatment can be considered viable options must also be considered in the results of the EMERALD-1 study. This was a prospective phase III study that demonstrated a time-limited improvement in progression-free survival in patients who received durvalumab plus bevacizumab as an adjuvant regimen after TACE compared with those treated with placebo or single durvalumab; however, it failed to show an OS benefit according to
the highly immature available data. This outcome introduces additional considerations to the complex landscape of intermediate-stage HCC.

To conclude, the decision to select TACE as the first-line treatment for intermediate-stage HCC is often correct; however, this choice is particularly committing because TACE implies a significant risk of delivering non-radical treatment. Therefore, the exclusion of surgical options must be very well pondered.

Comprehensibly, there could be some hesitance to propose aggressive treatments for patients who are suboptimal candidates for some of these treatments, despite no discount on the incidence of adverse events, fearing that these treatments would be less effective than in ideal candidates.

In this scenario, a clear distinction must be made between the two surgical options, LT and LR. With regard to LT, we must surely take into consideration the limited availability of grafts, which suggests adjunctive caution if we fear a reduced survival benefit compared with ideal candidates. Conversely, although LR might be slightly less beneficial for suboptimal candidates than for optimal ones (e.g., very early-stage HCC), it can nonetheless represent the best option in terms of survival probability for the patients involved, with very few downsides except for the risk of post-surgical liver failure, which should be adequately assessed with a careful evaluation of the expectedly remaining liver function.

In conclusion, despite its effectiveness, TACE cannot be considered as the only first-line treatment option for intermediate-stage HCC. This decision was already questionable when no effective strategy was available to reduce tumor burden at the time of diagnosis; however, it is becoming even more outdated after the advent of intriguing strategies to downstage patients, such as with TARE or new systemic anticancer treatment, namely, immune checkpoint inhibitors, which among their numerous benefits also showed promising activity as a neoadjuvant tool to downstage the cancer, potentially ensuing curative treatments for patients with HCC.

A PARADIGM SHIFT IN STAGING SYSTEMS

Two recent publications have shown that the prognosis of patients with HCC was independently associated with the treatment received, irrespective of the initial BCLC stage of the disease. In other words, the authors identified a hierarchical order of the different treatments for HCC, which ranged in order of survival benefit from liver transplantation to the best supportive care.

Interestingly, the study by Vitale et al. was able to provide a hazard ratio of the survival benefit of every single treatment measured against best supportive care in a large cohort of 4,867 patients, which ranged from 0.19 for liver transplantation to 0.92 for systemic treatment (only sorafenib at the time of the analysis).

These considerations led the Italian multi-society guidelines to endorse the concept of a therapeutic hierarchy approach, in which the pivotal aspect to consider when deciding which treatment to allocate is the suitability of an HCC patient to receive a certain kind of treatment rather than the patient's staging class.

A similar approach was already recommended by Asia-Pacific, Korean and Japanese guidelines. However, the shift in recommendations endorsed by Western scientific societies is particularly relevant. In fact, various causes, including the high prevalence of HBV infection in Asia, have historically caused a tendency to be more aggressive in terms of treatments in Eastern countries since HCC developing from HBV is less frequently associated with cirrhosis and usually develops at a younger age, leading clinicians toward more radical treatments, such as surgery or ablation.

With these premises, the shift in Western guidelines toward a treatment-oriented decision algorithm rather than a cancer-stage-oriented algorithm is a relevant novelty and makes the various proposed substaging systems for intermediate-stage HCC outdated.

This approach is linked to multidisciplinary competence. A tailored approach to guarantee the most effective individual treatment is only possible if patients are managed together by multiple experts. Indeed, a hepatologist will not be able to determine whether a patient is a suitable candidate for surgery. Similarly, an expert interventional radiologist is required to determine the best approach for intra-arterial treatment. Likewise, it is necessary to include a hepatologist in the team because the increased tendency and willingness to undergo radical and invasive treatments require an even more accurate assessment of liver function, whose role remains central in the management of HCC.

Interestingly, the survival benefit of a multidisciplinary approach has been demonstrated in several studies, including a meta-analysis involving more than 15,000 patients, leading to different guidelines for recommending this approach.

It must be emphasized that despite being considered a rigid algorithm, the BCLC includes the concept of treatment stage migration, which allows more flexibility in treatment allocation. Furthermore, despite being a cancer stage-oriented algorithm, the recent subclassification of the intermediate stage is heavily influenced by the patient's suitability for liver transplantation, demonstrating some analogies and influences from the treatment hierarchy concept.

http://e-jlc.org
CONCLUSION AND FUTURE DIRECTIONS

A valuable staging system should aim to furnish prognostic information as a primary objective, with subsequent consideration for enhancing treatment allocation. Indeed, the inclusion of prognostic information is essential. Without precise data on patient prognosis, the comparison of survival benefits across various treatments and the design of informative clinical trials would be challenging.

Although it remains imperative to design and refine an effective form of cancer stratification with utmost precision, as in every other cancer entity, the patient-oriented paradigm focused on the possibility of allocating any given patient to the most effective available treatment rather than the cancer stage seems more inclined to warrant the best treatment option for our patients and ultimately to improve their survival.

This aspect is particularly significant in patients with intermediate-stage HCC, where the possible treatment options range from liver transplantation to systemic treatment depending on the patient and tumor characteristics.

Recent guidelines adopted by several Eastern and Western scientific societies have accepted this new paradigm.

Although some aspects are still not fully embraced by other algorithms or guidelines, real-world clinical practice has already progressed toward these concepts in the majority of cases, lowering the centrality of pure staging systems in the management of patients with HCC and increasing the focus on tailored HCC treatment.

Conflict of Interest

Fabio Piscaglia has received honoraria in the past 2 years from AstraZeneca, Bayer, Bracco, Esaote, Eisai, Exact Sciences, GE, Ipsen, MSD, Roche, Samsung, and Siemens Healthineers for attending advisory boards, speaker bureaus and consultancies. All the other authors have no conflict to declare.

Ethics Statement

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