




Critical Analysis of the Updated Barcelona Clinic Liver Cancer (BCLC) Group Guidelines

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Following the 2018 Barcelona Clinic Liver Cancer (BCLC) guidelines, the BCLC group has provided a 2022 update on the staging, prognosis, and treatment guidelines for hepatocellular carcinoma (HCC), which are used to guide clinical decision making for HCC worldwide.¹ The BCLC classification includes information related to the extent of disease, liver function, and patient performance status to define the disease stage.¹ We provide insight into the updated BCLC 2022 guidelines and potential areas for improvement.

MAIN UPDATES OF THE 2022 BCLC GUIDELINES

The recent 2022 BCLC guidelines have been updated to further refine intermediate-stage HCC (BCLC-B) and first- and second-line systemic therapy for patients with advanced-stage HCC (BCLC-C), as well as introduce the concept of treatment stage migration (TSM).¹ In particular, the 2022 BCLC edition stratifies BCLC-B into three groups of patients according to tumor burden and liver function. The first subgroup corresponds to patients who are candidates for liver transplantation (LT) if the patient meets the local extended LT criteria based on size and/or alpha-fetoprotein (AFP). The second subgroup comprises patients without an option for LT, but who had preserved portal flow and well-defined nodules allowing selective access to feeding tumor arteries. In turn, these patients are candidates

for transarterial chemoembolization (TACE). The third subgroup include patients with diffuse, infiltrative, and extensive bilobar liver involvement who are recommended to receive systemic therapy. Of note, compared with the 2018 version of the BCLC guidelines in which LT was only recommended for patients with multifocal HCC that were all < 3 cm, there are additional indications for LT in the latest 2022 version. Specifically, the new guidelines include a subgroup of BCLC-B patients with multifocal HCC who might be eligible for transplantation in case of successful downstaging by TACE.

In addition, the combination of atezolizumab with bevacizumab (atezo-bev) is currently considered as first-line treatment for patients with BCLC-C stage HCC. On the basis of recent data from the Imbrave150 clinical trial, atezo-bev has a demonstrated survival benefit compared with sorafenib, the previous standard first-line treatment over the past decade.² The combination of tremelimumab and durvalumab was also demonstrated to be superior to sorafenib—adding another first-line treatment option for patients with BCLC-C HCC.³ Second-line therapy for BCLC-C patients includes regorafenib (for individuals tolerant to sorafenib), cabozantinib (irrespective of tolerance to sorafenib) or ramucirumab (if AFP level is > 400 ng/dl, irrespective of tolerance to sorafenib).¹ Since transition to second-line treatment after sorafenib was traditionally the standard of care, future studies will need to refine systemic treatment guidelines as new data emerge with atezo-bev as the preferred first-line approach over sorafenib for BCLC-C individuals.

In the updated algorithm, the BCLC groupings have further highlighted the value of clinical decision making by introducing the concept of treatment stage migration (TSM) (i.e., treatment recommendations that would usually be considered for a more advanced stage). TSM is applied

on the basis of clinical judgement when first-line treatment based on a particular stage is not feasible owing to the patient's profile; in turn, treatment for a more advanced stage is therefore offered.^{4,5} In addition, the concept of untreatable progression has been introduced into the new BCLC guidelines. Untreatable progression is defined as treatment failure or progression after stage-appropriate treatment that necessitates consideration of more advanced-stage therapy despite a patient still fitting into an initial BCLC stage. Although TSM/untreatable progression have been long noted in real-life clinical practice, these concepts have only now been introduced into the latest BCLC guidelines. In turn, these concepts highlight the need ultimately to personalize treatment decision making after carefully evaluating each patient and the specific disease characteristics in a multidisciplinary setting. In particular, rather than blindly following an algorithm that establishes an initial general approach to treatment, the new guidelines provide more bandwidth to tailor HCC care.

As a result, the new BCLC algorithm appears much more complex than the previous version. In brief, patients with BCLC-0 HCC are generally recommended to undergo ablation as the preferred option; alternatives include resection or transplantation. Among patients with single BCLC-A HCC, resection is favored over ablation owing to lower recurrence especially treating tumors > 2 cm. In general, resection and ablation have been demonstrated to provide comparable long-term outcomes among individuals with HCC ≤ 2 cm. Among individuals with multifocal BCLC-A HCC (three or more nodules, each ≤ 3 cm), the 2022 BCLC updated guidelines do not recommend resection; rather, these patients are recommended to undergo ablation for non-LT candidates, while LT is suggested for acceptable LT candidates. Among BCLC-B HCC patients, transplant may be considered for patients meeting extended LT criteria or individuals beyond transplant criteria following successful downstaging with transarterial chemoembolization (TACE). TACE is recommended for individuals with well-defined nodules, preserved portal flow, and selective access to tumor feeding arteries; in contrast, systemic therapy is recommended for patients with diffuse or extensive bilobar liver involvement. In addition, systemic therapy is recommended for patients with BCLC-C HCC, whereas palliative or best supportive care should be considered for individuals with BCLC-D HCC (Fig. 1).

POTENTIAL AREAS OF IMPROVEMENT

While these changes in the latest BCLC guidelines represent an incremental improvement, there are potential areas that would benefit from further refinement. In

particular, the role of surgery, as well as the potential role of external beam radiotherapy warrant additional consideration in the BCLC treatment algorithm. Specifically, the 2022 BCLC guidelines updated the role of surgery in the treatment of HCC by including a role for LT in BCLC-B HCC beyond extended LT criteria after successful downstaging with TACE. Surgical resection is still recommended, however, only for BCLC-0 or single BCLC-A HCC. Substantial evidence exists to support the role of surgical resection among patients with multinodular HCC, especially BCLC-A tumors (three or more nodules, each ≤ 3 cm).⁴⁻⁶ In fact, the only randomized clinical trial to date comparing resection versus TACE demonstrated a survival benefit associated with resection even among patients with resectable multinodular HCC beyond Milan criteria (i.e., BCLC-B HCC).⁷ The role of performance status (PS) relative to HCC surgical treatment recommendations was also not revised in the latest version of the BCLC staging system.⁸ In particular, individuals with a PS 1-2 are still categorized as BCLC-C stage (i.e., advanced stage of HCC). In turn, this PS precludes patients from surgical consideration. Of note, the new 2022 guidelines refer to PS also relative to tumor-related symptoms and not simply baseline PS. At least one study noted that PS 1 is not necessarily an absolute contraindication for resection of HCC in real-world clinical practice.⁹

While the new BCLC guidelines categorize vascular invasion as advanced HCC stage, the role of biliary duct invasion in staging and treatment of HCC is not well defined. The prognosis of patients with biliary may mirror that of individuals with vascular invasion—being poor irrespective of treatment.¹⁰ As HCC invades the bile ducts to form a bile duct tumor thrombus, traditional tools such as the Child-Pugh grade or the albumin-bilirubin score may not be reliable in assessing liver function. The optimal treatment approach in the setting of bile duct invasion remains controversial and has not been addressed in the latest version of BCLC guidelines.

The 2022 updated guidelines also did not include any consideration of external beam radiotherapy (EBRT) in the revised treatment algorithm. Several recent trials have suggested, however, a role for EBRT among individuals with advanced-stage HCC.¹¹⁻¹³ A recent phase III RCT demonstrated superior outcomes with the combination of TACE and EBRT compared with sorafenib alone among patients with HCC with macrovascular invasion (i.e., BCLC-C HCC).¹² As such, the role of EBRT should be addressed as a potential expanded treatment option; in particular, EBRT relative to TSM warrants further elaboration in future refinements of the BCLC guidelines.

In summary, the new guidelines have incorporated several improvements based on recent HCC treatment data. The multidirectional treatment allocation and TSM make

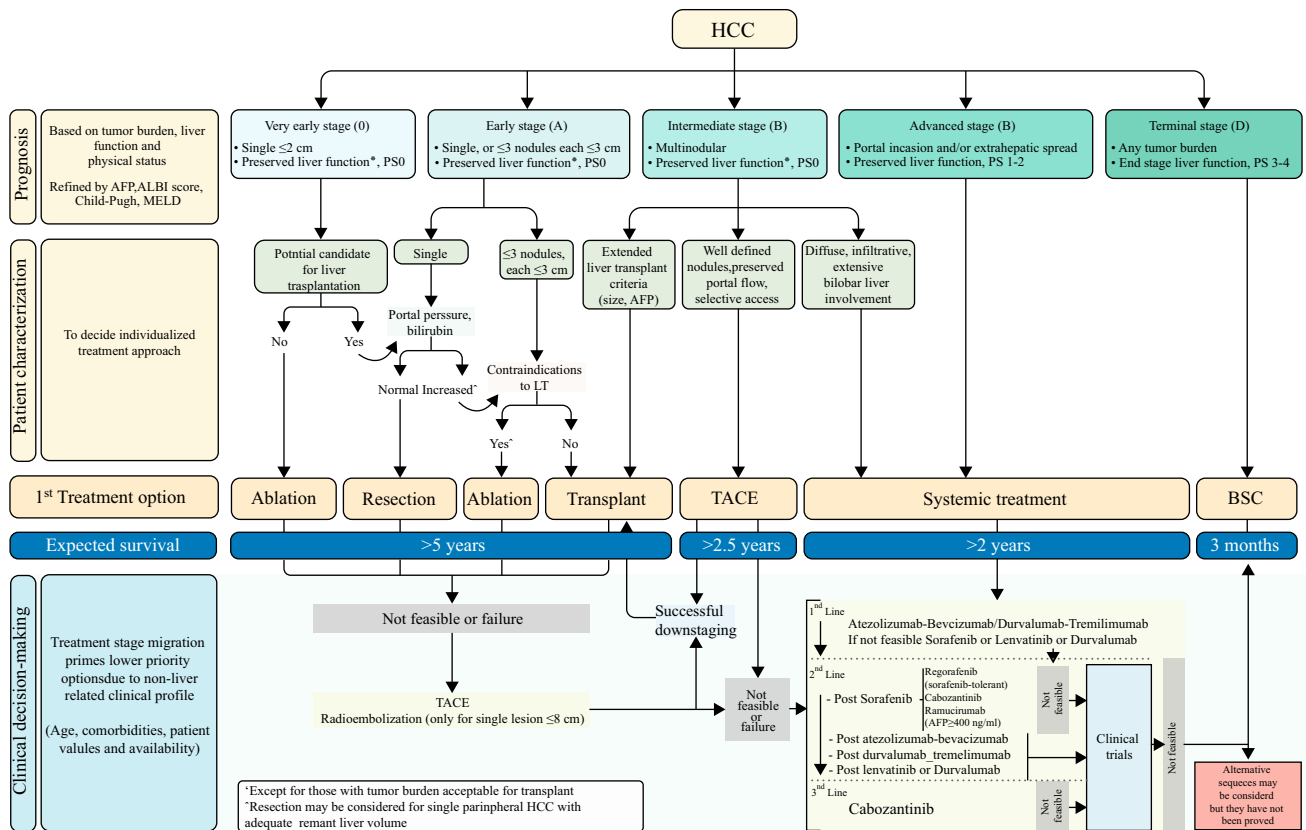


FIG. 1. BCLC guidelines version 2022

the algorithm more complex and nuanced, reflecting everyday clinical practice more closely. Future refinements will need to address the role of surgical resection, as well as incorporate the potential role of other locoregional therapies.

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