

with end-stage liver function. Moreover, even patients with decompensation are heterogeneous depending on the quantification of their decompensation, viz patients with minimal HE or mild ascites have a better prognosis than those with overt HE or tense ascites.<sup>7</sup> Hence, the use of a dichotomous classification might not serve the purpose of stage allocation and be subject to misinterpretation and consequent misclassification of patients. We do agree with the authors that treatment decisions for patients with HCC are often complex and should take into account multiple dimensions and not just a single variable, but the appeal of such staging systems lies in their unambiguity, so that they are not open to more than one interpretation.<sup>1</sup>

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### Supplementary data

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## BCLC 2022 update: Important advances, but missing external beam radiotherapy

To the Editor:

Congratulations to the Barcelona Clinic Liver Cancer (BCLC) group on the 2022 update of the staging, prognosis and treatment guidelines for hepatocellular carcinoma (HCC), which are commonly cited to guide clinical decision-making for HCC worldwide.<sup>1</sup> This update of the 2018 guidelines incorporates recent, practice changing trials of systemic therapies in patients with advanced HCC (BCLC C). The BCLC group has incorporated clinical decision making when the “first treatment option” is not feasible or if there is progression, which the group refers to as “treatment stage migration” (TSM). In this context, transarterial radioembolization (TARE)

has been incorporated as an option for select patients with BCLC 0-A HCC on the basis of a recent retrospective study.<sup>2</sup> We agree with the emphasis on a multi-disciplinary approach to HCC, which includes input from hepatology, surgery, radiology, medical oncology, interventional radiology and radiation oncology.

It is notable that the 2022 updated guidelines do not include external beam radiotherapy (EBRT) as a treatment option in the algorithms for HCC, which is surprising in the context of expanded treatment options that are commonly used when considering “TSM.” In addition to numerous retrospective studies, multiple prospective studies from multiple continents have demonstrated the safety and efficacy of EBRT, including stereotactic body radiotherapy and proton beam therapy (PBT), for all BCLC stages. A few important randomized controlled trials (RCTs) have been published since the 2018 BCLC update. For

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patients with recurrent BCLC A-B HCC, a phase III non-inferiority RCT comparing PBT vs. radiofrequency ablation (RFA) demonstrated that PBT was associated with lower risk of severe toxicity and liver decompensation, and similar local progression-free survival and survival (4 year survival ~75%).<sup>3</sup> For patients with HCC with macrovascular invasion, a phase III RCT demonstrated superior survival with transarterial chemoembolization + EBRT compared to sorafenib alone.<sup>4</sup> For patients with macrovascular invasion amenable to surgical resection, a phase III RCT demonstrated superior survival with pre-operative EBRT compared to resection alone.<sup>5</sup> Results of these phase III RCTs confirm findings from non-randomized studies.

The American Society for Radiation Oncology (ASTRO) recently published evidence-based practice guidelines for the use of EBRT for primary liver cancers.<sup>6</sup> The guidelines were developed by a multidisciplinary task force with representatives and peer reviewers from the American Society of Clinical Oncology (ASCO), American Society of Transplant Surgeons (ASTS), and the Society of Surgical Oncology (SSO). The guidelines have been endorsed by the European Society for Therapeutic Radiation Oncology (ESTRO), ASTS, and SSO. The guidelines are based on systematic review of published evidence, with consensus recommendations created using a modified Delphi approach. Based on a moderate or low quality of evidence, a strong recommendation was made for the use of EBRT as a potential first-line treatment option in patients with liver-confined HCC who are not candidates for surgery or ablation, as consolidative therapy after incomplete response to other liver-directed therapies, and as a salvage option for local recurrence. Based on a moderate or low quality of evidence, a conditional recommendation was made for the use of EBRT sequenced with systemic or catheter-based therapies for patients with multifocal or unresectable HCC or those with macrovascular invasion. Based on a low or moderate quality of evidence, a conditional recommendation was made for the use of EBRT as a bridge to transplant or prior to surgery in carefully selected patients with macrovascular invasion. Based on a low level of evidence, a conditional recommendation was made for palliative EBRT of symptomatic HCC.

Recent clinical practice guidelines from major groups worldwide including National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO),<sup>7</sup> American Association for the Study of Liver Diseases (AASLD),<sup>8</sup> and Asia Pacific Association for the Study of the Liver (APASL)<sup>9</sup> include EBRT as a treatment option for select patients with HCC, while also acknowledging the need for more data. For example, current NCCN guidelines include ablation, embolization, and EBRT as appropriate non-surgical treatment options for patients with liver-confined HCC.<sup>10</sup>

In our opinion, the current available evidence supports the incorporation of EBRT into BCLC guidelines, especially when “first treatment options” are not feasible or suitable, or if there is progression after first treatment. For future updates of the BCLC guidelines, we propose inclusion of EBRT as per recommendations of the ASTRO Guidelines: 1) for patients with BCLC 0-A HCC, EBRT should be considered as an alternative non-surgical treatment (along with ablation or embolization), either as definitive therapy or as a bridge to transplant; 2) for patients with BCLC B-C, EBRT is a treatment option with or without embolization or systemic therapy; 3) for patients with BCLC D

HCC, EBRT should be considered as a palliative treatment for tumor-related pain. We acknowledge the importance of current and future RCTs for all therapies in refining HCC treatment strategies, and we strongly support further RCTs of EBRT for HCC.

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## The updated BCLC staging system needs further refinement: A surgeon's perspective

To the Editor:

We read with great interest the recent update to the Barcelona Clinic Liver Cancer (BCLC) staging system,<sup>1</sup> which needed updating based on the remarkable high-level evidence on hepatocellular carcinoma (HCC) management that has been generated in recent years. The main updated contents included updating the recommended first- and second-line systemic drugs for advanced stage HCC (BCLC stage C), and refining intermediate stage HCC (BCLC stage B).<sup>1</sup> To our knowledge, it is the fifth “major” update since the BCLC staging system was first introduced in 1999 by 3 well-known hepatologists.<sup>2</sup> We, hepatic surgeons, appreciate the continuous efforts to improve the BCLC staging system, but we believe that this updated BCLC staging system is still not entirely satisfactory, and we have the following comments:

First, the role that performance status (PS), as defined by the Eastern Cooperative Oncology Group (ECOG), plays in HCC staging and treatment recommendations has not been revised in any updated edition of the BCLC staging system.<sup>3</sup> Specifically, the BCLC staging still considers patients with a PS score of 1–2 to be at an advanced-stage of HCC and that this PS score contraindicates hepatic resection. However, in real-world clinical practice, PS, especially PS 1, is often not used as an absolute contraindication to HCC resection.<sup>4</sup> Furthermore, even some patients with PS 3–4, such as selected patients with ruptured HCC and hemorrhagic shock, can have favorable long-term survival after emergency or staged HCC resection.<sup>5</sup> As assessment of PS for patients with HCC is subjective, and it is often difficult to decide whether the patients' symptoms at diagnosis of HCC are caused by the tumors or the underlying chronic liver diseases,<sup>3</sup> we agree with the recent comment made by Marrero JA *et al.*, “the PS for BCLC stages 0, A, and B has been changed to 0–1 to better reflect clinical practice, given the significant overlap that exists between PS 0 and PS 1 and the potential bias of patient-reported and physician-reported PS.”<sup>6</sup> Therefore, we suggest

that the latest updated version of the BCLC staging system should be adjusted to reflect this.

Second, although the BCLC constitutors tried very hard to take into consideration every possible situation, some patients with HCC have complicated clinical presentations. For example, the BCLC staging system considers portal vein invasion to be representative of an advanced HCC stage, but it never mentions biliary invasion<sup>7</sup> or hepatic vein invasion,<sup>8</sup> both of which are specific but not uncommon presentations of HCC. Previous studies showed that the prognosis of patients with biliary invasion or hepatic vein invasion is as poor as in those with portal vein invasion despite treatment. We wonder whether biliary invasion and hepatic vein invasion should also be included into the BCLC staging system. In our opinion, these special but not unusual presentations of HCC should be supplemented to fill up these blind spots in the updated BCLC staging system. As HCC invades into bile ducts to form a bile duct tumor thrombus, obstructive jaundice becomes a significant clinical manifestation of HCC, as such, neither Child-Pugh grade nor ALBI score are suitable for assessing a patients' liver function. Management of these patients requires methods to relieve jaundice such as percutaneous transhepatic cholangial drainage, and/or surgical resection with concomitant thrombectomy or hepaticojejunostomy.<sup>7</sup>

Admittedly, controversies exist among hepatologists, physicians and surgeons, as well as between clinicians in the East and the West regarding HCC management. However, as a Chinese proverb goes, “seeking common ground while reserving differences”, we, hepatic surgeons, sincerely hope that hepatologists and physicians can listen to the voices of hepatic surgeons and attach more importance to the evidence obtained from real-world clinical practice, as the common goal of all clinicians is to maximize survival benefit for patients with HCC.<sup>9,10</sup> By so doing, the upgraded version of the BCLC staging system can win support from surgeons all around the world. We hope to further discuss this with our peers and colleagues around the world, with the aim of making the BCLC staging system more applicable to clinical practice in the future.

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