

## CORRESPONDENCE

# Heterogeneity of intermediate-stage HCC necessitates personalized management including surgery

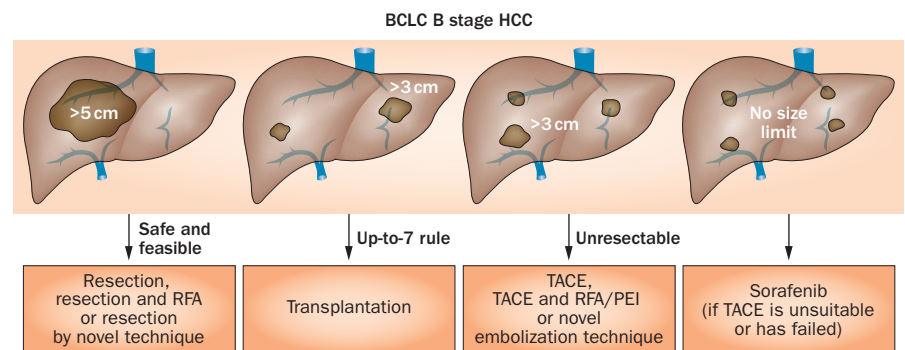
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We read with interest the Review by Forner and colleagues ([Treatment of intermediate-stage hepatocellular carcinoma](#) *Nat. Rev. Clin. Oncol.* **11**, 525–535; 2014),<sup>1</sup> which focused on recent advances in the stratification of and treatment allocation for patients with intermediate-stage hepatocellular carcinoma (HCC), that is, Barcelona Clinic Liver Cancer (BCLC) stage B disease. We agree with the authors that the patient population with intermediate-stage HCC is highly heterogeneous with regard to tumour burden, liver function, and clinical characteristics. However, according to Forner *et al.*,<sup>1</sup> transarterial chemoembolization (TACE) and sorafenib should be the only standard treatments for intermediate-stage HCC. We disagree with this stance, as studies in both Eastern and Western countries have indicated that hepatic resection is safe and results in longer survival in selected patients with intermediate-stage HCC as compared with TACE and/or sorafenib therapy.<sup>2,3</sup>

The current definition of intermediate-stage (BCLC B) HCC is extensive multifocal disease without vascular invasion or extrahepatic spread in patients with preserved liver function and no cancer-related symptoms (Figure 1). The BCLC staging system is endorsed by the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL) and the European Organisation for Research and Treatment of Cancer (EORTC), and therefore, these organizations do not advocate hepatic resection in patients with BCLC B stage HCC.<sup>4,5</sup> However, the BCLC treatment recommendations are based on findings in populations of patients with intermediate-stage HCC as a whole and, therefore, do not provide guidance as to which modality will yield the best results in individual patients. As such, deviations from the guidelines are highly frequent in clinical practice. A survey of 21 studies published in English

since January 2000, involving a total of 4,945 patients with HCC who underwent liver resection for multinodular disease (that is, BCLC B stage disease), reported a median overall survival of 41 months and a 5-year survival rate of 30%, outcomes apparently better than those observed after TACE in similar patient cohorts.<sup>6</sup> Despite the fact that the retrospective nature of the studies included might have resulted in an unintentional selection bias, this survey does provide informative data. Considering the heterogeneity within the intermediate-stage HCC patient population and the utility of hepatic resection in treating selected patients within this group, several guidelines for the management of HCC, including those by the Asian Pacific Association for the Study of the Liver

(APASL), the Japan Society of Hepatology (JSH), American Hepato-Pancreato-Biliary Association (AHPBA), and National Comprehensive Cancer Network (NCCN), definitively state that tumour multifocality is not a contraindication to hepatic resection.<sup>7–9</sup> Notably, the first randomized controlled trial to investigate whether resection or TACE yields better outcomes in patients with BCLC B stage HCC clearly indicated superiority of resection over TACE.<sup>10</sup> This well-designed study demonstrated a median survival duration of 41 months for patients treated with hepatic resection, much longer than the 14 months observed among those patients who underwent TACE.<sup>10</sup> Multivariate analysis showed that the type of treatment used was independently correlated with survival, with a



**Figure 1** | Treatment allocation for BCLC B stage HCC. The BCLC B classification comprises a heterogeneous group of patients with Child–Pugh class A or class B liver function and large and/or multifocal HCC (defined as more than three tumours regardless of size, two to three tumours >3 cm in maximal diameter, or one single unresectable tumour >5 cm), and without cancer-related symptoms, macrovascular invasion, or extrahepatic spread. Liver resection is the priority treatment, if resection is feasible and safe, although RFA (or another ablation technique) can sometimes be a viable alternative. Transplantation can be associated with optimal survival in patients whose tumour burden meets the ‘up-to-7’ rule. The up-to-7 rule proposes that transplantation should be considered only if the sum of the size of the largest tumour in centimeters and the total number of tumours is less than or equal to seven; for example, patients with one tumour of up to a maximum size of 6 cm ( $6 + 1 = 7$ ), two tumours up to a maximum size of 5 cm ( $5 + 2 = 7$ ), three tumours up to a maximum size of 4 cm ( $4 + 3 = 7$ ), and so on, meet this criteria. TACE or related treatment modalities are only recommended for those with unresectable tumour(s); if TACE is not feasible or has failed, sorafenib is the alternative choice. Indeed, any of these treatment approaches can be used in BCLC B stage HCC, when appropriate. Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

2.3-fold greater likelihood of mortality in the TACE cohort.<sup>10</sup> Thus, it seems that debate is now focused on when to perform hepatic resection and which patients with intermediate-stage HCC are ideal candidates for this procedure, rather than whether or not resection should be offered to such patients.<sup>11</sup>

Currently, an efficient and evidence-based system for stratification of patients with intermediate-stage HCC is urgently needed to facilitate appropriate treatment allocation and accurate prediction of prognosis. Fortunately, several proposals for subclassification have been raised. Bolondi *et al.*<sup>12</sup> initiated the stratification of intermediate-stage HCC by dividing the BCLC B classification into B1 to B4 subgroups based on the following criteria: the 'up-to-7' rule (whether or not the size of the largest tumour in centimeters plus the total number of tumours is greater than seven; Figure 1); Child–Pugh score; and the severity of clinical jaundice and/or ascites. Liver transplantation, TACE, and sorafenib were recommended as either the first-line or alternative treatment options according to BCLC B subclassification.<sup>12</sup> Although this proposed system has been externally validated,<sup>13,14</sup> it still does not acknowledge the great value of hepatic resection among patients with BCLC B stage HCC. A novel HCC treatment algorithm, the Hong Kong Liver Cancer (HKLC) classification,<sup>3</sup> was formulated by analysing data from 3,856 consecutive patients with HCC treated at a centre in Asia. The HKLC guideline recommends curative therapies for selected patients with slightly impaired physical function status, large or multiple tumours, and even with intrahepatic venous invasion<sup>3</sup>—patients who would be classified as having intermediate-stage or advanced-stage HCC under the BCLC staging system and would, therefore, receive TACE or systemic treatment only.<sup>1</sup> Among the BCLC B stage HCC population, patients who were classified as having HKLC-II disease according to the HKLC system experienced a significant survival benefit after curative treatment

compared with those who underwent TACE (5-year survival rates of 52.1% versus 18.7%;  $P < 0.0001$ ). Surprisingly, in patients with BCLC C disease who met the HKLC-II classification criteria, the survival benefit of radical therapies versus systemic therapy was more pronounced (5-year survival was 48.6% versus 0.0%;  $P < 0.0001$ ). Therefore, the HKLC staging system enables hepatic resection to be pursued in subgroups of patients with intermediate-stage or advanced-stage HCC with an otherwise truly dismal prognosis, although external validation of this guideline is required.

Overall, as long as hepatic resection is technically feasible and safe, this intervention should be offered to selected patients with BCLC B stage HCC (Figure 1). Given that patients with BCLC B disease who undergo tumour resection have a high rate of intrahepatic recurrence (70%),<sup>10</sup> active post-recurrence treatment with re-resection, radiofrequency ablation (RFA), TACE, or sorafenib might collectively contribute to improved survival, and approaches to retreatment demand further study. At present, when treating patients with BCLC B stage HCC, multidisciplinary decision-making on a patient-by-patient basis, dependent on the particular clinical features presented, is mandatory. Moreover, new technical advances, such as the combination of resection and intraoperative RFA, and the Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy (ALPPS) procedure,<sup>15</sup> widen the applicability of surgical intervention for BCLC B stage HCC.

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#### Competing interests

The authors declare no competing interests.

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