Review

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The treatment of intermediate stage tumours beyond TACE: From surgery to systemic therapy

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Summary

Treatment of hepatocellular carcinoma (HCC) is dependent on the stage of the disease. Intermediate stage HCC encompasses the largest subgroup of patients with the disease, and is characterized by substantial heterogeneity. The standard therapeutic approach, transarterial chemoembolization (TACE), is probably over-used and may not be appropriate for all patients with intermediate stage HCC. In patients with extensive tumour bulk, multi-nodular spread or impaired liver function, TACE may not be optimal and other treatments can be considered as a first-line treatment. These include surgery, percutaneous ablation, radioembolization or systemic treatment. In addition, patients who do not achieve complete or partial necrosis (TACE failure) and patients with early recurrence after TACE, should be managed individually, considering systemic treatments usually reserved for advanced disease. In selected cases and in patients who achieve downstaging, radical approaches such as hepatic resection or even liver transplantation can be considered. In this review, we evaluate the current literature for the treatment strategies for patients with intermediate Barcelona Clinic Liver Cancer (BCLC) B stage HCC.

Keywords: Hepatocellular carcinoma; BCLC; Intermediate stage; TACE; Tumour; Surgery; Liver transplantation.

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Introduction

The Barcelona Clinic Liver Cancer (BCLC) classification, which includes four disease stages (A, early; B, intermediate; C, advanced; D, end-stage), is the most utilized staging system in Western countries for estimating the prognosis of patients with hepatocellular carcinoma (HCC) and helps clinicians choose the most appropriate treatment for each stage.[1] The BCLC B stage consists of patients with cirrhosis with a Child-Pugh score of A or B, tumour burden outside the Milan criteria and preserved performance status. Although the definition of BCLC A stage is quite specific, and able to help identify different subgroups according to liver function, portal hypertension and tumour size and number, the definition of BCLC B stage is broad. It includes a heterogeneous patient population, according to either tumour extension (from bifocal HCC to subtotal tumour replacement of liver parenchyma) or liver function (from Child-Pugh compensated A5 cirrhosis to decompensated B9).[2] In general, the recommended treatment modality for BCLC B HCC stage is transarterial chemoembolization (TACE). However, not all patients with intermediate stage HCC are good candidates for TACE, particularly patients with wide tumour bulk, multi-nodular spread or impaired liver function, and therefore other treatments should be considered (including surgery, percutaneous ablation, radioembolization and sorafenib treatment.[2–5]) Patients who do not achieve complete necrosis (TACE failure) and patients with early large HCC recurrence after TACE should be managed individually, taking into consideration systemic treatments, which usually are reserved for advanced cases. Furthermore, a number of studies have suggested that hepatic resection (HR) may be efficacious in selected cases in the BCLC B stage, and that patients receiving significant downstaging from TACE or combined treatments may be considered for radical treatments such as HR or even liver transplantation (LT). This flexible approach to the BCLC B stage is now considered in most guidelines[6–11] but clinical decisions differ from centre to centre because of the lack of strong scientific evidence for many of the treatments for patients in this stage, as well as discrepancies between guideline recommendations.[12]

Key point

Intermediate stage HCC is characterized by high heterogeneity, which poses a great clinical challenge in terms of identifying the most effective treatment for each individual patient.

Key point

Curative interventions (HR, LT and RFA) may produce superior outcomes in some intermediate stage patients with preserved liver function.

Since the BCLC B stage includes the largest number of patients with HCC requiring treatment (both at first diagnosis and during the course of the disease), we believe that this area of scientific and clinical uncertainty could benefit from a comprehensive overview of the literature. We adopted a search strategy on PubMed based on the following search criteria: "HCC BCLC B", finding 304 entries (October 15, 2016), and "((hcc) OR (hepatocellular carcinoma)) AND ((therapy) OR (treatment)) AND (("BCLC B") OR (intermediate))" during years 2005–2016, finding 578 entries (October 18, 2016). A selection of papers of interest based on title and (optionally) on abstract was evaluated, as well as added studies known to the authors or cited in previous reviews. A final total number of 167 studies was selected, and we divided them into the following chapters: hepatic resection, liver transplantation, percutaneous treatment, transarterial chemoembolization, radioembolization, systemic treatment, radiotherapy and multimodal approaches, to provide an overview of the treatment strategies in this BCLC B stage HCC patient group.

Surgery

There are two main aspects limiting the surgical treatment of HCC in the BCLC B stage: the presence of an adequate liver functional reserve when performing HR, and the scarcity of available donors when offering LT.[13]

Hepatic resection

Since the development and the adoption of BCLC guidelines there has been much debate on the level of tumour burden that may be considered as intermediate stage.[14,15] Whether single HCC above 5 cm in size should be classified as early or as intermediate stage is particularly relevant for the surgical option, because the BCLC criteria often defined these tumours as 'intermediate "large" HCCs, not fulfilling Milan criteria', without any distinction from multi-nodularity.[7,16] In addition, the BCLC system does not define whether "large" resectable HCCs should belong to the early rather than to the intermediate stage, when resection is performed under predefined clinical criteria (*i.e.* no portal hypertension and total bilirubin less than 1.0 mg/dl). Thus, the inclusion of "large" HCCs in the intermediate stage seems like a reasonable interpretation, rather than wrong; however, it has produced some interesting studies in recent years.[15,17,18]

In the recent EASL-EORTC clinical practice guidelines for HCC, the BCLC B stage was defined as multi-nodular HCCs only; the target 5-year survival for the BCLC A stage was set between 40% and 70%.[8] However, it should be noted that the 5-year survival after resection of single HCC <5 cm is expected to be about 70% at best, with a lower post-operative survival in larger tumours (only 30% for tumours reaching ⩾10 cm in diameter).[19] Thus, whether a single "large" tumour should be considered as early or intermediate stage remains debatable. As a consequence, the available literature addressing surgery in BCLC B patients, includes a mix of multi-nodular (⩾3 lesions) and "large" tumours treated with HR. By continuing to classify "large" HCCs in the intermediate stage, Torzilli *et al.* reported in 2013 that the 5-year patient survival was up to 57%, and concluded that in the current practice, HR is widely applied among patients with multi-nodular and large HCCs; in this situation, it is considered palliative.[15] Ishizawa tried to change opinion on "large" tumours by showing that the presence of multiple tumours was not a significant predictor of overall survival (OS) after HR but independently increased the risk of recurrence, compared to single tumours.[17] The 5-year survival in patients with Child-Pugh A cirrhosis and multiple tumours was 58%. These surgical cases made the role of TACE questionable in these patients.[20]

A better level of evidence has been provided in a randomized study on 173 patients in BCLC B stage with resectable multiple HCC outside Milan criteria: HR outperformed TACE with a 3-year survival of 51.5% *vs.* 18.1% after TACE.[21] This study makes retrospective analyses published in the past more robust, as they all highlight that survival benefit can be achieved by HR compared to TACE.[15,22,23] In the study by Ho *et al.* in 2009,[22] carried out in 1,080 patients with multiple tumours, 27.2% received surgery and 37.4% TACE. After covariate adjustment, it was reported that TACE had a hazard ratio of 1.61, compared to resection (p <0.001). A study by Hsu *et al.* from 2012 with propensity score adjustment, showed significantly better survival in 268 patients with intermediate HCC who underwent surgery compared to 455 patients treated using TACE, with 5-year survival rates of 43% *vs.* 15% (p <0.001).[24] However, limiting the intermediate stage to multinodular tumours only, means that fewer HCCs are suitable for HR.[17]

There is a reluctance to propose resection for the intermediate stage because these patients represent "non-optimal" surgical candidates,[25] but even "non-optimal" candidates can gain survival possibility with surgery, compared to alternative treatments (although it may not be as beneficial compared to candidates in early stage). The same question has been extensively debated for resection in BCLC A, where HR could still represent a good option.[26] The indication for TACE in BCLC B is based on studies and meta-analyses comparing TACE/transarterial embolization (TAE) to best supportive care. However, until recently these analyses have excluded the comparison of other treatment modalities (such as HR), as previously discussed.[21,27] This lack of clear evidence has led physicians to have different expec-

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