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OPINION ARTICLE

A farewell to Barcelona Clinic Liver Cancer (BCLC) classification for hepatocellular carcinoma

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Summary

Hepatocellular carcinoma (HCC) is the most common primary liver cancer with expected increasing frequency in the next few decades. At early stages, HCC is curable, with most common therapeutic modalities to include surgical resection and liver transplantation. The Barcelona Clinic Liver Cancer (BCLC) Staging System is widely adopted tool to guide the therapeutic algorithms of patients with HCC. This classification is guiding the clinical practice for the last 2 decades. However, there are emerging data demonstrating that patients beyond the traditional criteria of operability, resectability or transplantability actually can benefit from surgical treatment, emphasizing the need of refinement or even change of current BCLC criteria.

Key words: *hepatocellular carcinoma, BCLC, tumor burden score*

Prelude

Hepatocellular carcinoma (HCC) is the most frequent primary liver malignancy and the third cause of cancer-related death in the Western Hemisphere, with the projection to increase during the next few decades [1,2]. The well-established causes of HCC are alcoholic cirrhosis, chronic liver infections such as hepatitis B virus (HBV) or hepatitis C virus (HCV), and nonalcoholic fatty liver disease (NAFLD) [3]. Clinical presentation varies widely from asymptomatic disease to symptomatology extending from right upper abdominal quadrant pain and weight loss to obstructive jaundice and lethargy due to encephalopathy and liver failure. Imaging is the first key and one of the most important aspects at all stages of diagnosis, therapy and follow-up of patients with HCC [4].

During the last 30 years, several staging systems have been proposed for the stratification of the prognosis and management of HCC. Despite the fact that there is no consensus regarding the implementation of one universal staging system, since all of the proposed classifications have deficiencies, the Barcelona Clinic Liver Cancer (BCLC) Staging System remains the most widely classification system used for HCC management guidelines [4]. Initially proposed in 1999 and updated in 2003, the BCLC staging classification incorporates tumor size, presence of metastatic disease, portal hypertension, Child-Turcotte-Pugh score, total bilirubin and performance status, and stratifies patients into five groups: Stage 0 (very early HCC), stage A (early HCC) which is divided into four subgroups A1-A4; stage B (intermediate HCC); stage C (advanced HCC); stage D (end-stage HCC). The therapeutic recommendations are based on the stage of the disease and currently include: a) resection for stage 0 to A2, b) liver transplant or local ablation for stage A2 to A4, c) transarterial chemoembolization (TACE) for stage B, d) sorafenib for stage C, e) and supportive care for stage D. The median survival

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for the various stages is over 60 months for BCLC 0-A, 20 months for BCLC B, 11 months for BCLC C and less than 3 months for BCLC D [5,6].

Due to recent advances in surgical techniques as well as in the postoperative management of patients with liver disease undergoing major liver resections or transplantation, there is an emerging body of literature identifying patients who are not considered eligible for any surgical intervention of curative intent by current BCLC recommendation but can actually benefit oncologically from surgical treatment [7-11]. This can be contributed to several factors such as the fact that BCLC staging classification treats patients with highly heterogeneous disease the same way since they are classified under the same stage. Also advances in technology and minimally invasive liver surgery facilitated bloodless, parenchymal sparing liver resections that were shown to be equivalent to anatomic in terms of long-term outcomes [12-19]. Thus, there is an unmet need to identify and reclassify these patients who might benefit from other treatments. The present opinion piece advocates for the adaptation of a revised staging system in the management of HCC that will focus on including variables relevant to the disease biology [20,21].

Adequacy of surgical resection in HCC

Recent multi-institutional data showed that early recurrences (<24 months) are common and can be found in both patients with wide and narrow negative margins after resection of HCC (<1 cm: 70.3% versus>1 cm: 85.7%, p=0.141) and usually the recurrence is intrahepatic. However, 1-, 3-, and 5-year RFS among patients with margin<1 cm were significantly lower than those in patients with margin>1cm (77%, 48.9%, and 35.3% versus 81.7%, 65.8%, and 60.7%, p=0.02) [22]. Among patients undergoing anatomic resection (AR), resection margin did not impact RFS whereas in the non-anatomic resection group (NAR), margin width >1 cm was associated with a better RFS [23]. On the contrary, a recent study focusing on HCC patient with solitary tumors showed that there was no significant survival difference among narrow, intermediate, and wide margin groups with a median RFS of 33.0 months [24]. To address this inconsistency, a recent meta-analysis of 12,429 HCC patients showed no difference between AR and NAR in terms of perioperative morbidity and mortality. However, AR was associated with a RFS benefit (p<0.0001), finding that was more profound in non-cirrhotic patients [24].

Post-hepatectomy liver failure is a rare but potentially lethal complication in patients undergoing liver resection. It is more common in patients with background liver disease, since the functional liver remnant (FLR) required to maintain liver function is higher [25]. A recent technical advance, the Associating Liver Partition and Portal vein ligation for Stage hepatectomy (ALPPS) generated a lot of enthusiasm since it seems that blood flow manipulation and parenchymal transection triggers rapid liver regeneration potential thus facilitating resection of liver tumors that were previously though unresectable [26]. ALPPS was initially applied in patients with unresectable colorectal liver metastatic disease [27], however there are emerging data supporting its efficacy in patients with HCC [28,29]. Major drawbacks for this procedure are the high mortality and morbidity rates despite the achievement of R0 in all cases. Oncologically, recent systematic reviews demonstrated that recurrence rate was 18.9% and RFS varied from 3 to 60 months with a median of 10 months and overall survival (OS) ranged from 3 to 60 months with a median of 11 months [30,31]. Additional technical modifications, including hepatic artery clamping as well as hepatic vein embolization seem to further trigger liver regeneration with mechanisms related with liver preconditioning and hypoxia [32-34].

Surrogates of tumoral behavior can identify patients who benefit from surgical management beyond traditional criteria

Development of international multi-institutional datasets can provide a methodologically solid platform to identify HCC patients who can benefit from surgery or transplantation. Despite their retrospective nature, these databases are usually granular enough to provide sufficient data to support novel hypotheses and clinically important conclusions. Also, they limit the population bias attributed to genetic and phenotypic heterogeneity of patients included in national administrative datasets [35]. Data from a large multi-institutional HCC consortium of 1037 patients who underwent resection for HCC, showed that TBS can discriminate the patients at risk of worse survival after resection of multinodular HCC beyond the Milan criteria. Interestingly, patients with low TBS achieved a 73.7% 5-year OS survival whereas patient with high TBS only 13.1% (p<0.001). This study supported the role of using surrogates of disease biology such as TBS to identify patients who can benefit from surgical resection with indication outside the traditional BCLC criteria of resectability and operability of HCC [36].

Not surpisingly, when analyzing patients with BCLC 0/A (within BCLC resectability criteria) to

BCLC B/C (beyond resectability) in the same multi-institutional setting, it seems that BCLC B/C patients have higher risk for early (<2 years) or multiple intrahepatic recurrences compared to BCLC 0/A (p=0.011), and shorter 5-year OS (51.6% for BCLC B/C versus 76.9% for BCLC 0/A, p=0.003). The striking finding of the analysis is obviously the fact that half of the selected patients with advanced HCC who undergo surgical resection can actually survive for 5 years, finding that clearly exceeded any expectation from other recommended treatment for these patients such as TACE and sorafenib. Again, tumor biology and resection margins are important since AFP> 400 ng/mL (HR=1.84, 95% CI 1.07-3.15) and R1 resection (HR=2.36, 95% CI 1.32-4.23) were associated with higher risk of recurrence among BCLC B/C patients [37]. Deeper analysis between patients with BCLC-A and B revealed that interestingly patients with medium TBS can achieve significantly longer OS compared to patients with BCLC-A and high TBS (58.9% versus 45%; p=0.005). This finding further supports the conclusion that HCC patients are highly heterogeneous and treatment strategies should take into consideration the biology of the disease, with TBS being a very reliable surrogate [38]. Moreover, a machine-learning analysis showed that preoperative factors such as comorbidities and high AFP as well as postoperative factors including TBS and lymphovascular invasion can be the best predictors of OS in patients with BCLC-A and TBS was the single best predictor of outcomes in patients with BCLC-B undergoing resection for HCC [39]. The latter indicates that in patients with BCLC-B HCC, tumoral behavior as reflected by TBS is probably the most important prognostic factor of outcomes. In patients undergoing liver transplantation, it seems that high TBS had worse OS (p<0.0001) and RFS (p<0.0001). When TBS was compared to the Milan criteria, a higher TBS was able to discriminate patients within (HR=1.20; 95%CI, [1.04-1.37]; p=0.011) and beyond Milan criteria (HR=1.53; 95%CI, [1.16-2.01]; p=0.002) who had higher risk of recurrence. Despite the fact that median and 5-year RFS were 2.8 years and 36.6%, respectively, the chance of being cured after HCC resection was 42.2% and the median time to cure was 3.35 years. Not surprisingly, factors indicative of tumoral behavior such as preoperative AFP, tumor size, tumor number, and surgical adequacy such as margin status were independent predictors of cure. The cure fraction for patients with an AFP ≤10 ng/mL, largest tumor size ≤5 cm, ≤3 nodules, and R0 resection was 61.6% whereas AFP >11 ng/mL, nodules ≥4, size >5cm, R1 resection had a cure fraction of 15.8%. Strikingly, the probability of cure was 47.6% among BCLC-A patients, while patients undergoing resection for BCLC-B HCC had a 37.6% cure fraction. Only AFP levels predicted the probability of cure among Barcelona Clinic Liver Cancer-B patients [40].

Final remarks

Advances in surgical techniques, improvement of outcomes of major operations such as hepatectomy and liver transplantation, better postoperative management of oncological patients and deeper understanding of tumoral behavior, create a unique landscape in the management of HCC. Current treatment algorithms should be updated or changed to meet the emerging needs of patient with HCC.

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