Conflicts of interest
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Adjusting Barcelona Clinic Liver Cancer Staging System to the Evolving Landscape of Hepatocellular Carcinoma: A Look to the Future

Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol 2022;76:681–693.

The prediction of prognosis in hepatocellular carcinoma (HCC) and the choice of the treatment strategy is particularly complex, because of the impact of the underlying liver disease and function and the need for multidisciplinary management (Gastroenterology 2017;152:1954–1964). The frequent coexistence of advanced liver disease may substantially worsen the prognosis and limit the implementation of potentially curative treatments even in patients with otherwise early tumors.

In 1984, the Okuda score was born pioneering prognostication of HCC through the combined evaluation of tumor bulk and liver function explored by the serum levels of bilirubin and albumin (Cancer 1985;56:918–928). However, the new score quickly showed its suboptimal prognostic power in patients with stage 1 HCC, a group that included patients with compensated cirrhosis but also with very large tumors (occupying $\leq$50% of the liver), and thus with very limited therapeutic opportunities. The advent of the Barcelona Clinic Liver Cancer (BCLC) staging in 1999 (Semin Liver Dis 1999;19:329–338) was a major step forward. By combining tumor bulk, Child–Pugh classification of liver impairment, the presence of clinically significant portal hypertension and the performance status of the patient (according to the Eastern Cooperative Oncology Group), BCLC staging allowed more granularity in patients stratification.

A major novelty of the BCLC was the identification of the intermediate stage HCC, characterized by bulky intrahepatic tumor with no portal invasion, thus clinically segregating it from early and advanced cancer and allowing selection of the best therapeutic option for each of the four tumor stages of the system, which run from early to end-stage tumor disease (Semin Liver Dis 1999;19:329–338). Most important, the BCLC staging became the patriarch of evidence-based combined prognostic–therapeutic algorithms for HCC management. After its repeated external validation in Europe and abroad, the BCLC staging and its updates was recommended by the Western liver societies (Hepatology 2018;68:723–750; J Hepatol 2018;69:182–236). Patients with early cancer (stage A) were identified as ideal candidates for radical therapy, such as local ablation, surgical resection, or liver transplantation. Patients with stage A disease are clearly separated from patients with stage B and C disease, for whom palliative treatments with chemoembolization or systemic treatments were recommended, respectively. The granularity of the system was further expanded by including stage 0, that is, a tumor of $<$2 cm in diameter in a patient with a well-compensated liver. During the past 2 decades, the therapeutic armamentarium for the treatment of HCC has increased dramatically. Recognizing the changing landscape in HCC management, the founders and supporters of the BCLC staging gathered recently in a consensus conference that proposed an updated version of BCLC (J Hepatol 2022;76:681–693), which is discussed in this summary.

Comment. The BCLC system holds the great merit of having introduced an evidence-based approach to the prognostication and the treatment of patients with HCC. For each stage, it suggests the most recommendable treatment modality and thus has been endorsed by the American Association for the Study of Liver Diseases (Hepatology 2018;68:723–750) and the European Association for the Study of Liver (J Hepatol 2018;69:182–236). Furthermore, it made the design of clinical studies more standardized and reliable. Over the years, however, some limitations of BCLC have emerged owing to the presence of subjective components (ie, performance status) and oversimplified recommendations for treatment modality that did not keep abreast of the many advances in the management of the patients and the changing epidemiology of the disease. As such, many multidisciplinary tumor boards, while still discussing the cases in the framework of the BCLC, ended up recommending motivated exceptions, consistent with the trend toward the personalization of treatment.

The updated BCLC reflects many of these challenges and it is expected to improve the "real-life" applicability of the score. The updated BCLC score includes a number of important changes and additions. Among them, (1) the confirmation of the albumin–bilirubin score (J Clin Oncol 2015;33:550–558) for a more granular assessment of liver function in compensated patients, (2) the integration of the alpha fetoprotein (AFP) value, for a better biological characterization and a more accurate prognostic prediction, (3) the subclassification of the intermediate stage with different therapeutic options (including extended liver transplant criteria), (4) the inclusion of radioembolization as a backup for early and intermediate stages, (5) the inclusion of a wide range of first- and second-line systemic therapy options for compensated patients with advanced HCC and for those with intermediate HCC who were unfit or failed to respond locoregional therapies, (6) the concept of stage migration, and of untreatable migration, (7) a proposal on how to categorize patient with radiological progression, and (8) a clear introductory statement that highlights the role of

multisciplinary tumor boards in the ultimate management of the patient with HCC.

Resuming the functional core of the Okuda system (Cancer 1985;56:918–928), albumin–bilirubin score (J Clin Oncol 2015;33:550–558) has emerged to be a better prognostic tool than Child Pugh score in stratifying patients across the different stage of BCLC, namely, in predicting survival and recurrence in patients with early HCC undergoing liver resection and local ablation as well. The addition of the AFP concentration, irrespective of tumor burden, is another innovative element in the new version of the BCLC. Higher levels of this marker have been shown to be associated with a worse prognosis, namely, an increased recurrence after liver transplantation and worse overall survival among those with advanced stage disease. In the previous versions of the BCLC, measurements of AFP, already considered useful for prognosis of patients in research trials, were not considered to determine therapeutic choices.

Over the years, other refinements of the BCLC system have been explored and brought into focus, one above all the concept of treatment stage migration. A proportion of patients in each stage do not fulfil the criteria for the treatment allocation, thereby requiring the patient to be offered the next suitable treatment option. Examples are the expanded criteria for liver transplantation if the tumor burden can be successfully and stably down-staged within Milan criteria (N Engl J Med 1996;334:693–700), and the separation of patients with intermediate tumors who are ideal candidates to transarterial chemoembolization from those who can cross through the borders of radical therapies.

An ideal staging system should be simple and intuitive; it should provide information on prognosis and guide therapeutic decisions. However, a prognostic evaluation of HCC needs models that take account of changes during the course of disease. With this in mind, the BCLC authors, properly managing progression as a time-dependent variable (Hepatology 2013;58:2023–2031), found that the development of new extrahepatic foci or vascular invasion were independent predictors of impaired survival. This prognostic stratification offered by the classification of patients according to their pattern of progression has been validated repeatedly. It is important to consider that the risk of liver decompensation and that risk of tumor recurrence or progression compete with respect to survival in patients with underlying cirrhosis. In fact, decompensation of liver disease during or after any HCC treatment can negatively affect the possibility of further treatments, in case of recurrence, or of subsequent therapeutic lines in case of progression (J Hepatol 2017;67:65–71). In this line, time to hepatic decompensation, decompensation-free survival, and the type of decompensation should be considered as a safety measure in studies on HCC (J Hepatol 2021;74:1225–1233) and could be endorsed or included in future BCLC updates.

Another merit of the BCLC 2022 update (J Hepatol 2022;76:681–693) is to address the complexity and heterogeneity of intermediate (BCLC-B) stage, with the identification of three substages aiming to better tailor treatment. In the first subgroup are included patients beyond Milan Criteria with well-defined HCC nodules, absence of portal invasion, and no cancer-related symptoms. These patients are candidates for liver transplantation; with extended transplantation criteria, they might benefit from down-staging strategies, taking into account dynamic AFP measurements and the risk of higher recurrence rate and lower long-term survival. The second subgroup includes patients excluded by any liver transplant program, patent portal vein, and well-defined tumor. These patients are proper candidates for transarterial chemoembolization and systemic therapy eventually. In the third subgroup are included patients with infiltrative or diffuse HCC. Although these patients are formally included in the BCLC-B stage, they do not benefit from locoregional treatments and should be referred to receive systemic therapy. In this regard, little is said on the stopping rules to be followed after locoregional transarterial therapies when the HCC remains vital and progresses; these would be important to anticipate the shift to systemic therapies.

Some critical aspects of the BCLC staging remain present, however. The molecular characteristics and the pathobiology of the tumor are not accounted for by the BCLC system, whereas such potentially important biological variables as microvascular invasion and signature gene expression profiling may profoundly impact tumor growth, responsiveness to treatment, and ultimately survival. These considerations should also restore its proper value to the use of biopsy and more largely of tissue-based diagnosis in HCC management (Transl Gastroenterol Hepatol 2021;6:20).

In the era of laparoscopic and minimally invasive approach (Hepatology 2020;72:2206–2218), the treatment space reserved for resection still seems smaller than its real value, not to speak about the clinical benefits of the pharmacological control of viral hepatitis B and C that translate in increased safety of surgery and improved life expectancy owing to the prevention of clinical decompensation. Many think that including the etiology of cirrhosis among the prognostic variables of HCC, might help refining criteria of systemic therapy of HCC as well, owing to the fact that different etiologies of cirrhosis could be associated with a different response to immune checkpoint inhibitors or tyrosine kinase inhibitors.

In conclusion, the history of BCLC has been at least in part a reflection, and simultaneously a guide, of the history of HCC management and treatment over the past 20 years; the 2022 update will spark further discussion among hepatologists (in the largest definition of the term) and further strengthen the multidisciplinary approach, that leads to true personalization of care and improved outcomes for patients with HCC.

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Long-Term Risk for Colorectal Cancer in Patients With Index Serrated Polyps

Li D, Doherty AR, Raju M, et al. Risk stratification for colorectal cancer in individuals with subtypes of serrated polyps [published online ahead of print August 11, 2021]. Gut doi: 10.1136/gutjnl-2021-324301.

Serrated polyps (SPs) are part of a pathway which may account for up to 30% of all colorectal cancers (CRC) (Gastroenterology 2020;159:105–118 e25; Gastrointest Endosc Clin N Am 2020;30:457–478). There are four subsets of SPs including hyperplastic polyps (HPs), sessile SPs (SSPs; also referred to as sessile serrated lesions), traditional serrated adenomas (TSAs) and unclassified SPs. HPs are believed to have a benign course with minimal risk for CRC. Conversely SSPs and TSAs have malignant potential and are associated with an increased CRC risk. Less is known about the risk of unclassified polyps.

There are several reasons why endoscopists are concerned about optimal management of SSPs (Gut 2021 Aug 11;gutjnl-2021-324301), perhaps more so than TSAs. As compared with the rarely encountered TSAs, SSPs are relatively common, accounting for approximately 10% of all SPs (Gastrointest Endosc 2017;85:1188–1194). They are often flat in appearance with indistinct borders, making them difficult to detect. Thus, it is not surprising that studies have demonstrated a wide variation of detection rates among endoscopists. Finally, a major concern is the difficulty in pathologically distinguishing them from HPs (J Clin Gastroenterol 2018;52:524–529).

Thus, the surveillance of SPs can be a challenge for endoscopists. Much of the data supporting US Multisociety Task Force on Colorectal Cancer 2020 postpolypectomy surveillance guidelines are from studies examining the metachronous risk for alternative lesion categorizations such as large SPs (Gastroenterology 2018;154:117–127 e2; Gastroenterology 2020;158:1131–1153 e5). Reliance on such categories as large SPs is due in part to the low frequency of significant lesions such as large HPs in practice. One long-term study examining CRC risk included only 83 large SPs and did not further categorize the polyps by histology (Gut 2015;64:929–936). However, 1 Danish study in particular observed a higher long-term risk for CRC in individuals with SSPs (Gastroenterology 2016;150:895–902 e5).

In the current study, the investigators use a nested case-control design to examine the risk of index polyps for post colonoscopy CRC. They use natural language processing to collect data from >300,000 individuals enrolled in a large health maintenance organization in California. Index SPs were reclassified by pathologists according to today's histological classifications into SSPs, HPs, TSAs, or if an unequivocal distinction of SSP and HP was not possible, unspecified SPs. The investigators included 785 patients who had ≥1 SP on index examination and 162 of this group were diagnosed with CRC. They also included data from 3380 other patients, of whom 533 individuals were diagnosed with CRC.

The authors present many different outcomes based on index lesions categorized by histology, size, location, and number. A major finding for polyp histology is that, after adjustment, the authors observed that individuals with SSPs were more likely to develop CRC than patients without polyps, similar to Erichsen et al (Figure 1). Interestingly, the same was found for individuals with unspecified SPs. Conversely, there was no increased risk for individuals with unequivocal HPs, regardless of location. TSAs were associated with an increased risk for CRC when detected with a synchronous adenoma. Unfortunately, there were too few large HPs or solitary TSAs to examine their CRC risk independently.

SSP risk was moderated by several factors, including size, location, presence of dysplasia, and synchronous adenomas. SSPs associated with a particularly high risk were those that were large (≥1 cm) and proximal, had dysplasia, or were diagnosed with synchronous advanced adenoma. It must be noted that, although the point estimates for these odds ratios [ORs] were higher than other groups, the 95% confidence interval [CI] often overlapped, precluding definite conclusions on their relative risks. For example, individuals with SSP plus advanced adenomas (OR, 11.6; 95% CI, 4.2–32.3) had a substantially higher suggested risk than SSPs alone (OR, 2.9; 95% CI, 1.8–4.8).

Comment. These data are important for endoscopists who need to risk stratify their patients with SPs and determine optimal surveillance intervals. It is reassuring that these data support both the US and the European guidelines, which recommend close follow-up of 3 years for large SPs or SPs with dysplasia (Gastroenterology 2020;158:1131–1153 e5; Endoscopy 2020;52:687–700). In addition, the US Multisociety Task Force on Colorectal Cancer recommends a closer follow-up of multiple SSPs, which is also supported by these data. Although the data support close follow-up for SSPs, they suggest that unequivocal HPs may have minimal risk, although after pathological reassessment there were too few large (≥1 cm) HPs to examine. Thus, the sample may have been underpowered to examine important HP subsets.

Although this study was similar in design to that by Erichsen et al (Gastroenterology 2016;150:895–902 e5), and supports many of the earlier findings (Figure 1), there are some noteworthy differences. This study was situated in a setting with background screening, and had a reassessment of SP pathology which followed more recent World Health Organization criteria for diagnosis of SP subtypes. Thus, the