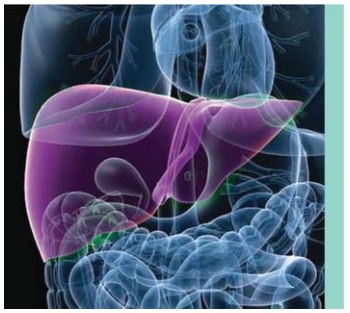

Limitations of the Barcelona Clinic Liver Cancer Staging System With a Focus on Transarterial Chemoembolization as a Key Modality for Treatment of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the most common primary liver malignancy[1] and is one of the leading causes of cancer-related death in the United States.[2] Prognosis of HCC remains poor, driven by advanced tumor burden at diagnosis in two-thirds of cases.

Cancer staging systems are important for prognostication and determination of therapy. HCC has unique characteristics for which it is more difficult to use standard cancer staging strategies. First, there is enormous heterogeneity with regard to patient characteristics and HCC biology. Second, in the Western world, the majority of HCC occurs in patients with significant underlying liver disease, making liver function and functional status important in determining outcome. Lastly, tissue diagnosis is not often required, and radiological diagnosis is often the standard. Various staging systems (Table 1) have been proposed to incorporate these variables, but there is no universal worldwide consensus.[3] Two of these staging systems [Barcelona Clinic Liver Cancer (BCLC) and Groupe d'ETUDE et de Traitement du Carcinome Hepatocellulaire (GRETCH)] include performance status, with the BCLC being validated in various geographical settings and with very large data sets.[4] As a result, the BCLC staging system is the most accepted system in the United States, having received the endorsement of both the American Association for the Study of Liver Diseases and the European Association for the Study of Liver diseases (Figure 1).[5] Its main advantage is the unique way in which it provides therapy guidelines based on staging, making it a very useful clinical tool.[6]

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; CTP, Child-Turcotte-Pugh; CUPI, Chinese University Prognostic Index; DM, , diabetes mellitus; GRETCH, Groupe d'ETUDE et de Traitement du Carcinome Hepatocellulaire; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HTN, hypertension; JIS, Japan Integrated Staging; TACE, transarterial chemoembolization.

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TABLE 1. CHARACTERISTICS OF SEVEN STAGING SYSTEMS FOR HCC

Staging System	Hepatic Function	Performance Status	Tumor Variables
BCLC	CTP	Yes	Size, number of nodules and portal vein thrombosis
CLIP	CTP	Yes	Number of nodules, tumor greater or less than 50% of liver, portal vein thrombosis, and AFP
CUPI	Bilirubin, ascites, alkaline phosphatase	Presence of symptoms	TNM and AFP
GRETCH	Bilirubin, alkaline phosphatase	Yes	Portal vein thrombosis and AFP
JIS	CTP	No	TNM
Okuda	Albumin, ascites, and bilirubin	No	Tumor greater or less than 50% of liver
TNM	No	No	Number of nodules, tumor size, presence of portal vein thrombosis, presence of metastasis

Abbreviations: CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; JIS, Japan Integrated Staging; AFP, alpha-fetoprotein.

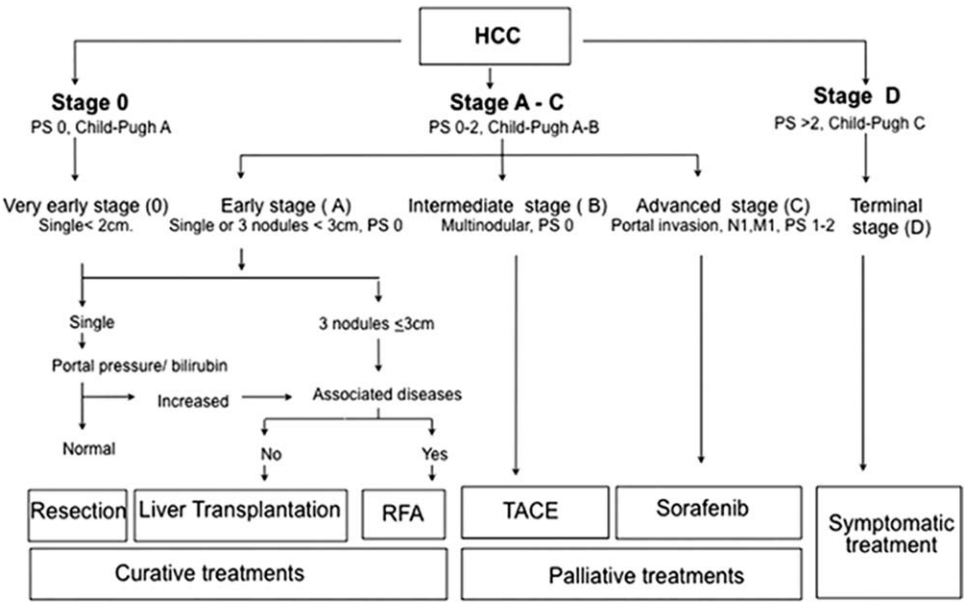

FIG 1 BCLC staging system. Adapted from *Hepatology*.[5] Copyright 2011. American Association for the Study of Liver Diseases.

Although it remains one of the best HCC staging systems, BCLC does have some shortcomings, particularly in regard to intermediate stage (stage B) HCC. In BCLC, transarterial chemoembolization (TACE) is recommended for stage B patients, whereas curative interventions such as surgical resection are recommended only for very early and early disease stage disease (stage 0 or A). Sorafenib and supportive care are recommended for advanced (stage C) and terminal stage (stage D) disease, respectively.[5] In practice, these guidelines are not often followed for many reasons.[7] One reason is that stage B comprises a highly heterogeneous population with respect to tumor burden, liver function, and cause of underlying liver disease; this latter component is not accounted for in BCLC. Consequently, the prognosis and suitability for treatment are quite variable within this stage. Examples of different stage B patients are listed in Table 2, where all are classified as stage B HCC, but the question remains: Would they benefit from TACE?

The cause of the liver disease is also not included in BCLC, yet the presence of comorbid conditions such as diabetes or cardiovascular disease in patients with nonalcoholic steatohepatitis-related HCC will influence treatment

TABLE 2. EXAMPLES OF INTERMEDIATE-STAGE HCC

Patient No.	Age (years)	Comorbidities	Child's Score	Cause	Nodules (n)	Size of Largest	Outcome
1	60	Tobacco	A (6)	HCV	5	1.4 cm	Needed 1 TACE, with complete response
2	65	DM, HTN, tobacco	B (7)	HCV	5	2 cm	Needed 1 TACE, with progression
3	64	DM, HTN, tobacco	A (5)	HCV	3	5 × 5 cm	Needed 4 TACEs, but only partial response
4	62	Tobacco	B (8)	HCV	1	2 × 5.1 cm	Needed 1 TACE, with complete response

Abbreviations: DM, diabetes mellitus; HCV, hepatitis C virus; HTN, hypertension.

options. Thus, recommendations as prescribed by BCLC in this population may not be feasible. In addition to disease etiology, there are also questions whether the classification of performance status within BCLC is optimized.[8] Although performance status is clearly an important component of prognosis in HCC, it is not clear that excluding patients with performance status worse than 0 is ideal for patients with stage B HCC.[8]

In addition to intrinsic difficulties in staging patients, the recommended intervention is also somewhat controversial. For example, surgical intervention is recommended for only early-stage disease, but there is now emerging evidence demonstrating surgical resection may have better long-term outcomes in patients with stage B as compared with TACE,[9] prompting the question whether resection should be restricted to stage 0/A disease and not expanded to stage B disease.

For patients with more advanced disease, it is also not clear that TACE is not beneficial. Recommendations of TACE for stage B disease were born from analyses of studies showing negative predictors of survival, such as vascular invasion, performance status >0, and BCLC stage C disease. Much of the data were based on conventional TACE, whereas recent advances have made drug-eluting beads TACE and Y90 more commonly available and generally better tolerated. There is continued evidence of individual interdisciplinary decisions resulting in treatment stage migration in the nonsurgical population. Although only approximately 10% to 12% of new HCC diagnoses fall into stage B disease, TACE is easily the most commonly used treatment modality, with almost half the treatments worldwide being used in stage C patients.[10] This may be explained by both DEB-TACE and Y90-TACE demonstrating better efficacy as compared with conventional TACE,[11] which may expand the reaches of this treatment modality to patients with stage C HCC.

As a result of a highly heterogeneous patient population in stage B HCC, patient selection has become crucial to the success of TACE. Within stage B, patients with higher tumor burden and less preserved liver function have poorer responses to TACE.[7] In our own study, we found that the best predictor of outcome after TACE was not BCLC but Child-Turcotte-Pugh (CTP) score and tumor burden. Similar findings have been noted by other groups. In an attempt to improve risk stratification and avoid TACE-related harm, multiple groups have been working on creating subclassifications within stage B and scoring systems to better guide therapeutic decision making. This includes Bolondi et al.'s work in developing subclasses with stage B,[12] as well as the HAP (Hepatoma Arterial-embolisation Prognostic) and STATE (Selection for TrAnsarterial chemoembolisation TrEatment) scores, which help identify the best patients for initial TACE procedure while limiting procedural harm and lower morbidity and mortality.[10] It should be recognized that response to TACE is also an important factor that will not be captured with any pretreatment staging systems.

In addition to routine clinical variables to determine risk stratifications, there is growing interest in biomarkers or alternative patient characterization tools that may predict outcome in HCC. Although functional status is clearly an important patient variable, we and others did not find that Eastern Cooperative Oncology Group (ECOG) score was predictive of outcome after TACE.[7] This may be reflective of the intrinsic qualitative nature of the scoring system. In an attempt to better characterize the patient population, we have used a novel methodology (analytic morphomics) to assess patient characteristics by using quantitative image analysis of the readily available computed tomography imaging studies.[13,14] Analytic morphomics is an image-processing technique that assesses body composition measures such as body dimensions, visceral fat, and muscle mass, and

links them to clinical outcomes.[13] This provides a more objective manner of assessing functional status. Our results demonstrated that in comparison with the BCLC staging system, a model that included analytic morphomics provided a highly accurate prognosis in the nonsurgical population. Because all patients with HCC generally have cross-sectional imaging, this method has the potential to provide added information from existing scans that may improve prognostication.

Even though BCLC is the most widely accepted HCC staging system in the Western hemisphere and provides very important guidelines for treatment, there are shortcomings. With regard to recommendations for TACE in intermediate-stage HCC, there are concerns around a restrictive prescription of therapy to a highly heterogeneous patient population. Thus, it is important to recognize that BCLC should not be used as a conscripted algorithm. Decisions in practice are likely to be affected by local preferences and availability of resources such as transplantation. It should be noted that HCC therapy is best done with multidisciplinary model input from experts in hepatology, hepatobiliary surgery, and interventional radiology to reduce variability and enhance patient selection. Further research in this area will likely yield better predictors of survival and improve patient selection.

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