Staging and prognostic factors in hepatocellular carcinoma

AUTHORS: Steven A Curley, MD, FACS, Carlton C Barnett, Jr, MD, Eddie K Abdalla, MD, FACS
SECTION EDITOR: Kenneth K Tanabe, MD
DEPUTY EDITOR: Sonali M Shah, MD

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Literature review current through: **Sep 2023.**
This topic last updated: **Sep 16, 2022.**

INTRODUCTION

Hepatocellular carcinoma (HCC) is an aggressive tumor that frequently occurs in the setting of chronic liver disease and cirrhosis (see "Epidemiology and risk factors for hepatocellular carcinoma"). It is typically diagnosed late in the course of these diseases, and the median survival following diagnosis ranges from approximately 6 to 20 months [1]. Available therapeutic options for HCC are dictated by the complex interplay of tumor stage and the extent of underlying liver disease.

This topic review will provide an overview of staging and prognostic scoring systems for HCC. Surgical and nonsurgical treatments for HCC are discussed separately. (See "Overview of treatment approaches for hepatocellular carcinoma".)

STAGING AND PROGNOSTIC SCORING SYSTEMS

A number of systems have been proposed to predict the prognosis for hepatocellular carcinoma (HCC), none of which has been universally adopted [2-8]. These schema variably incorporate four features that have been recognized as being important determinants of survival: the severity of underlying liver disease, the size of the tumor, extension of the tumor into adjacent structures, and the presence of metastases [2,3,9-11]; some (eg, the Hong Kong and French prognostic staging systems) also incorporate performance status [5,8]. The four most

commonly used systems are the tumor, node, metastasis (TNM), Okuda and Barcelona Clinic Liver Cancer (BCLC) systems, and the Cancer of the Liver Italian Program (CLIP) score. A new, evidence-based score that was specifically derived from patients with HCC, the albumin-bilirubin (ALBI) grade, may allow more objective assessment of the severity of liver dysfunction in patients with HCC across a wide spectrum of treatments. (See 'Albumin-bilirubin (ALBI) score' below.)

Tumor, node, metastasis (TNM) staging — The current version of the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM staging system from 2017 (table 1) [12] contains some significant changes in the primary tumor (T) classification relative to the 2010 version [13]:

- T1 has been subdivided into two subcategories: T1a (solitary tumors ≤2 cm) and T1b (solitary tumors without vascular invasion >2 cm).
- T2 now includes a solitary tumor with vascular invasion >2 cm, or multiple tumors, none >5 cm.
- The previous T3a category (patients with multiple tumors, any of which are >5 cm) is now recategorized as T3, while tumors that were previously considered T3b (single or multiple tumors of any size that involve a major portal vein or hepatic vein) are now T4, as are tumors with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum.

The discriminatory prognostic potential of subdividing primary tumors according to size and microvascular invasion in the new 2017 TNM classification has been validated in patients undergoing resection (figure 1) [14]. Although neither the presence of cirrhosis nor histologic grade is used to assign the final tumor stage, the fibrosis score of the underlying liver is included as a clinically significant prognostic factor [15-19], as is alpha-fetoprotein (AFP) level, the presence or absence of cirrhosis, and the Model for End Stage Liver Disease (MELD) score [12].

The TNM staging system is the only one that is validated in patients treated with either hepatic resection [14,15] or transplantation [20] for HCC.

However, for patients with severe underlying liver disease, it is underlying liver function that dominates prognosis. The importance of underlying cirrhosis was demonstrated in a study from Hong Kong, which described survival according to TNM stage and tumor size in patients with and without cirrhosis related to hepatitis B (HBV) [21]. Five-year survival was similar in those with and without cirrhosis who had solitary tumors ≤5 cm (61 versus 62 percent). On the other

hand, five-year survival was worse in patients with cirrhosis with tumors >5 cm (28 versus 40 percent). In such patients, the Okuda and CLIP systems are more useful than the TNM stage to stratify prognosis.

Okuda system — In contrast to the TNM classification, the prognostic scoring system proposed by Okuda includes tumor size and three measures of the severity of cirrhosis (the amount of ascites and the serum albumin and bilirubin levels) (table 2) [2]. The Okuda system does not stratify patients by vascular invasion or the presence or absence of nodal metastases. Because most patients staged according to this system are not candidates for resection, it is a purely clinical scoring system.

Cancer of the Liver Italian Program (CLIP) score — The CLIP score is another prognostic scoring system for HCC. It combines tumor-related features (macroscopic tumor morphology, serum AFP levels, and the presence or absence of portal vein thrombosis) with an index of the severity of cirrhosis to determine a prognostic score ranging from 0 to 6 (table 3).

Several studies from varied geographic regions have suggested that CLIP performed better at predicting survival compared with the earlier versions of the TNM, Okuda, or Child-Pugh systems [3,4,22-24], particularly among patients undergoing nonsurgical therapy (eg, transarterial chemoembolization [TACE]) [25]. The CLIP score is not used much anymore.

Some groups are investigating whether prognostication with the CLIP score can be improved by the addition of serum factors such as vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF-1). (See 'New prognostic markers and methods under investigation' below.)

The Barcelona staging classification — The BCLC staging classification comprises of five stages that are based on the extent of the primary lesion, performance status, vascular invasion, and extrahepatic spread; this classification was updated in 2022 (figure 2) [26].

Early stage (A) patients have preserved liver function and tumors ≤2 cm that are suitable for radical therapies; intermediate stage (B) patients have preserved liver function and no more than three HCC, all ≤3 cm; advanced stage (C) patients have multinodular tumors but have preserved liver function. Patients with stage D disease have an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or 4 (table 4), or clearly decompensated end stage liver dysfunction. Stage B and C patients are not good candidates for resection, but may be candidates for liver transplantation, chemoembolization, palliative systemic therapy, or new agents in the setting of phase II investigations or randomized controlled trials. Patients with stage D tumors have an extremely poor prognosis, and treatment should be geared toward supportive care. Notably, in earlier versions, liver function was assessed according to the Child-Pugh score (table 5). The updated guidelines from BCLC suggest that liver function be

evaluated beyond the conventional Child-Pugh score [26]. However, beyond jaundice, refractory ascites, and encephalopathy, which reflect non-preserved liver function, they are vague as to how best to categorize a patient as having "preserved liver function."

In at least two comparative studies, early versions of the BCLC model outperformed other prognostic models (including the AJCC TNM staging system) in patients undergoing surgical therapy [27,28], several larger series show that other prognostic scoring systems outperform the BCLC staging classification [20,29], and still others show that treatment outside of the BCLC guidelines (particularly resection for BCLC stage B disease) impacts outcomes and that its utility is limited in patients undergoing surgical therapy [30-32]. (See "Surgical management of potentially resectable hepatocellular carcinoma".)

Albumin-bilirubin (ALBI) score — The importance of underlying liver function for the prognosis of HCC, the limitations and lack of validation for scoring systems such as the Child-Pugh classification in the setting of HCC, and the lack of a universally accepted prognostic system led an international group to develop a simple, objective tool for assessing liver function in patients with HCC [33]. The ALBI score was developed from data on 1313 Japanese patients with different stages of HCC; in multivariate analysis, bilirubin and albumin emerged as the only non-tumor-related variables that influenced survival in multivariate analysis. These two factors were combined into a model (the ALBI model) to compare against the Child-Pugh score. The linear predictor was calculated to = ($\log_{10}$ bilirubin x 0.66) + (albumin x -0.085), with bilirubin in micromol/L and albumin in g/L. Cutpoint analysis revealed three separate prognostic groups: ALBI grade I (score ≤-2.60), grade II (score >-2.60 to ≤-1.39), and grade III (>-1.39).

After application to training and validation sets of the initial Japanese cohorts, ALBI was further validated in more than 5000 patients from around the world (cohorts similar to the Japanese patients) and in other different treatment cohorts (525 patients treated with resection, 1132 treated with sorafenib for advanced disease, and 501 patients with chronic liver disease alone). The model proved to be discriminatory in all studied groups. Furthermore, survival in ALBI categories differed across all regions, although the model was discriminatory in every region and group tested. The majority (96 percent) of patients had Child-Pugh A cirrhosis at presentation, and within this grade, two distinct prognostic groups emerged across all regions.

The ALBI grade provides a simple, evidence-based, objective, and discriminatory method of assessing liver function in patients with HCC that may diminish interobserver variation (as occurs with grading of ascites and encephalopathy in the Child-Pugh scoring system) [33,34]. If independently validated, use of the ALBI score may allow better refinement of prognostic estimates in patients with HCC across a wide spectrum of treatments, particularly among those with better liver function. The ALBI score is also used to stratify risk associated with some

treatments such as transarterial radioembolization [35,36], a calculator for the ALBI score is available (calculator 1).

RETREAT and MoRAL scores — Several factors are associated with tumor recurrence after liver transplantation for HCC, but no reliable prognostic score has been established to determine individual recurrence risk. Investigators at the University of California, San Francisco, developed a scoring system (Risk Estimation of Tumor Recurrence after Transplant [RETREAT]) using data from 721 patients who met Milan criteria (single lesion ≤5 cm; up to three separate lesions, none larger than 3 cm; no evidence of gross vascular invasion; and no regional nodal or distant metastases) and were transplanted for HCC between 2002 and 2012 at three academic transplant centers; the model was validated in a separate cohort of 341 patients also meeting Milan criteria who were transplanted at a fourth academic center over the same time period [37]. (See "Liver transplantation for hepatocellular carcinoma", section on 'Indications for transplantation'.)

Three variables were independently associated with disease recurrence (microvascular invasion, serum AFP level at the time of transplantation, and the sum of the largest viable tumor diameter for all viable tumors on explant), and they were used to construct a scoring system to predict one- and five-year recurrence risk.

Another tool (the Model of Recurrence after Liver Transplantation [MoRAL] score, based on serum levels of protein induced by vitamin K absence II [PIVKA-II, des-gamma carboxyprothrombin] and AFP) has been developed to predict tumor recurrence after living-donor liver transplantation for HCC both within and beyond the Milan criteria [38]. The MoRAL score was defined as 11 times the square root of PIVKA-II (in milli-Anson units [mAU]/mL) plus two times the square root of the serum AFP (in ng/mL). Most laboratories in the United States measure des-gamma carboxyprothrombin in ng/mL; the conversion is 1 ng = 52.6 mAU of purified des-gamma carboxyprothrombin. In both groups, a low MoRAL score (≤314.8) was associated with significantly longer recurrence-free and overall survivals. The MoRAL score appeared to outperform the RETREAT score in both cohorts.

Although promising, these models require independent validation.

Choice of staging system — There is no consensus as to which staging system is best in predicting the survival of patients with HCC [27,39,40]. In general, pathologic staging systems such as the TNM staging system predict prognosis better than do clinical systems, particularly when assessing the outcomes of resection. As noted above, only the AJCC staging system has been validated in independent cohorts of patients undergoing either hepatic resection or transplantation. The Okuda, Barcelona, and CLIP systems are more useful for predicting

outcomes in patients with poor liver function who have advanced HCC and are undergoing nonsurgical therapy [25].

The consensus of the Americas Hepato-Pancreato-Biliary Association (updated in 2010) reasserts the need to use different systems in different patients. Their consensus statement recommends the use of the TNM system to predict outcome following resection or liver transplantation and the BCLC scheme for patients with advanced HCC who are not candidates for surgery [41].

OTHER FACTORS INFLUENCING SURVIVAL

In addition to the severity of liver disease and the tumor characteristics discussed above, several other features related to survival have emerged from a large number of heterogeneous studies. (See "Management of potentially resectable hepatocellular carcinoma: Prognosis, role of neoadjuvant and adjuvant therapy, and posttreatment surveillance", section on 'Long-term outcomes'.)

High- versus low-incidence regions — Overall survival appears to be shorter in high-incidence regions compared with low-incidence regions. The median survival of untreated patients from the time of hepatocellular carcinoma (HCC) diagnosis ranged from less than one to three months in high-incidence areas of Africa and Asia to between two and four months in relatively low-incidence Western countries in a number of reports [11,42,43]. This difference may in part be explained by variability in the frequency of extrahepatic metastasis at the time of diagnosis. Metastases were present in greater than 50 percent of African and Asian patients, while in Western patients, only one-third of those without cirrhosis and one-half of those with cirrhosis had metastasis at diagnosis [42-44].

Tumor histology — Well-differentiated clear cell tumors and the presence of tumor encapsulation have been associated with a better prognosis [45]. Some suggest the utility of using tumor grade to select patients for treatment (eg, liver transplantation) [46], although this has not yet been accepted into practice.

Serum alpha-fetoprotein level — The serum alpha-fetoprotein (AFP) level at presentation correlates with tumor size and extent [47]. The relationship between tumor growth and the rise in serum AFP was evaluated in a report that included 22 Japanese patients with cirrhosis and HCCs that were fewer than 3 cm who were followed for up to 37 months without treatment [48]. Serum AFP levels tended to increase when the mass attained a diameter of greater than 3 cm; in particular, a sudden acceleration in the rate of increase in AFP level often coincided with a

significant change in the ultrasonographic appearance of the tumor. The serum AFP levels progressively rose to between 1000 and 10,000 ng/mL as the tumors increased in size past 5 cm in diameter.

The serum AFP level also appeared to be an independent predictor of survival in some reports even after adjusting for its interaction with tumor size and histology. In one report, for example, survival in patients with a serum AFP of greater than 10,000 ng/mL at diagnosis was significantly shorter compared with those with a serum AFP <200 ng/mL (7.6 versus 33.9 percent) [49]. High AFP levels were associated with poorly differentiated tumors.

Whether preoperative AFP levels represent an independent prognostic factor in patients undergoing resection for HCC is unclear; the data are mixed. Several studies indicate a worse postresection prognosis in patients with higher levels of AFP [50-53], while others have failed to find such an association [54-57].

Variant estrogen receptors — A variant form of the wild-type estrogen receptor has been identified in some patients with HCC in which the receptor maintains constitutive transcriptional activity [58]. Tumors containing this variant tend to be more aggressive with shorter doubling times. The presence of variant estrogen receptors was a better predictor of an unfavorable prognosis compared with the Cancer of the Liver Italian Program (CLIP) and Barcelona classifications in a study involving 96 patients (44 of whom had the variant receptor) [24]. At present, testing for the variant receptor is not performed routinely.

Hepatitis B and C — The role of hepatitis B virus (HBV) infection in determining the risk of posthepatectomy tumor recurrence is controversial; the available data are conflicting [21,59-61]. Some reports show an adverse effect of hepatitis B e antigen (HBeAg)-positive status as compared with HBeAg-negative status in terms of HCC recurrence and survival after hepatectomy, perhaps as a result of more active viral replication and a greater predisposition to multiple carcinogenesis in those who are HBeAg positive [61,62]. Nomograms have been developed to predict survival after resection in Chinese populations with HBV-related HCC that include positivity for HBeAg [63]. (See "Management of potentially resectable hepatocellular carcinoma: Prognosis, role of neoadjuvant and adjuvant therapy, and posttreatment surveillance", section on 'Underlying liver dysfunction'.)

Most studies have found a higher tendency for earlier recurrence in patients with resected HCC who are hepatitis C virus (HCV) infected versus HBV infected [64-66]. This is likely the result of a high frequency of metachronous carcinogenesis in these patients.

Antiviral therapy for HBV-related hepatocellular carcinoma — Among patients with hepatitis B virus (HBV)-related HCC, higher viral load (serum HBV DNA of >106 copies/mL) has

been associated with higher rates of recurrence after resection, particularly late recurrence [67,68]. These data suggest that antiviral therapy to suppress HBV replication might reduce the rate of HCC recurrence and improve outcomes. Unfortunately, the available data on interferon and nucleoside analogs are insufficient to answer the question of whether antiviral therapy after a potentially curative resection of HCC will prevent disease recurrence. This subject is addressed in detail elsewhere. (See "Management of potentially resectable hepatocellular carcinoma: Prognosis, role of neoadjuvant and adjuvant therapy, and posttreatment surveillance", section on 'Antiviral therapy'.)

Diabetes mellitus — Diabetes mellitus (DM) is a risk factor for HCC. (See "Epidemiology and risk factors for hepatocellular carcinoma", section on 'Diabetes mellitus'.)

In addition, having the disease also impacts prognosis. A meta-analysis of 21 cohort and case-control studies with a total of 9767 HCC patients came to the following conclusions [69]:

- The pooled hazard ratios (HRs) for the association of DM with overall survival or disease-free survival were 1.46 (95% CI 1.29-1.66) and 1.57 (95% CI 1.21-2.05), respectively.
- For patients undergoing hepatic resection, DM was associated with both poorer overall survival and poorer disease-free survival, while for patients undergoing nonsurgical treatment including radiofrequency ablation alone, DM was associated with poorer overall survival.

New prognostic markers and methods under investigation — Other markers might improve staging and prognostic stratification:

- Patients with advanced HCC and low serum vascular endothelial growth factor (VEGF) levels have much longer survival at each stage (CLIP or Barcelona classification) than do those with higher VEGF levels [70,71]. Combining VEGF with CLIP has been termed "V-CLIP" staging.
- Patients with high plasma levels of insulin-like growth factor 1 (IGF-1) have better survival than do those with low levels [71,72]. The addition of plasma IGF-1 levels to CLIP has been referred to as "I-CLIP" staging.
- Measurement of cancer cell survival and growth factors, and gene expression profiling may improve prognostication. Examples include overexpression of the forkhead box M1 (*FOXM1*) gene, which is associated with poor outcome [73]; expression of the *AKR1B10* (aldo-keto reductase enzyme) gene, which may be associated with less aggressive tumor behavior [74]; gene expression profiling in both tumor tissue and adjacent normal liver

tissue, which has been associated with prognosis following resection [75-77]; and epigenetic factors such as DNA methylation profile [78].

These and other histologic, serologic, and molecular markers combined with conventional staging approaches hold promise, but further study is needed.

- Positron emission tomography (PET) with fluorodeoxyglucose (FDG) is being investigated as a complementary staging tool that may help to define prognosis in some patients. As examples:
  - Patients with non-FDG-avid HCC beyond the Milan criteria may have a good outcome from liver transplantation [79].
  - FDG avidity may correlate with therapeutic efficacy for treatments such as TACE [80], sorafenib [81], and external beam radiation therapy [82].
- Also under investigation are radiogenomic and radiomic methods to predict prognosis or better identify prognostic factors such as microvascular invasion not currently possible with standard imaging methods. Examples include radiogenomic correlation between CT imaging findings and tumor molecular profiles to create correlation maps used to predict vascular invasion based on CT imaging [83].

These and other radiologic, histologic, serologic, and molecular markers combined with conventional staging approaches hold promise, but further study is needed.

Clinical implications — A critical component to the development of a treatment plan for patients with HCC is the recognition that carefully selected patients can undergo aggressive treatment (such as liver resection) with excellent outcomes, even if they have poor prognostic factors. As examples, some patients with major vascular invasion benefit from hepatic resection [84,85], and long-term survival can be achieved following resection of multinodular HCC [15,86,87].

Thus, while algorithms are useful for conceptualizing the various treatment options that are available for individual patients (algorithm 1), algorithms that exclude patients from consideration for aggressive treatment based on the presence of poor prognostic factors (eg, highly elevated AFP, major vascular invasion, multinodular tumors, or even cirrhosis) should not be used to supersede careful, multidisciplinary consideration of each patient before treatment plans are devised. (See "Overview of treatment approaches for hepatocellular carcinoma".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hepatocellular carcinoma".)

SUMMARY

- **Staging and prognostic scoring systems based on liver function and tumor extent**
  - A number of systems have been proposed to predict the prognosis for hepatocellular carcinoma (HCC). These schema variably incorporate four features that are important determinants of survival in HCC:
    - The severity of the underlying liver disease
    - Tumor size
    - Extension of the tumor into adjacent structures
    - The presence or absence of metastases
  - The four most commonly used systems are the tumor, node, metastasis (TNM) system of the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) (table 1), the Okuda system, the Barcelona Clinic Liver Cancer (BCLC) system, and the Cancer of the Liver Italian Program (CLIP) score. A new, evidence-based score, the albumin-bilirubin (ALBI) grade, if independently validated, may allow more objective assessment of the severity of liver dysfunction in patients with HCC across a wide spectrum of treatments. (See 'Staging and prognostic scoring systems' above.)

    There is no single staging system that is best in predicting the survival of patients with HCC, and none of these schema have been universally adopted or is applicable to all patients. The consensus of the Americas Hepato-Pancreato-Biliary Association (updated in 2010) reasserts the need to use different systems in different patients. Their consensus statement recommends the use of the TNM system to predict outcome following resection or liver transplantation and the BCLC scheme for patients with advanced HCC who are not candidates for surgery. (See 'Choice of staging system' above.)
- **Other prognostic factors** – In addition to the severity of the underlying liver disease and the extent of disease spread, other factors influencing survival include whether patients are living in high-incidence versus low-incidence areas, the histologic grade of

differentiation, and levels of serum alpha-fetoprotein (AFP) at diagnosis. (See 'Other factors influencing survival' above.)

- **Clinical use** – Algorithms have been developed that are useful for conceptualizing the various treatment options that are available for individual patients based on tumor extent and liver function (algorithm 1); an alternative algorithm is available from the BCLC (figure 2). However, algorithms that exclude patients from consideration for aggressive treatment based on the presence of poor prognostic factors should not be used to supersede careful, multidisciplinary consideration of each patient before treatment plans are devised. Carefully selected patients can undergo aggressive treatment (such as liver resection) with excellent outcomes, even if they have poor prognostic factors.

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Topic 2476 Version 35.0

GRAPHICS

Hepatocellular cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≤2 cm, or >2 cm without vascular invasion
T1a	Solitary tumor ≤2 cm
T1b	Solitary tumor >2 cm without vascular invasion
T2	Solitary tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm
T3	Multiple tumors, at least one of which is >5 cm
T4	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups			
When T is…	**And N is…**	**And M is…**	**Then the stage group is…**
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II

T3	N0	M0	IIIA
T4	N0	M0	IIIB
Any T	N1	M0	IVA
Any T	Any N	M1	IVB

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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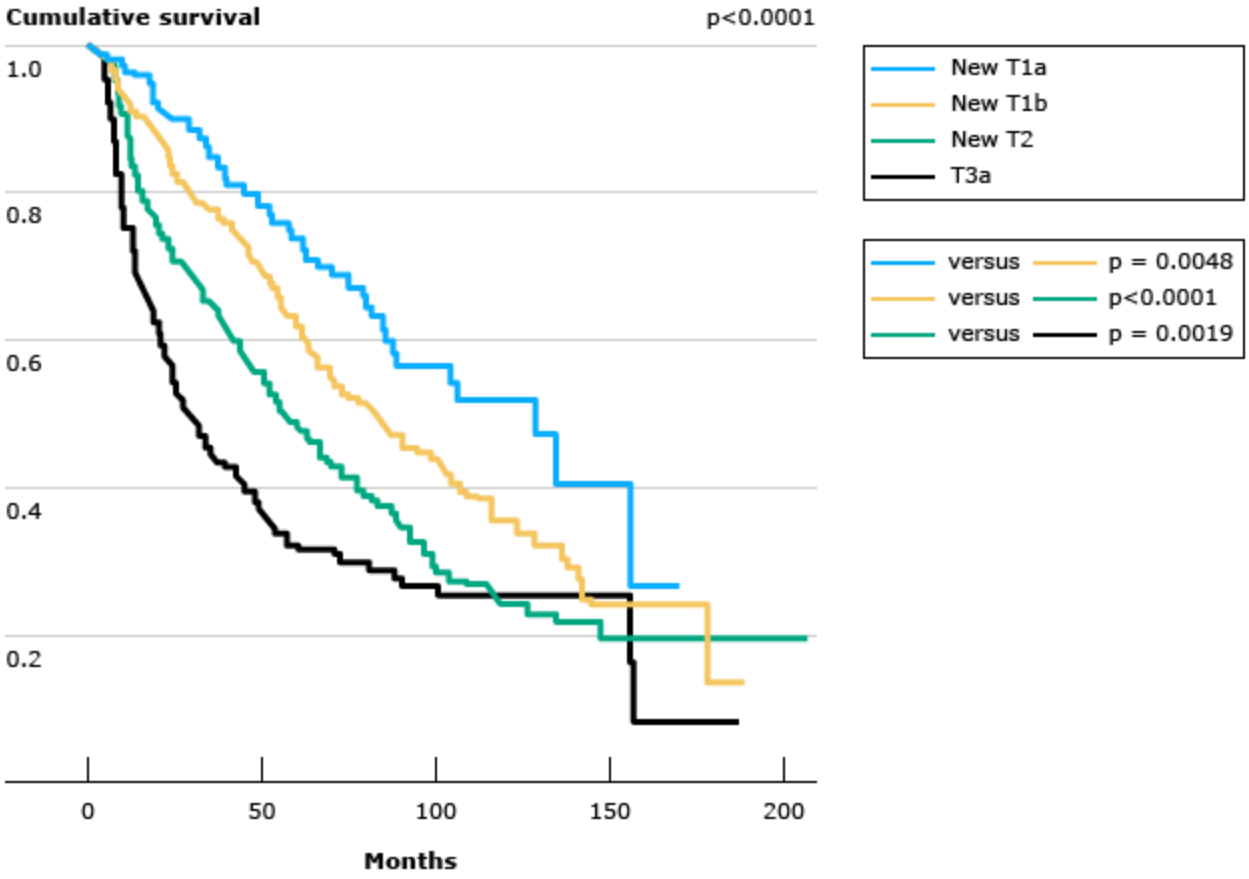
Graphic 110835 Version 8.0

Prognostic influence of tumor size and microvascular invasion on prognosis of HCC after surgical resection, using the revised primary tumor (T) stages from the 8th edition AJCC/UICC TNM classification, 2017



Survival of patients with solitary HCC according to tumor size and microvascular invasion, and new classification of HCC. Proposed new classification by stage.

HCC: hepatocellular carcinoma; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; TNM: tumor, node, metastasis.

Graphic 110834 Version 8.0

Okuda staging system for hepatocellular carcinoma

Criteria	Positive	Negative
Tumor size*	>50%	<50%
Ascites	Clinically detectable	Clinically absent
Albumin	<3 g/dL	>3 g/dL
Bilirubin	>3 mg/dL	<3 mg/dL
Stage		
I	No positive	
II	One or two positives	
III	Three or four positives	

The Okuda system is commonly used for staging hepatocellular carcinoma. Survival correlates with the Okuda stage in untreated patients (8.3, 2.0, and 0.7 months for stages I, II, and III, respectively).

* Largest cross-sectional area of tumor to largest cross-sectional area of the liver.

Adapted from: Okuda K, Ohtuiki T, Obata H, et al. Cancer 1985; 56:918.

Graphic 56735 Version 4.0

CLIP (Cancer of the Liver Italian Program) scoring system for hepatocellular cancer

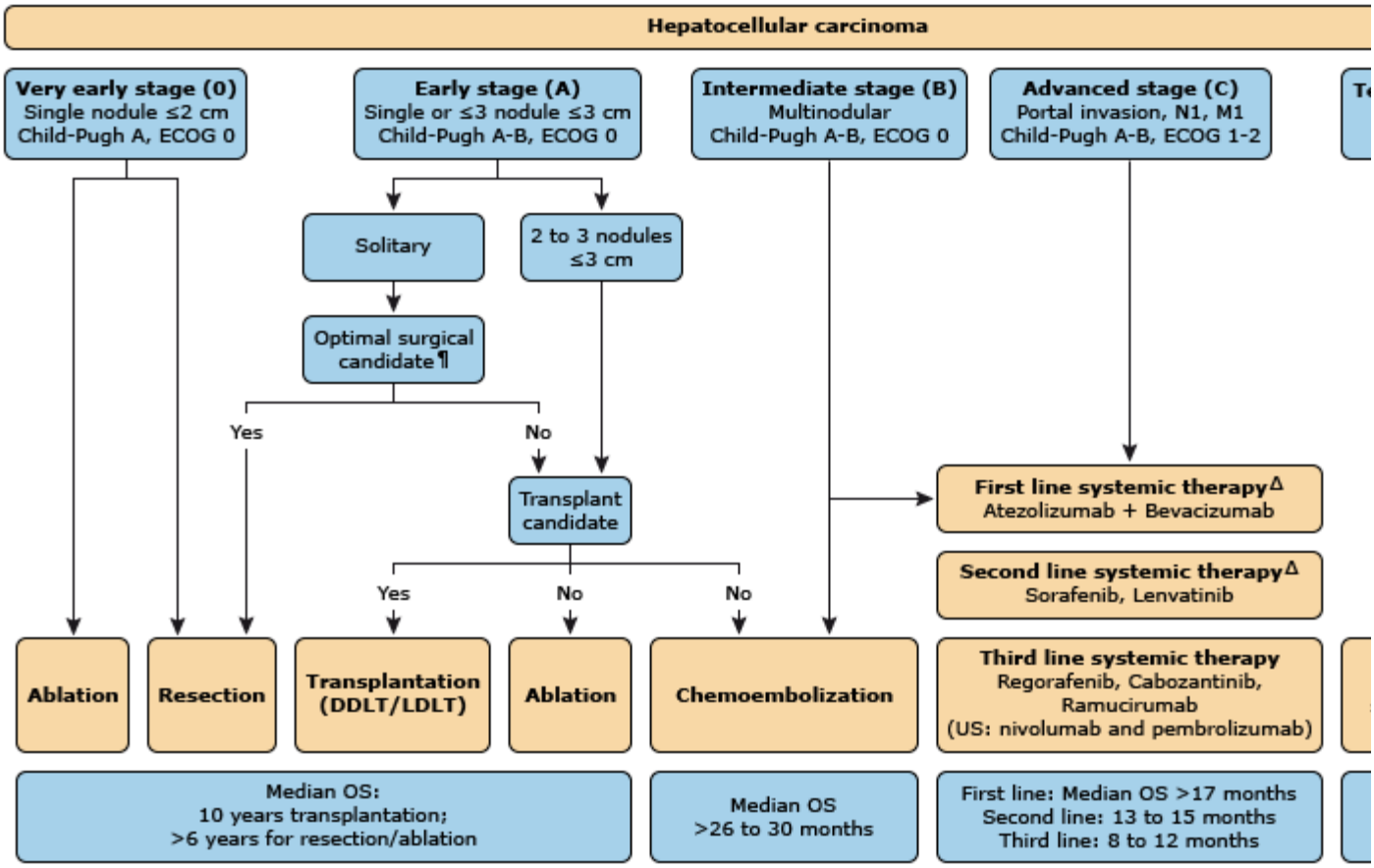
Variable	Score
Child-Pugh stage	
A	0
B	1
C	2
Tumor morphology	
Uninodular and extension ≤50%	0
Multinodular and extension ≤50%	1
Massive or extension >50%	2
Alpha-fetoprotein	
<400	0
≥400	1
Portal vein thrombosis	
No	0
Yes	1

The Cancer of the Liver Italian Program (CLIP) score has been used to predict survival in patients with hepatocellular carcinoma. The total score is derived by adding each of the subscores. In one study, median survival was 36, 22, 9, 7, and 3 months for patients in CLIP categories 0, 1, 2, 3, and 4 to 6, respectively.

Prospective validation of the CLIP score: A new prognostic system for patients with cirrhosis and hepatocellular carcinoma. Hepatology 2000; 31:840. Copyright © 2000 Elsevier Science.

Graphic 69726 Version 5.0

Updated Barcelona Clinic Liver Cancer (BCLC) treatment strategy for managing hepatocellular carcinoma, 2022



Management of patients with HCC is guided by the BCLC staging system, which takes into account both tum the severity of the underlying liver disease and defines five prognostic subgroups with respective treatment for early-stage tumors is with curative intent, and options include RFA, hepatic resection, and liver transplan Patients with intermediate or advanced HCC are candidates for chemoembolization or systemic therapies, re

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ECOG: Eastern Cooperative Oncology Group; N1: lymph node metastasis; M1: distant metastasis; DDLT: dece liver transplantation; LDLT: living donor liver transplantation.

* Patients with end-stage liver disease if Child-Pugh class C should first be considered for liver transplantatic

¶ Patients with preserved hepatic function Child-Pugh class A with normal bilirubin and no portal hypertens candidates for hepatic resection.

Δ Atezolizumab plus bevacizumab has been approved as new first-line treatment for advanced HCC. Noneth sorafenib and lenvatinib are still considered first line options when there is a contraindication for the combi treatment.

From: Llovet JM, Villanueva A, Marrero JA, et al. Trial Design and Endpoints in Hepatocellular Carcinoma: AASLD Consensus Conference 2021; 73 Suppl 1:158-191. https://aasldpubs.onlinelibrary.wiley.com/doi/10.1002/hep.31327. Copyright © 2021 American Association Liver Diseases. Reproduced with permission of John Wiley & Sons Inc. This image has been provided by or is owned by Wiley. Further p needed before it can be downloaded to PowerPoint, printed, shared or emailed. Please contact Wiley's Permissions Department either

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Graphic 139139 Version 1.0

Eastern Cooperative Oncology Group (ECOG) performance status

Performance status	Definition
0	Fully active; no performance restrictions.
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work.
2	Capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair >50% of waking hours.
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

Adapted from: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649.

Graphic 72901 Version 12.0

Child-Pugh classification of severity of cirrhosis

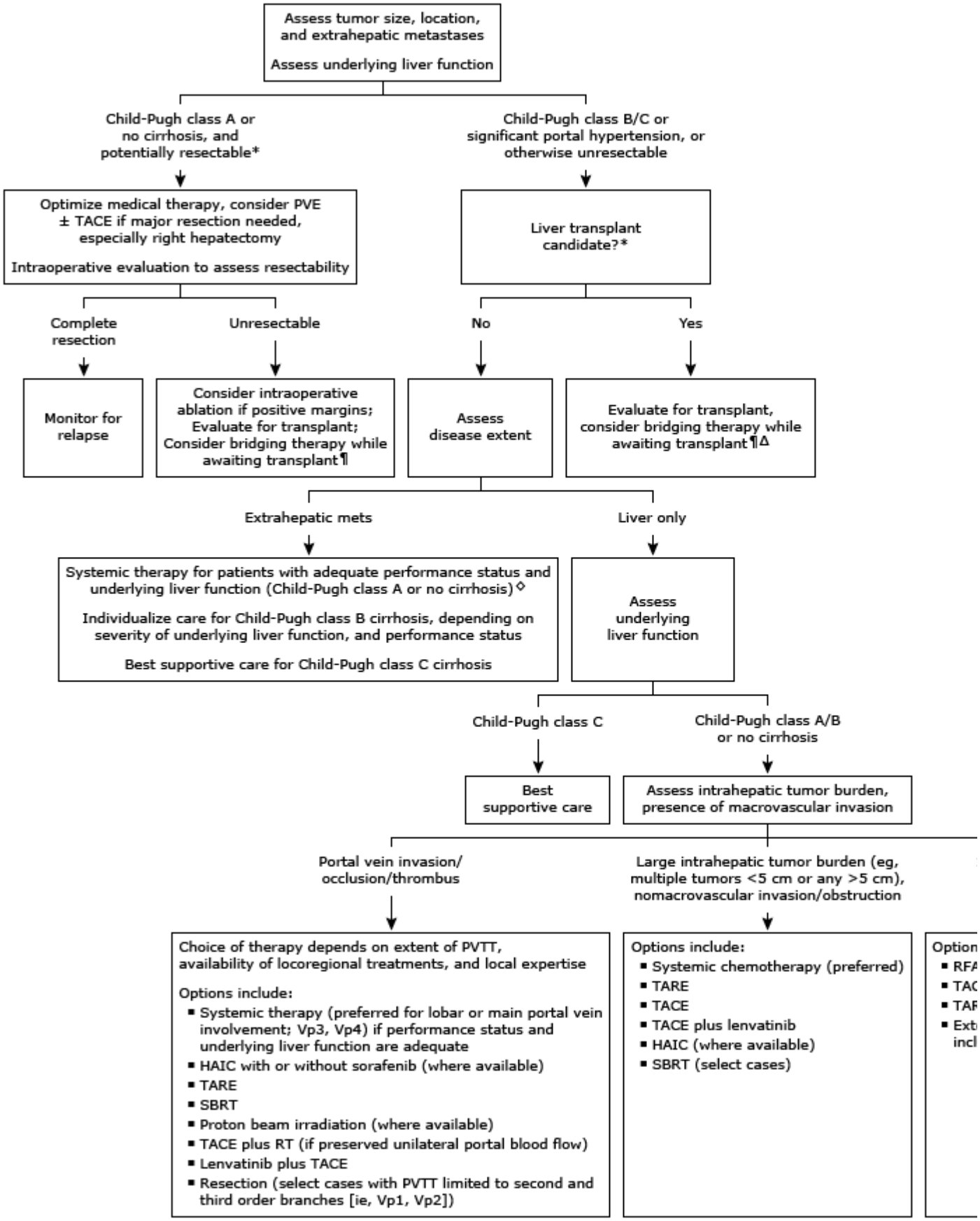
Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time (seconds over control) or	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh class A (well-compensated disease), 7 to 9 is class B (significant functional compromise), and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100 and 85%; class B: 80 and 60%; and class C: 45 and 35%.

INR: international normalized ratio.

Graphic 78401 Version 15.0

Overview of treatment algorithm for hepatocellular carcinoma



PVE: portal vein embolization; TACE: transcatheter arterial chemoembolization; PVTT: portal vein tumor thro arterial infusional chemotherapy; TARE: transarterial radioembolization; SBRT: stereotactic body radiation th radiofrequency ablation; HCC: hepatocellular carcinoma.

* Selected patients with Child-Pugh class B cirrhosis may be amenable to limited resection.

¶ Bridging therapy refers to the administration of local treatment (typically RFA or TACE) while awaiting orth transplantation in order to reduce risk of progressing beyond Milan criteria.

Δ In the United States, patients with underlying chronic liver disease (cirrhosis, hepatitis C virus infection) ar orthotopic liver transplant if they fulfill the Milan criteria (ie, solitary HCC ≤5 cm in diameter or up to three s which is larger than 3 cm, no evidence of gross vascular invasion, and no regional nodal or distant metastas extended liver transplantation criteria may undergo downstaging therapy (eg, RFA, arterially-directed therap reassessment for liver transplantation.

◇ Options for initial systemic therapy include participation in a clinical trial (preferred), atezolizumab plus be plus tremelimumab, sorafenib, or lenvatinib (refer to UpToDate text).

§ RFA is most effective at treating smaller tumors, and many institutions restrict RFA to lesions <4 cm.

Graphic 57014 Version 16.0

Contributor Disclosures

Steven A Curley, MD, FACS No relevant financial relationship(s) with ineligible companies to disclose. **Carlton C Barnett, Jr, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Eddie K Abdalla, MD, FACS** Consultant/Advisory Boards: Sirtex [Trials preparation]. Speaker's Bureau: Sirtex [Surgery for primary and secondary liver tumors]. Other Financial Interest: Sirtex [Primary and secondary liver tumors]. All of the relevant financial relationships listed have been mitigated. **Kenneth K Tanabe, MD** Patent Holder: EGF SNP to determine risk for HCC [Cirrhosis, hepatocellular carcinoma]; Use of EGFR inhibitors to prevent HCC [Cirrhosis, hepatocellular carcinoma]. Consultant/Advisory Boards: Cancer Expert Now [GI cancers, melanoma]; GSK [GI Cancers]; Imvax [GI cancers]; Leidos [Melanoma, GI cancers]; Teledoc [GI cancers, melanoma]. Other Financial Interest: American Cancer Society [Honoraria as editor of Cancer]. All of the relevant financial relationships listed have been mitigated. **Sonali M Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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