Overview of treatment approaches for hepatocellular carcinoma

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INTRODUCTION

Hepatocellular carcinoma (HCC) is an aggressive tumor that usually occurs in the setting of chronic liver disease and cirrhosis. (See "Epidemiology and risk factors for hepatocellular carcinoma".)

Although the best long-term survival is observed after surgical therapies, most patients are not eligible because of tumor extent or underlying liver dysfunction. Surgical resection is a potentially curative therapy for patients without cirrhosis or for those patients with cirrhosis who lack portal hypertension, and liver transplantation is a potentially curative therapy for select patients who are not candidates for resection. (See "Surgical management of potentially resectable hepatocellular carcinoma" and "Liver transplantation for hepatocellular carcinoma".)

Several other noncurative treatment modalities are available, including:

- Liver-directed therapies:
  - Thermal ablation (radiofrequency ablation, microwave ablation, and cryoablation)
  - Percutaneous ethanol or acetic acid ablation (rarely used if thermal ablation is available)
  - Irreversible electroporation, a non-thermal form of ablation
  - Transarterial chemoembolization and bland embolization

- Transarterial radioembolization (also called radioembolization)
- External beam radiation therapy, including stereotactic body radiation therapy
- Hepatic arterial infusion chemotherapy (requires specific center expertise)

- Systemic therapies, including:
  - Molecularly targeted therapies
  - Immunotherapy using immune checkpoint inhibitors
  - Cytotoxic chemotherapy (rarely used given better outcomes with molecularly targeted therapies and immunotherapy)
- Newer approaches that combine liver-directed and systemic therapies

For individual patients, appropriate treatment options are determined both by the extent of the HCC and the severity of underlying liver disease, which can limit tolerance to all therapies (medical, interventional, or surgical).

This topic provides an overview of the treatment of HCC, focusing on the integration of systemic and locoregional therapies. Detailed discussions on individual treatment options are available.

- (See "Surgical management of potentially resectable hepatocellular carcinoma".)
- (See "Management of potentially resectable hepatocellular carcinoma: Prognosis, role of neoadjuvant and adjuvant therapy, and posttreatment surveillance".)
- (See "Liver transplantation for hepatocellular carcinoma".)
- (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates who are eligible for local ablation".)
- (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates not eligible for local thermal ablation".)
- (See "Systemic treatment for advanced hepatocellular carcinoma".)

Issues surrounding the diagnosis of HCC and screening for HCC in patients at risk, as well as response assessment for patients receiving systemic or nonsurgical locoregional therapy are also addressed in detail elsewhere. (See "Clinical features and diagnosis of hepatocellular carcinoma" and "Assessment of tumor response in patients receiving systemic and nonsurgical locoregional treatment of hepatocellular cancer".)

TREATMENT ALGORITHMS

Our general approach — An overview of our general approach to treatment of HCC is shown in the algorithm (algorithm 1). Support for this approach is presented in the sections below.

The availability, efficacy and safety of specific therapeutic approaches, especially nonsurgical liver-directed therapies, tend to vary based upon the available expertise. We strongly urge that patients with HCC be referred to specialized centers of excellence with multidisciplinary expertise so that the entire range of potentially available treatments can be offered. (See 'Importance of multidisciplinary care' below.)

BCLC algorithm — The Barcelona Clinic Liver Cancer (BCLC) staging system has been a dominant approach to HCC internationally [1]. 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 1) [2].

However, growing movements in the West and in Asia disagree with some principles of the algorithm [3,4]. The main points of disagreement are as follows:

- The BCLC algorithm does not acknowledge the potential value of resection for patients that do not fit their eligibility criteria, including some patients with single large tumors and those with multiple nodules [2], or limited macrovascular invasion. Selected patients with large or multifocal tumors, or limited vascular invasion may in fact benefit from surgical resection, as described below. However, the best results are achieved with careful patient selection, which should be done in the setting of multidisciplinary evaluation and in high-volume centers with surgical expertise. (See "Surgical management of potentially resectable hepatocellular carcinoma", section on 'Preoperative assessment' and "Management of potentially resectable hepatocellular carcinoma: Prognosis, role of neoadjuvant and adjuvant therapy, and posttreatment surveillance", section on 'Preoperative evaluation'.)

  As examples:

  - In one large multi-institutional study among 2046 consecutive patients undergoing resection for HCC in high-volume centers, nearly one-half (1012) were not directed by the Barcelona algorithm to have surgery, yet survival was far better than that predicted by the BCLC (five-year overall survival rates were 61, 57, and 38 percent for patients with Barcelona stage 0/A, B, and C, respectively; overall 90-day mortality was <3 percent) [4].

  - A meta-analysis of seven studies (one randomized trial, six propensity score-matched retrospective analyses, total 2487 patients) concluded that for patients with BCLC stage B HCC, partial hepatectomy was associated with better overall survival than transarterial chemoembolization (TACE; hazard ratio [HR] 1.65, 95% CI 1.48-1.84) [5].

- Large tumor size does not appear to impact survival when vascular invasion is absent (eg, T1 tumors according to the Tumor, Node, Metastasis [TNM] staging system of the American Joint Committee on Cancer [AJCC]/Union for International Cancer Control [UICC] (table 1)) [6]. Further, patients with T2 tumors (a solitary tumor with vascular invasion or multiple tumors, none more than 5 cm) may be suitable candidates for resection when liver function permits. Others have shown benefit from hepatic resection for patients with single HCCs over 5 cm in diameter and selected patients with tumors ≥10 cm. For these patients, multidisciplinary discussion is recommended to discuss surgical resection versus liver transplantation.

- In another analysis of 278 patients with therapy-naïve HCC and portal vein tumor thrombus (PVTT), resection was associated with better outcomes than TACE, transarterial radioembolization, or sorafenib among patients whose portal vein thrombus was limited to a subsegmental branch (ie, Vp1), but not for more extensive invasion [7]. (See 'Patients with portal vein tumor thrombus' below.)

- Others question the use of performance status (table 2) to define advanced stage disease for which surgical resection is not indicated, regardless of tumor size or other characteristics [8].

- BCLC stage C (figure 1) represents a heterogeneous group. Although the algorithm suggests systemic chemotherapy for all patients, some may benefit from locoregional treatments (including resection) rather than systemic therapy. As an example, patients with a subsegmental branch tumor thrombus involving the portal vein (ie, Vp1 or Vp2) have a better prognosis and are potential candidates for certain locoregional treatments or surgical resection. By contrast, patients with more extensive tumor-associated thrombus involving the main portal vein (Vp3 or 4) have a less favorable outcome with most locoregional treatments, and may be better candidates for initial systemic chemotherapy. These issues and the classification system for PVTT is described in more detail below. (See 'Patients with portal vein tumor thrombus' below.)

Asia-pacific consensus and intermediate-stage HCC — The best way to manage intermediate-stage HCC (BCLC B classification, (figure 1)) is debated. If transplantation is not an option, the BCLC algorithm suggests TACE for "well-defined nodules with preserved portal flow," and chemotherapy for those with "diffuse, infiltrative, extensive bilobar involvement" [2].

Patients with limited BCLC stage B disease who are initially beyond the classic Milan Criteria and who respond to TACE or other locoregional therapy may be downstaged to where they are eligible for liver transplantation. Several studies have shown that patients who present with

BCLC stage B disease who are successfully downstaged have good overall survival and low recurrence post-transplant. The XXL trial also demonstrated that patients who undergo liver transplantation after downstaging have significantly better survival than those patients who continue locoregional therapy alone [9]. (See "Liver transplantation for hepatocellular carcinoma", section on 'Requirements for listing and management while on the wait list' and "Liver transplantation for hepatocellular carcinoma", section on 'Downstaging through neoadjuvant locoregional therapy'.)

The 2019 Asia-Pacific consensus conference was designed to further refine which patients with HCC in the intermediate risk category were suitable for TACE versus better served with systemic therapy [10,11]. They used a slightly different definition of intermediate-stage HCC, adding a single tumor with maximum size ≥5 cm, to the usual criteria for BCLC stage B. They defined "Up-To-Seven" criteria (ie, HCC with no more than seven as the sum of the size of the largest tumor [in cm] plus the number of tumors total) the same as the initial description that was first used to aid in the selection of patients with HCC beyond the Milan criteria for liver transplantation [12]. Based on a number of reports indicating that repeated TACE procedures led to a deterioration of liver function in individuals with HCC beyond the "Up-To-Seven" criteria ("Up-To-Seven" criteria-out) [13-17], and the finding that poor liver function as assessed by the modified albumin-bilirubin (ALBI) score [15,17] was associated with poor survival and rapid progression after TACE, they defined the following patients as being "TACE-unsuitable":

- Confluent multinodular type, massive or infiltrative type, simple nodular type with extranodular growth, poorly differentiated type, intrahepatic multiple disseminated nodules.
- Beyond the "Up-To-Seven" criteria (especially bilobar multifocal HCC).
- ALBI score ≥2 (calculator 1). (See "Staging and prognostic factors in hepatocellular carcinoma", section on 'Albumin-bilirubin (ALBI) score'.)

Our approach to individuals with unresectable HCC who are ineligible for transplant, and lack macrovascular invasion but have a large intrahepatic tumor burden is discussed below. (See 'Large intrahepatic tumor burden' below.)

Limitations — Algorithmic approaches help conceptualize the available treatment options, but may not be applicable in all settings. Several challenges complicate the development of algorithmic approaches to the treatment of HCC:

- Tumor extent alone cannot be used to select treatment. Many of the staging systems (including the TNM staging system of the combined AJCC/UICC (table 1)) are based

upon surgical findings and do not incorporate other important factors, such as underlying liver dysfunction and performance status. (See "Staging and prognostic factors in hepatocellular carcinoma", section on 'Choice of staging system'.)

Outside of the context of hepatic resection, most expert groups acknowledge that there is no universal perfect staging system but many endorse the BCLC staging system since it is the most widely validated [18-20]. (See "Staging and prognostic factors in hepatocellular carcinoma".)

- For patients with cirrhosis, the Child-Pugh classification (table 3) is used most widely to stratify prognosis according to underlying liver function. However, this score has not been validated in patients with HCC; other measures (such as the ALBI score, which have been validated in patients with HCC, are increasingly used (calculator 1). (See "Staging and prognostic factors in hepatocellular carcinoma", section on 'Staging and prognostic scoring systems' and "Assessing surgical risk in patients with liver disease".)

  Notably, in earlier versions of the BCLC algorithm, liver function was assessed only according to the Child-Pugh score [21]. The updated guidelines from BCLC suggest that liver function be evaluated beyond the conventional Child-Pugh score [2]; 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" [22].

- The availability, efficacy, and safety of specific therapeutic approaches, especially nonsurgical liver-directed therapies, tend to vary based upon the available expertise. We strongly urge that patients with HCC be referred to specialized centers of excellence with multidisciplinary expertise so that the entire range of potentially available treatments can be offered.

- New treatments for HCC and indications for various treatments are evolving rapidly. This is especially true in the area of systemic therapy. Given recent advances, the best way to integrate systemic and locoregional therapies is increasingly difficult to delineate as eligibility for individual treatments becomes blurred. (See 'Locoregional plus systemic therapy' below.)

  These new developments have particular implications for the management of patients with liver-limited disease who are not surgical candidates because of large tumor size, number of lesions, or technically inoperable disease, but whose liver function is adequate to tolerate some form of therapy (intermediate stage, BCLC B stage, (figure 1)). In this setting, locoregional liver-directed therapies have been the mainstay of therapy because of

high local response rates and generally favorable safety profiles. However, not all patients who receive these therapies have a survival benefit, and some will never receive systemic therapy because of disease progression or decline in hepatic function. The increasing arsenal of effective systemic therapies, especially immunotherapies, has raised new questions about appropriate selection of patients with unresectable HCC for locoregional versus systemic therapies, including whether patients should be deemed refractory to locoregional therapy before switching to systemic therapies, and whether combination strategies would improve outcomes [23].

These issues are in evolution, and the approach is variable among specialized centers of excellence:

- At some institutions, systemic therapy is no longer reserved until failure of all local liver-directed therapies, but instead, used earlier, and sometimes in place of locoregional therapy, especially for patients with a large intrahepatic disease burden or PVTT. This practice is based on lower objective responses and higher risk of liver dysfunction with locoregional therapies in these settings when compared with patients with more limited tumor burden. Although there is no consensus definition for "TACE unsuitable" patients, the Asia-Pacific Consensus statement suggests that patients with tumor burden beyond "Up-to-Seven" Criteria, those with infiltrative disease, or those with bilobar multifocal disease are better candidates for up-front systemic therapy [10]. (See 'Asia-pacific consensus and intermediate-stage HCC' above.)

  This approach is supported by a propensity-score matched analysis which demonstrated the superiority of lenvatinib over TACE in this setting [24]. (See 'Large intrahepatic tumor burden' below.)

- However, at other institutions, locoregional therapy is still a preferred approach for eligible patients, even those with a large intrahepatic tumor burden. (See 'Large intrahepatic tumor burden' below.)

IMPORTANCE OF MULTIDISCIPLINARY CARE

We strongly urge that patients with HCC (especially liver-localized HCC) be referred to specialized centers of excellence with multidisciplinary expertise so that the entire range of potentially available treatments can be offered, along with monitoring, assessment, and treatment of the underlying liver disease.

The wide variety of treatments for HCC are offered by different specialties: surgery, transplant hepatology, interventional radiology, radiation oncology, and medical oncology. Multidisciplinary evaluation, planning, and management is frequently coordinated by hepatologists and improves patient outcomes [25-27]. Multidisciplinary teams typically provide more thoroughly vetted recommendations and are less likely to recommend suboptimal therapies driven by provider expertise rather than individual patient factors. In particular, and as noted below, for patients with apparently liver-isolated tumors, determining resectability is highly dependent on the skill, expertise, and comfort level of the treating surgeon/center. (See 'Patient selection for hepatic resection' below.)

Most patients with HCC have underlying liver disease and are at risk for progression to liver failure. Proper monitoring, assessment, and treatment of the underlying liver disease (especially hepatitis C virus [HCV] [28]) can improve long-term survival. The comprehensive care of patients with cirrhosis includes antiviral therapy for hepatitis B and C virus, immunization against hepatitis A and B virus (if indicated), regular surveillance for HCC with abdominal imaging, and endoscopic screening and surveillance for varices. (See 'Role of adjuvant therapy' below and "Epidemiology and risk factors for hepatocellular carcinoma" and "Cirrhosis in adults: Overview of complications, general management, and prognosis".)

OVERVIEW OF TREATMENT OPTIONS

What follows is a brief overview of the available treatment options, including the usual eligibility/ineligibility criteria for individual approaches. An algorithmic outline of our general approach to treatment is provided (algorithm 1).

Potentially resectable disease

Patient selection for hepatic resection — Hepatic resection is a potentially curative therapy and the preferred treatment for eligible patients. The ideal patient for resection has a solitary potentially resectable HCC confined to the liver that shows no radiographic evidence of invasion of the hepatic vasculature, and well-preserved hepatic function (Child-Pugh class A) without evidence of portal hypertension. Long-term relapse-free survival rates average 40 percent or better, and five-year survival rates as high as 90 percent are reported in carefully selected patients. (See "Surgical management of potentially resectable hepatocellular carcinoma", section on 'Preoperative assessment' and "Management of potentially resectable hepatocellular carcinoma: Prognosis, role of neoadjuvant and adjuvant therapy, and posttreatment surveillance", section on 'Long-term outcomes'.)

However, there is no consensus on the appropriate selection of patients for hepatic resection and practice is variable:

- The 2022 BCLC algorithm largely restricts upfront resection to those patients who are not candidates for transplantation, have preserved liver function, a performance status of 0 (table 2), and a single nodule with normal portal pressures (figure 1) [2]. Although these treatment guidelines are endorsed by several groups, including the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) [19,29], others, including many of the authors and editors affiliated with UpToDate, disagree with this stringent definition of resectability. Notably, EASL and AASLD guidelines both support resection in patients who have mild portal hypertension, particularly with the introduction of minimally invasive techniques. (See 'BCLC algorithm' above.)

  By contrast, in the Asia-Pacific region, surgical resection may be offered to selected patients with more advanced disease, including those with portal vein tumor thrombus (PVTT) limited to the first branch of the main portal vein or above (ie, Vp1,Vp2, or Vp3, (figure 2)) [30-35]. (See 'Patients with portal vein tumor thrombus' below.)

- Perhaps more importantly, "resectability" is highly subjective concept in HCC, and this makes it difficult to develop algorithmic approaches to selecting patients for resection that are strictly based upon tumor location, size, number, or extent, and underlying liver function:

  - Judging the resectability of a tumor is highly dependent on the skill, expertise, and comfort level of the surgeon and center. As an example, most consider American Joint Committee on Cancer (AJCC) stage IIIB, IVA, and IVB disease to be incurable by resection (table 1). These stages are defined by invasion of a major portal or hepatic vein, direct invasion of organs other than the gallbladder, perforation of the visceral peritoneum, and nodal or distant metastases. However, hepatic resection for stage IIIB and IVA disease may be considered on a case by case basis in a center of excellence because clinical benefits and long-term survival can be achieved in a properly selected, though admittedly small, minority of patients. (See "Surgical management of potentially resectable hepatocellular carcinoma", section on 'Preoperative assessment'.)

    Tumor location is another important factor. As an example, a 2 cm HCC necessitating resection of segment 3 in the left lateral sector is a lower risk tumor for resection than a 2 cm tumor adjacent to the right hepatic vein and inferior vena cava that would require a right hepatic lobectomy.

- While most centers agree that Child-Pugh class B cirrhosis (table 3) or portal hypertension are strong relative contraindications to resection, limited resection might be feasible in selected patients. (See "Surgical management of potentially resectable hepatocellular carcinoma", section on 'Assessment of hepatic reserve' and "Management of potentially resectable hepatocellular carcinoma: Prognosis, role of neoadjuvant and adjuvant therapy, and posttreatment surveillance", section on 'Underlying liver dysfunction'.)

  For others, transplantation is preferred over resection for eligible patients. (See "Liver transplantation for hepatocellular carcinoma", section on 'Requirements for listing and management while on the wait list'.)

These data underscore the importance of referral of patients to a high-volume center of excellence with multidisciplinary expertise so that the full range of treatment options is available. (See 'Importance of multidisciplinary care' above.)

Resection versus ablation — Most patients who are eligible for resection are also candidates for thermal ablation. While thermal ablation is a less morbid procedure, and long-term outcomes may be similar, particular for tumors <2 cm in size, we suggest resection rather than ablation for most patients, particularly if resection can be done using a laparoscopic approach which reduces patient recovery time.

The benefit of radiofrequency ablation (RFA) relative to resection for potentially resectable HCC has been addressed in several randomized trials conducted in China, Japan, and Hong Kong [36-42], which have had mixed results; some conclude that surgery is superior, while others note similar outcomes. Two meta-analyses are available:

- A 2017 Cochrane analysis of four of these trials [36,37,40,41] concluded that resection was not significantly superior to RFA (hazard ratio [HR] for all-cause mortality 0.80, 95% CI 0.6-1.08) but that cancer-related mortality was significantly lower with surgery (odds ratio 17.4 versus 37.4 percent, HR 0.35, 95% CI 0.19-0.65) [43]. The risk of serious adverse events was significantly higher with surgery (23.3 versus 1.7 percent). However, many of the trials had a high risk of bias, and the quality of the evidence was deemed to be low.

- A year 2021 meta-analysis of seven randomized trials comparing resection with local ablation (RFA, microwave ablation [MWA], with or without transarterial chemoembolization [TACE]) also concluded that overall survival was not significantly better with resection (HR for five-year overall survival 0.85, 95% CI 0.55-1.29) but that both five-year relapse-free survival (HR 0.75, 95% CI 0.62-0.92) and local recurrence rates (HR 0.45, 95% CI 0.26-0.79) both favored surgery [44]. All studies were considered to have a risk of bias because of

lack of information on randomization method, baseline imbalances between the two groups in important prognostic factors (eg, Child-Pugh classification), or missing data.

Guidelines from the American Association for the Study of Liver Diseases suggest resection over RFA for adults with Child-Turcotte-Pugh class A cirrhosis (table 3) and resectable T1 or T2 HCC (table 1) [19]. Consensus-based guidelines from the National Comprehensive Cancer Network (NCCN) also state that resection is preferred over locoregional nonsurgical therapies, if feasible [20]. On the other hand, the updated BCLC classification suggests either is appropriate for a tumor ≤2 cm, no worse than Child-Pugh class A cirrhosis (figure 1) [2].

Role of adjuvant therapy — The high recurrence rate of HCC after surgical resection has prompted a search for effective postoperative "adjuvant" therapies. Postoperative antiviral therapy improves outcomes after potentially curative treatment of HCC that is related to hepatitis B virus (HBV) or HCV, and is recommended for those with active viral infection. The benefit of any other form of adjuvant therapy remains unproven and is not a standard approach. (See "Management of potentially resectable hepatocellular carcinoma: Prognosis, role of neoadjuvant and adjuvant therapy, and posttreatment surveillance", section on 'Postoperative therapy'.)

Unresectable liver-isolated disease — Patients who are not candidates for resection because of tumor extent or underlying liver dysfunction may be candidates for one of the following options:

- Liver transplantation (if they meet classic Milan criteria, are downstaged to within criteria, or have a potential living donor candidate)
- Locoregional liver-directed therapies (eg, thermal ablation, arterially-directed therapies [embolization and hepatic arterial infusion chemotherapy (HAIC)], and external beam radiation therapy [EBRT], including stereotactic body radiation therapy [SBRT])
- Systemic therapy

Although small case series suggest that radioembolization or systemic immunotherapy may downstage some patients who are not initial candidates for resection because of tumor extent to the point of potential resectability [45-47], this is not yet a widely accepted approach. (See 'Limited intrahepatic tumor burden' below.)

Liver transplantation — Liver transplantation is a potentially curative therapy for patients with HCC who are not surgically candidates (typically because of the degree of underlying liver dysfunction). Expanded transplantation criteria and downstaging to achieve transplant eligibility

are now widely accepted. Most patients will require bridging therapy prior to transplant because of time on the wait list.

- **Allocation of donor organs and the MELD exception score for HCC** – In the United States, deceased donor livers are allocated for orthotopic liver transplantation (OLT) by the Organ Procurement Transplantation Network (OPTN), which is operated under contract with the United States Department of Health and Human Services by the United Network for Organ Sharing (UNOS). Organ allocation for both adults and children is based upon the Model for End-Stage Liver Disease (MELD) score, a statistical model based upon predicted survival in patients with cirrhosis (calculator 2). (See "Model for End-stage Liver Disease (MELD)".)

  Patients with HCC are prioritized using a MELD exception score, which is a supplemental system designed to provide patients with HCC faster access to an allograft. Prioritization scores are based upon tumor size and number. To receive priority MELD points, the HCC must be stage T2 (table 4) and have an AFP level <1000 ng/mL [48]. Exception points are added after the patient has been waitlisted for at least six months, with the maximum exception points for waitlisted patients with HCC being limited to the median MELD score at the region of the donor hospital, minus 3 points (MMAT-3). Patients with recurrence after achieving complete response (eg, prior complete resection) who are eligible for transplantation are awarded immediate exception points to MMAT-3 without the six-month waiting period. Of note, these MELD exception criteria apply to patients with HCC only in the setting of cirrhosis. (See "Liver transplantation for hepatocellular carcinoma", section on 'Requirements for listing and management while on the wait list'.)

- **Bridging therapy** – The waiting time for a donor organ can be long and varies significantly region to region and country to country. Even among patients within the Milan criteria who have higher priority MELD exception scores, waiting times for a donor organ may be longer than one year. Bridging therapy is generally recommended for a patient with an estimated ≥6 months on the waiting list for OLT in order to maintain their eligibility. Options for bridging therapy include embolization, RFA, EBRT, or partial hepatectomy. The selection of bridging therapy is discussed in detail elsewhere. (See "Liver transplantation for hepatocellular carcinoma", section on 'Bridging therapy'.)

- **Extended transplant criteria and downstaging** – Patients with HCC tumor burden beyond the Milan criteria treated with locoregional therapies are eligible for the OPTN's downstaging protocol (UNOS-DS) [49]. Patients meeting criteria for the OPTN

downstaging protocol may be eligible for standard MELD HCC exception points and given priority if HCC tumor burden can be downstaged to, and maintained within, Milan criteria with an AFP level <1000 ng/mL using locoregional therapies. (See "Liver transplantation for hepatocellular carcinoma", section on 'Patients who meet expanded transplant criteria'.)

The specific options for downstaging (in those with tumor burden exceeding usual transplant criteria) using locoregional therapies to increase eligibility for OLT are discussed in detail elsewhere. (See "Liver transplantation for hepatocellular carcinoma", section on 'Downstaging through neoadjuvant locoregional therapy'.)

- **Living donor liver transplantation** – Living donor liver transplantation (LDLT) provides the opportunity to avoid the extended waiting period for a deceased donor organ. This can be a significant benefit in patients with HCC since tumor growth during the waiting period can worsen prognosis. LDLT can also be considered for select patients beyond UNOS-DS criteria, although most centers will still require a response to downstaging locoregional therapy and an AFP level <1000 ng/mL. (See "Liver transplantation for hepatocellular carcinoma", section on 'Living donor transplantation'.)

Ineligible for transplant, no macrovascular invasion — There is no single best approach to these patients, and clinical practice is variable. Selection of treatment is influenced by the severity of underlying liver disease, the size and distribution of the intrahepatic tumors, the vascular supply, the patient's overall performance status and local expertise/availability of specialized techniques. We based our approach on the extent of disease burden within the liver (algorithm 1).

In the past, these patients were largely managed by liver-directed approaches such as ablation (if feasible), arterially-directed therapy or RT. (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates who are eligible for local ablation" and "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates not eligible for local thermal ablation".)

However, the rapidly changing landscape of potentially effective and survival-prolonging systemic therapies in HCC has enabled clinicians to consider systemic rather than locoregional therapy in this setting, even if patients are eligible for liver-directed therapy. The variability in care at expert centers reflects uncertainty in the relative benefits of these approaches and guidelines from expert groups are disparate:

- 2022 guidelines from the Barcelona Clinic Liver Cancer (BCLC) group for patients with intermediate (B) or advanced stage (C) HCC suggest initial systemic therapy rather than

arterially-directed therapy for those with diffuse infiltrative, extensive bilobar liver involvement, any degree of portal invasion, or a performance status of 1 or 2 (figure 1) [2]. By contrast, arterial embolization is a preferred approach for those with well-defined nodules, preserved portal flow, and a performance status of 0. However, these decisions are arbitrary, and there are few trials directly comparing these strategies in these patient subgroups, especially addressing the benefits of combined locoregional and systemic therapy, although these are areas of active ongoing research. (See 'BCLC algorithm' above.)

- Other guidelines recommend locoregional therapies for patients with liver-limited HCC not amenable to resection or transplantation and without macrovascular involvement [19], and many centers continue to prefer locoregional liver-directed therapy over systemic therapy for fit patients who have limited tumor burden and adequate liver reserve.

- As noted above, the Asia-Pacific conference considers that the following patients have "TACE-unsuitable" disease, for which systemic therapy is a preferred approach (see 'Asia-pacific consensus and intermediate-stage HCC' above):

  - Confluent multinodular type, massive or infiltrative type, simple nodular type with extranodular growth, poorly differentiated type, intrahepatic multiple disseminated nodules or sarcomatous changes after TACE [50,51]; discovery of some of these issues would require liver biopsy.

  - "Up-To-Seven" criteria-out nodules (especially bilobar multifocal HCC).

  - Albumin-bilirubin (ALBI) score ≥2 (calculator 1).

- Updated guidelines for treatment of HCC from the NCCN now include systemic therapy as an alternative to locoregional therapy for these patients with extensive intrahepatic tumor burden [52].

Limited intrahepatic tumor burden — For most patients with liver-isolated, unresectable HCC who are ineligible for transplantation and who have a limited intrahepatic tumor burden and no PVTT, we suggest locoregional liver-directed therapy (ie, ablation, arterially-directed therapies, external beam RT) rather than initial systemic therapy. Liver-directed therapies have high local response rates (up to 70 percent) favorable rates of local tumor control (66 to 90 percent), and favorable safety profiles. (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates not eligible for local thermal ablation", section on 'Indications and efficacy' and "Localized hepatocellular carcinoma: Liver-directed therapies for

nonsurgical candidates not eligible for local thermal ablation", section on 'Stereotactic body radiation therapy'.)

There is no evidence that initial systemic therapy is safer, better tolerated, or more effective in this setting, in contrast to those with more advanced disease, in which at least three trials have shown that embolization is not superior to initial systemic therapy. (See 'Large intrahepatic tumor burden' below.)

Choice of locoregional approach — For patients who are eligible for a liver-directed nonsurgical therapy, the choice of procedure is individualized and guided by the following principles:

- Local thermal ablation (RFA, MWA) is a preferred approach for those with one or a few relatively small tumors. The best results are in patients with one or two tumors <3 cm in diameter. For cirrhotic patients, most clinicians restrict these approaches to those with Child-Pugh class A or B severity only (table 3). Ablation is also an option for those with potentially resectable HCC who are inoperable due to extensive comorbidity. RFA and MWA can also be used as "bridging" therapy in patients awaiting liver transplantation to reduce the likelihood of becoming ineligible due to tumor progression. (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates who are eligible for local ablation".)

- Other liver-directed treatments (ie, TACE and bland embolization, transarterial radioembolization [TARE], HAIC, and EBRT, including SBRT) are generally reserved for tumors that are confined to the liver but not amenable to local ablation:

  - Hepatic arterial embolization is an option for patients with a large unresectable or multifocal HCC who have relatively preserved liver function (ie, Child-Pugh class A or B cirrhosis (table 3)) and no extrahepatic tumor spread, vascular invasion, or tumor thrombus involving the main portal vein or one of its lobar branches (ie, Vp1 or Vp2, (figure 2)). Few randomized trials have directly compared different techniques for hepatic artery embolization, and there is little consensus as to the best approach. These issues are addressed in detail separately. (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates not eligible for local thermal ablation".)

  - Selected patients may benefit from a combined locoregional approach to liver-directed therapy. As an example, TACE plus RFA is a preferred approach over TACE or RFA alone for intermediate-sized HCC (ie, 3 to 5 cm). (See "Localized hepatocellular carcinoma:

Liver-directed therapies for nonsurgical candidates not eligible for local thermal ablation", section on 'TACE plus local treatments'.)

- The choice of SBRT over other liver-directed therapies depends on institutional expertise and patient preference, although increasing literature suggests high rates of local disease control; SBRT generally requires several visits to plan and execute. (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates not eligible for local thermal ablation", section on 'External beam RT'.)

- There may be a role for multiagent HAIC without embolization in centers with local expertise in this procedure, but how this approach compares with other locoregional treatment modalities is unknown. Most of the available data on HAIC are in patients with large intrahepatic tumor burden or PVTT. (See 'Large intrahepatic tumor burden' below and 'Patients with portal vein tumor thrombus' below.)

Locoregional plus systemic therapy — Locoregional therapies are increasingly being tested in combination with systemic therapies for HCC, including molecularly-targeted agents and immunotherapy. Randomized trials have not demonstrated benefit from the addition of systemic therapy to TACE or any other form of arterial embolization compared with arterially directed therapy alone, and this is not a standard approach, at least for patients with a limited intrahepatic tumor burden. (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates not eligible for local thermal ablation", section on 'Does sorafenib or lenvatinib add benefit to TACE?'.)

Notably, most of these studies were conducted with sorafenib, and there is now evidence that lenvatinib and immune checkpoint inhibitor immunotherapy approaches are superior to sorafenib for first-line therapy of advanced HCC. (See "Systemic treatment for advanced hepatocellular carcinoma", section on 'First-line therapy'.)

Larger, well-designed phase III trials using these newer agents are needed before it can be concluded that there is any benefit for the addition of systemic agents to any form of arterially-directed therapy for patients with limited intrahepatic tumor burden and without macrovascular invasion or extrahepatic spread. One such trial, the LAUNCH trial, demonstrated significantly improved survival for lenvatinib plus TACE versus lenvatinib alone in previously untreated patients with advanced HCC, but most of the enrolled patients had HBV-related HCC, and a large tumor burden (ie, large tumors, multifocal disease, PVTT, or extrahepatic tumor spread). Whether these results can be extrapolated to other populations is uncertain. This subject is discussed below. (See 'Lenvatinib alone or with TACE' below and 'Benefit of individual therapies' below.)

Treatment at progression

- **Child-Pugh class C cirrhosis, extensive comorbidity** – For patients with radiologic progression after resection or locoregional liver-directed therapy who have Child-Pugh class C cirrhosis (table 3) and for those with a poor functional status or extensive comorbidity, supportive care alone is appropriate.

- **Relatively preserved liver function** – Treatment of patients with radiologic progression after resection or locoregional liver-directed therapy who retain adequate liver function and performance status (table 2) must be individualized. Some patients with recurrence, particularly those within Milan Criteria, can be considered for liver transplantation. (See "Liver transplantation for hepatocellular carcinoma".)

  Additional liver-directed therapy might be possible depending upon tumor location and underlying liver function. The selection for and safety and efficacy of repeated applications of TACE and TARE are discussed in detail elsewhere. (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates not eligible for local thermal ablation", section on 'Retreatment' and "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates not eligible for local thermal ablation", section on 'Retreatment'.)

  There is no consensus on when to transition from locoregional to systemic treatment in patients who continue to have liver-limited disease after an initial treatment course with locoregional therapy, and practice is variable. However, an important issue is that a late decision to transition might jeopardize gains in overall survival since only patients with Child-Pugh class A cirrhosis have shown benefit from newer systemic therapies such as bevacizumab/atezolizumab, or durvalumab/tremelimumab, and lenvatinib. (See "Systemic treatment for advanced hepatocellular carcinoma", section on 'Evolution of systemic therapy'.)

  However, there is increasing recognition for the role of systemic therapy after failure of, or poor tolerance to local therapy in these patients if performance status and underlying liver function are adequate [23]. With the growing number of active systemic regimens in patients with advanced HCC, the definition of "failure of local therapy" is evolving. Although this was once considered to mean "once all forms of locoregional liver-directed therapy were exhausted," the rapidly changing availability of potentially effective and survival-prolonging systemic therapies in HCC has enabled clinicians to offer alternatives to patients who have locally progressive intrahepatic disease, even if they may be eligible for additional liver-directed therapy. Specifically, the acceptance of the toxicity of a risky

local procedure in a patient with borderline indications may be tempered by having viable alternative systemic options that did not previously exist. Unfortunately, there are no published randomized trials directly comparing any form of salvage local therapy versus any form of systemic therapy, especially combined atezolizumab plus bevacizumab. This remains a very active area of clinical investigation. (See 'Extrahepatic disease or otherwise ineligible for locoregional therapy' below.)

Large intrahepatic tumor burden — For patients with liver-isolated HCC who are not candidates for surgical resection or liver transplantation, and who have a large intrahepatic tumor burden, we suggest initial systemic chemotherapy rather than locoregional treatment alone or combined systemic and locoregional treatment. For most patients, we suggest atezolizumab plus bevacizumab or, if there is a contraindication to bevacizumab, durvalumab plus tremelimumab, rather than molecularly targeted therapy. Where the technical expertise is available, HAIC is an alternative to upfront systemic treatment; however, given the lack of data directly comparing HAIC versus systemic therapy, we do not consider HAIC to be a preferred approach. Based upon the LAUNCH trial, another option is lenvatinib plus TACE, although the trial was conducted entirely in Asian patients with a predominance of HBV-related HCC (87 percent), and whether the results can be extrapolated to other populations is uncertain. (See 'Lenvatinib alone or with TACE' below.)

Importantly, there is no consensus definition for the degree of "large intrahepatic tumor burden" at which point a patient would be considered unsuitable for liver-directed therapies, and better treated with systemic therapy. One option is to use the "Up-To-Seven" criteria-out from the Asia-Pacific group (ie, HCC with more than seven as the sum of the size of the largest tumor [in cm] plus the number of tumors total) [12]. (See 'Asia-pacific consensus and intermediate-stage HCC' above.)

There are no randomized trials comparing locoregional liver-directed therapy versus immunotherapy. The available trials of locoregional versus systemic therapy have used either sorafenib or lenvatinib as the comparator arm.

Sorafenib

- **Trials of radioembolization versus sorafenib** – Whether results with TARE are better than those that can be achieved with systemic sorafenib was directly addressed in two different multicenter trials, both of which concluded that while TARE was associated with a higher objective tumor response rate, median survival was not improved compared with sorafenib [53,54]:

- In the multicenter phase III randomized SIRveNIB trial, 360 Asia-Pacific patients with newly diagnosed unresectable HCC without extrahepatic spread (approximately 30 percent with portal vein thrombus, 24 percent with >50 percent liver involvement, 89 percent Child-Pugh class A cirrhosis (table 3)) were randomly assigned to sorafenib (400 mg twice daily) or a single injection of 90Y microspheres [53]. 90Y was associated with a significantly higher tumor response rate (16.5 versus 1.7 percent), and fewer adverse events (constipation, diarrhea, fatigue, rash, hand-foot skin reaction, hypertension), compared with sorafenib. However, the overall disease control rate (objective response plus stable disease; 41.8 versus 42.7 percent), time to tumor progression (5.88 versus 5.36 months), and median overall survival (8.8 versus 10 months) were not significantly different. One-year all-cause mortality was higher in the TARE group (63 versus 53 percent).

- Similar results were noted in a second trial conducted in France in which 467 patients (83 percent Child-Pugh class A cirrhosis) with a new locally advanced HCC not eligible for resection, transplantation, or thermal ablation; previously cured HCC (after resection or thermal ablation); or HCC after two unsuccessful rounds of TACE were randomly assigned to TARE or sorafenib [54]. Over one-half of enrolled patients had multiple tumors, approximately 20 percent had bilobar disease, and 34 percent had a tumor burden involving >25 percent of the liver. TARE was associated with a modestly higher objective tumor response rate (19 versus 12 percent), and fewer adverse events (fatigue, diarrhea, hand-foot skin reaction), but liver dysfunction rates were similar. Median survival was not improved with TARE (8 versus 9.9 months, HR 1.15, 95% CI 0.94-1.41), but there were 19 treatment-related deaths with TARE (8 percent) versus 12 in the sorafenib group (5 percent).

- **Sorafenib versus TACE plus sorafenib**

  - The phase III STAH trial randomly assigned 339 patients with advanced (AJCC stage III, IVA or IVB (table 1), extrahepatic spread [36 percent of those enrolled], or PVTT [28 percent Vp3-4]) HCC to sorafenib with or without concurrent TACE [55]. The addition of TACE did not improve overall survival compared with sorafenib alone, but it did worsen liver function. Hyperbilirubinemia was approximately three times more common in the group receiving TACE plus sorafenib (14.5 versus 4.4 percent).

  - Benefit could also not be shown for the addition of radioembolization to sorafenib in the phase III Sorafenib and Micro-therapy Guided by Primovist Enhanced MRI in Patients with Inoperable Liver Cancer (SORAMIC) trial, conducted in 424 patients who were not eligible for TACE (90 percent had Child-Pugh class A cirrhosis) [56]. The

addition of radioembolization to sorafenib did not result in a significant improvement in overall survival compared with sorafenib alone (median 12.1 versus 11.4 months), and combined therapy was associated with higher rates of grade 3 or 4 adverse events.

- **Cochrane analysis –** Additional information is available from a year 2020 Cochrane analysis of the three studies described above, which concluded that the evidence on the effects of radioembolization with or without sorafenib compared with sorafenib alone was highly insufficient [57]. Compared with sorafenib alone, radioembolization seemed to achieve similar survival but fewer serious adverse effects, but the quality of the evidence and level of certainty was very low.

Lenvatinib alone or with TACE — The available data on lenvatinib are as follows:

- **Propensity-score-matched analysis** – A propensity score-matched retrospective cohort study demonstrated that liver function may be better preserved and survival may be longer for patients with a large intrahepatic tumor burden (ie, beyond the "Up-To-Seven" criteria as defined by the Asia-Pacific Consensus statement) who are treated with first-line lenvatinib rather than TACE (median overall survival 37.9 versus 23.1 months, HR for death 0.48, p <0.01) [24]. (See 'Asia-pacific consensus and intermediate-stage HCC' above.)

- **LAUNCH trial** – Better outcomes with combined lenvatinib plus TACE versus lenvatinib alone were suggested in the Chinese phase III LAUNCH trial in which 338 patients with no prior locoregional treatment for HCC (87 percent HBV-related) were randomly assigned to lenvatinib monotherapy (8 or 12 mg once daily depending on body weight) or lenvatinib plus "on-demand" TACE (either conventional or DEB-TACE, first session within one day after starting lenvatinib, and repeated thereafter if there was incomplete necrosis or tumor regrowth) [58]. The enrolled patient population had relatively locally advanced disease (70 percent PVTT, 80 percent multifocal, 68 percent large tumors) or extrahepatic disease spread (55 percent). The median number of TACE sessions was three (range one to six).

  In an interim analysis after median follow-up 17 months, median overall survival was significantly longer in the TACE plus lenvatinib group (17.8 versus 11.5 months, HR 0.45, 95% CI 0.34-0.55), as was median progression-free survival (PFS; 10.6 versus 6.4 months, HR 0.43, p <0.001), and the objective response rate was also higher (54 versus 25 percent). Grade 3 or 4 adverse events were more common with combined therapy, including alanine transaminase (ALT) elevation (17.6 versus 1.2 percent), aspartate transaminase (AST) elevation (22.9 versus 1.8 percent), and hyperbilirubinemia (9.4 versus 3.0 percent). The median duration of treatment was longer with TACE plus lenvatinib as compared with lenvatinib alone (8.2 versus 5.1 months).

Although these results are intriguing, in our view, additional experience with lenvatinib plus TACE is needed in Western populations, in which the cause of HCC is more often alcoholic cirrhosis than HBV, before it can be concluded that lenvatinib plus TACE is a preferred approach over systemic therapy alone, especially upfront immunotherapy.

HAIC without embolization — TACE has been a standard approach for treatment of large unresectable HCCs, and some have shown that the use of multiagent chemotherapy rather than a single agent plays an important role in improving survival while the addition of particle embolization increases the frequency of adverse effects but does not contribute to a survival advantage [59]. Furthermore, it is often difficult to perform a complete embolization of large HCCs because of plentiful extrahepatic collateral arteries. This has led to interest in HAIC using multiagent chemotherapy, which provides sustained local high concentrations of chemotherapy agents in tumors, without the need for embolization. (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates not eligible for local thermal ablation", section on 'TACE and bland particle embolization'.)

The potential benefit of this strategy over repeated courses of TACE alone was shown in a phase III trial in which 315 patients with unresectable large (≥7 cm) HCC without macrovascular invasion or extrahepatic spread were randomly assigned to HAIC via the hepatic artery using FOLFOX (oxaliplatin 130 mg/m^2 plus fluorouracil [FU] bolus 400 mg/m^2 on day 1, and followed by FU infusion 2400 mg/m^2 for 24 hours, once every three weeks for up to six courses) versus superselective TACE (using epirubicin, lobaplatin, and lipiodol and polyvinyl alcohol particles) repeated every six weeks [60]. The entire patient population was Asian, and had predominantly Child-Pugh class A cirrhosis (81 percent) and HBV as the underlying HCC risk factor (89 percent). The benefits of HAIC over TACE included significantly better median overall survival (23.1 versus 16.1 months; HR 0.58, 95% CI 0.45-0.75), a higher objective response rate (46 versus 18 percent), a longer median PFS (9.6 versus 5.4 months), and better tolerability (incidence of serious adverse effects during treatment 19 versus 30 percent). However, abdominal pain was observed in 37 of the 157 patients receiving HAIC when oxaliplatin was injected, and it resolved when the injection was stopped. Furthermore, 12 patients had thrombosis or dislocation of the catheter tip in this group, and required catheter revision, and four developed gastric ulcers during therapy, one of which had upper GI bleeding that required endoscopic hemostasis.

There are several concerns about this study which renders interpretation of the results difficult:

- The study was open label, and there were significant differences in poststudy treatment that may have been influenced by investigator decisions, and affected the overall survival outcomes. As an example, more patients in the HAIC group underwent subsequent

hepatic resection (38 versus 18 in the TACE group). Crossover to the alternative treatment was much more frequent in the TACE group (20 versus 8 patients).

- Eligibility was limited to patients with either no cirrhosis or cirrhosis of no worse than Child-Pugh class A. However, the number of patients without cirrhosis was not reported. Whether the results are generalizable to a broader population, including those with cirrhosis or HCC etiologies other than HBV, is uncertain.

Furthermore, HAIC is expensive, requires specific technical expertise and an invasive procedure (percutaneous access of the hepatic artery) every three weeks, and inpatient management of the chemotherapy infusion.

The data on combined therapy with HAIC plus sorafenib, most of which are in patients with PVTT, are discussed in detail below. (See 'Locoregional treatments' below.)

Patients with portal vein tumor thrombus

Definition and extent — PVTT is the most common form of macrovascular invasion in HCC [61,62]. The development of PVTT is usually accompanied by worsening liver function, vulnerability to spread of metastatic disease, a higher incidence of complications related to portal hypertension, and intolerance for treatment compared with patients without PVTT. PVTT, particularly those with Vp3 or Vp4 involvement, is associated with a dismal prognosis; among patients treated with supportive care only, median survival is only two to four months [63].

The extent of PVTT is a major prognostic factor for HCC; patients with involvement of a lobar branch or the main trunk of the portal vein have a significantly worse outcome than do those with more proximal involvement [7,64]. A number of classifications have been proposed to describe the extent of tumor thrombus; we use the five-tier classification system of the Liver Cancer Study Group of Japan (figure 2) [65]:

- Vp0 – No tumor thrombus in the portal vein;
- Vp1 – Segmental tumor thrombus distal to the second-order branches of the portal vein without direct involvement;
- Vp2 – Invasion of a second order (right anterior or posterior, left anterior or posterior) branch of the portal vein;
- Vp3 – Presence of the tumor thrombus in a first-order (right or left lobar) branch of the portal vein;
- Vp4 – Tumor thrombus in the main trunk of the portal vein or a portal vein branch that is contralateral to the primarily involved lobe (or both).

Risk stratified treatment selection — For patients with tumor invasion, occlusion, or thrombus involving the portal vein, we utilize the extent of PVTT to select therapy. In general, extensive involvement of a lobar or the main portal vein (ie, Vp3 or Vp4 disease, (figure 2)) is associated with short survival in patients treated with locoregional therapies or sorafenib; for these patients, we suggest initial systemic therapy rather than locoregional therapy alone. For most patients, we suggest atezolizumab plus bevacizumab or, if there is a contraindication to bevacizumab, durvalumab plus tremelimumab, rather than molecularly targeted therapy.

Another option in this setting, where local expertise is available, is HAIC with or without sorafenib. Based upon the LAUNCH trial, another option is lenvatinib plus TACE, although the trial was conducted entirely in Asian patients with a predominance of HBV-related HCC (87 percent), and whether the results can be extrapolated to other populations is uncertain. (See 'Locoregional plus systemic therapy' below.)

For patients with lesser degrees of PVTT (ie, Vp1 or Vp2), either locoregional therapy or systemic therapy are acceptable options. Decision making must be individualized, and best made in the setting of a multidisciplinary tumor board. (See "Systemic treatment for advanced hepatocellular carcinoma".)

For patients with HCC and tumor invasion, occlusion, or thrombus involving the portal vein, therapeutic options include locoregional therapy (ie, SBRT, TARE, TACE plus RT, proton beam irradiation [where available], or HAIC [where available]), initial systemic therapy, or lenvatinib plus TACE. There is no consensus on the best way to manage HCC with associated PVTT, and practice is variable. The variability in clinical practice, especially among Western (Europe, Americas) versus Eastern (Asia-Pacific) centers (reviewed in [62]), is reflected by the following disparate guidelines from expert groups:

- According to Western guidelines, including those of the EASL and AASLD, PVTT indicates advanced HCC for which potentially curative therapy is not available [2,19,29]. The BCLC algorithm considers systemic therapy to be the primary option for these patients (figure 1) [2]. However, there is increasing recognition that some patients, especially those with limited vascular invasion (Vp1 or Vp2) may benefit from locoregional therapy such as TARE. (See 'BCLC algorithm' above.)

- On the other hand, more aggressive locoregional anticancer treatments are recommended for selected patients with HCC and PVTT in Chinese, Japanese, South Korean, and other Asia-Pacific guidelines [30-34]. In some Asia-Pacific centers, hepatic resection with or without tumor thrombectomy is a widespread practice, even when the PVTT is more extensive than Vp1 (table 4) [66-68].

Benefit of individual therapies

Locoregional treatments — There are no trials directly comparing different forms of liver-directed therapy that have shown some benefit for patients with HCC complicated by PVTT (ie, TACE plus RT, TARE, SBRT, and HAIC). TARE may be safer than TACE in this setting due to a lower risk of arterial ischemia related to particle size. The benefits and selection of locoregional treatments in patients with HCC and PVTT are discussed in detail elsewhere; the following sections will highlight the available data comparing these locoregional approaches versus systemic therapy.

- **TACE with or without RT**

  - **TACE plus RT** – Transarterial chemoembolization (TACE) plus radiation therapy (RT) is commonly used for HCC with PVTT in Asia-Pacific countries [69-73]. The following data are available addressing efficacy:

    - In a registry database series of 412 patients with unresectable HCC complicated by PVTT (49 percent bilateral or main portal vein) who received focal three-dimensional conformal radiation therapy (3D-CRT) combined with TACE before or after RT (lipiodol, cisplatin gelatin sponge), 40 percent had an objective response in the PVTT, and 43 percent were still alive at one year; however, grade 3 or 4 hepatotoxicity was seen in 10 percent of patients during or within three months of completion of RT [73].

    - Results with combined therapy may be even better using newer planning methods for RT (eg, 3D-CRT or hypofractionated SBRT), with which objective response rates with RT alone directed to the portal vein thrombus range from 39 to 62 percent [69,74-81].

      As an example, one trial compared TACE plus RT (started within three weeks of the first TACE session, and with delivery of 45 Gy using 3D-CRT planning with a fraction size of 2.5 to 3 Gy) versus sorafenib (400 mg twice daily) in 90 treatment-naïve patients with liver-confined HCC invading the first or second branch of the portal vein with preserved unilateral portal blood flow (ie, no main portal vein thrombus) [82]. All patients had Child-Pugh class A liver function. The TACE procedure was repeated every six weeks for the first six months and every six to eight weeks thereafter. The group receiving TACE plus RT had a significantly higher PFS rate at 12 weeks (the main endpoint, 87 versus 34 percent), a higher radiographic response rate at 24 weeks (33 versus 2 percent), significantly longer median time to progression (31 versus 12 weeks), and significantly greater median overall

survival (55 versus 43 weeks). Potentially curative resection could be performed on five patients between 27 and 40 weeks after beginning TACE and RT; four remained alive at last follow-up with an overall survival time of 119 to 149 weeks. Notably, this study was conducted in an Eastern, HBV-predominant population; the results require validation in Western populations.

However, it should be noted that the control group received sorafenib, which has been shown to be a relatively ineffective agent in the setting of PVTT, especially extensive PVTT. There are no trials comparing TACE plus RT versus other chemotherapy regimens such as lenvatinib, atezolizumab plus bevacizumab, or durvalumab plus tremelimumab. (See 'Systemic chemotherapy' below.)

- **TACE alone** – While extensive (especially main trunk) PVTT is a relative contraindication to TACE because of the risk of hepatic infarction, an increasing number of studies (predominantly from Asia-Pacific centers) have demonstrated the safety of TACE (especially superselective TACE) in the management of patients with less extensive PVTT, as long as hepatic function is preserved. A meta-analysis concluded that the use of TACE was associated with a survival benefit for patients with HCC and branch portal vein involvement but not for those with main portal vein involvement [83].

- **Radioembolization –** TARE is gaining popularity as a treatment for HCC with PVTT. While main portal vein thrombus has historically been considered a contraindication to radioembolization, collective experience in over 200 patients with main portal vein thrombus suggests the safety and efficacy of this approach [84-87].There is theoretically less arterial ischemia induced by radioembolization because of the smaller particle size (32 versus 70 to 300 microns with beads), suggesting that it should be safer in the setting of portal vein thrombus. Compared with TACE, rates of severe adverse effects with radioembolization appear low [88].

  Several retrospective analyses suggest better survival with TARE than with initial sorafenib in patients with HCC complicated by PVTT [89,90]. However, as noted above, two open-label randomized trials comparing TARE versus sorafenib concluded that overall survival was not significantly better with TARE in individuals with locally advanced tumors, including those with macrovascular invasion [53,54]. The extent of vascular invasion was not addressed in either study. (See 'Large intrahepatic tumor burden' above.)

  Although TARE appears to be safe in many patients with branch or lobar tumor thrombus (ie, Vp2 or Vp3, (figure 2)), median survival is short in many series, particularly in those with cirrhosis beyond Child-Pugh class A, and main portal trunk thrombus, and adverse

effects seem worse in these groups [91]. The benefit of this approach remains uncertain in these groups, and in this setting, initial systemic therapy is preferred.

- **Radiation**

  - **EBRT** – External beam radiation therapy (EBRT) has only rarely been used as a sole modality for patients with HCC complicated by PVTT because of the low RT dose (30 to 35 Gy) that can be tolerated by the liver, and the risk of radiation-induced liver disease. (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates not eligible for local thermal ablation", section on 'External beam RT'.)

  - **Proton beam irradiation** – There is a growing body of evidence, primarily from Japan, supporting the use of proton beam irradiation, particularly for patients with large tumors or main portal vein thrombus. However, unresolved issues include whether these outcomes could be achieved with other approaches (including TACE with RT, SBRT, or initial systemic therapy) and which patients, if any, would do better with proton beam therapy, which is not widely available. There are no trials comparing proton beam irradiation versus any form of initial systemic therapy. Charged particle irradiation (ie, proton beam and carbon ion RT) has been used in a limited number of patients, especially in Japan [92,93]. Where available, proton beam irradiation is a reasonable approach for patients with a large HCC and associated portal vein thrombus, although SBRT may also be helpful in this situation. There is a growing body of evidence, primarily from Japan, supporting the use of proton beam irradiation, particularly for patients with large tumors or portal vein thrombus [92-101] (see "Radiation therapy techniques in cancer treatment", section on 'Particle therapy'). While proton therapy may be helpful for some patients, it is generally not available for most patients; there are only 27 proton facilities currently operational in the United States.

    As examples:

    - In one study, 162 patients with 192 HCCs were treated with proton beam irradiation [94]. Most tumors had a diameter of 3 to 5 cm. The majority of the patients had received some form of previous nonsurgical therapy. The five-year local control rate was 87 percent. Overall survival at five years was 24 percent, with most patients dying from metachronous intrahepatic lesions. Acute and late gastrointestinal toxicities were uncommon.

    - In another report of 44 patients with HCC (15 with tumor vascular thrombus) treated with hypofractionated proton beam irradiation (15 fractions of proton therapy to a maximum total dose of 67.5 Gy equivalent), the two-year local control

rate was 95 percent, although the majority progressed in other sites (two-year PFS 40 percent) [101].

- **SBRT** –Experience with stereotactic body radiation therapy (SBRT) for primary liver tumors complicated by PVTT is limited but increasing. There are no trials directly comparing SBRT with any form of systemic therapy.

  - Efficacy can be illustrated by a prospective evaluation of 102 patients with HCC who were not considered candidates for surgical resection, TACE, or RFA and were enrolled in sequential phase I and II trials of SBRT [102,103]. The median prescription dose was 36 Gy in six fractions. These were generally patients with advanced disease; 51 percent had a Cancer of the Liver Italian Program score of 2 to 4 (table 5), 61 percent had multiple lesions, the median diameter of the largest lesion was 7.2 cm, and 55 percent had PVTT. Despite these adverse features, the one-year local control rate was 87 percent, and the median time to local progression had not been reached at a median follow-up of 31.4 months. Although responses were observed in patients with tumor vascular thrombus, the fraction (response rate) was not reported. The one-year survival rate was 55 percent.

  - Whether results with SBRT are better than those that can be achieved with TARE in this setting is unclear; there are no randomized trials. A meta-analysis of 37 studies of TARE, SBRT, or 3D-CRT (all observational or single-arm prospective studies) concluded that while overall response and local control rates were different (and for the most part, favored SBRT over TARE), the response rate in the PVTT was similar with SBRT and TARE (39 versus 35 percent), as was overall survival at both one and two years [104].

Locoregional plus systemic therapy

- **HAIC with or without sorafenib** – Platinum-based hepatic arterial infusion chemotherapy (HAIC) is widely used in Japan as an alternative to sorafenib for patients with HCC and portal vein invasion [105]. HAIC with or without sorafenib has been directly compared with sorafenib alone in at least six Asian randomized trials that enrolled patients with locally advanced HCC either exclusively or predominantly with PVTT [106-111]. Four of the trials have suggested a significant survival benefit for HAIC over sorafenib alone, and in one of these, some patients were successfully downstaged to potentially resectable disease after HAIC [108]. However, combined treatment was more toxic than sorafenib alone in most of the trials.

- A randomized phase III trial directly compared sorafenib (400 mg twice daily) versus sorafenib plus HAIC (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil bolus 400 mg/m^2, all on day 1, followed by fluorouracil infusion 2400 mg/m^2 for 46 hours, every three weeks, given by repeated hepatic arterial catheterization rather than a fixed intra-arterial catheter) in 315 Chinese patients with HCC (81 percent HBV related) and PVTT [107]. The median age was 49, and approximately 37 percent had tumor invasion of the main portal vein (ie, Vp4 (figure 2)). Median overall survival, the primary endpoint, was significantly higher for combined therapy (13.4 versus 7.1 months, HR 0.35, 95% CI 0.26-0.48) but rates of treatment-related grade 3 or 4 neutropenia, thrombocytopenia, and vomiting were also higher.

- In a second trial, sorafenib was directly compared with repeated cycles of oxaliplatin-based HAIC in a trial of 262 patients previously untreated with systemic chemotherapy; 66 percent had macrovascular invasion, and approximately one-half had either >50 percent involvement of the liver and/or Vp-4 PVTT [108]. The median age was 54. Tumor downstaging occurred in 16 of 130 patients receiving HAIC (12 percent), including 15 who underwent potentially curative resection or ablation, and median overall survival was significantly longer as compared with those receiving sorafenib (10.8 versus 5.7 months, HR for death 0.343, 95% CI 0.219-0.538).

- A meta-analysis of four of the randomized trials [106,107,110,111], plus one retrospective analysis [112] (5 studies, totaling 726 patients) concluded that compared with sorafenib alone, combined therapy was associated with a significantly higher response rate (risk ratio 3.08, 95% CI 1.38-1.69), and a borderline higher median overall survival (HR for death 0.59, 95% CI 0.35-1.00), but more hematologic toxicity [113]. Given the small sample size and differing treatment procedures across the studies, the authors concluded that additional large-scale randomized trials were needed to define clinical benefit from combined therapy.

An important point is that the control group in all of these trials was sorafenib, which has been shown to be a relatively ineffective agent in the setting of PVTT, especially extensive PVTT. There are no trials comparing HAIC with or without sorafenib versus other chemotherapy regimens such as lenvatinib or immunotherapy such as atezolizumab plus bevacizumab. (See 'Systemic chemotherapy' below.)

Whether results with HAIC can be extrapolated beyond the Asia-Pacific region (where patients with HCC tend to be young with predominant HBV infection, as was seen in the two trials described above) is unclear. Furthermore, whether these results are better than those that can be achieved using sorafenib plus systemic chemotherapy with an

oxaliplatin-containing regimen or atezolizumab plus bevacizumab is also unclear [114]. Randomized trials are needed. HAIC is not widely available elsewhere and requires specific technical expertise, an invasive procedure (percutaneous access of the hepatic artery) every three weeks, and inpatient management of the chemotherapy infusion. (See "Systemic treatment for advanced hepatocellular carcinoma", section on 'Is there a role for sorafenib plus chemotherapy?'.)

- **TACE plus systemic chemotherapy** – At least two randomized trials have addressed the benefit of TACE in conjunction with systemic chemotherapy in the setting of HCC complicated by PVTT:

  - One randomized Chinese trial of TACE plus sorafenib or lenvatinib as first-line treatment for 64 patients with HCC for PVTT (26 percent with extensive involvement) concluded that TACE plus lenvatinib was safe, well-tolerated, and had more favorable efficacy than TACE plus sorafenib, but the median time to tumor progression in both arms was short (4.7 versus 3.1 months) [115]. Furthermore, the difference in median overall survival, which favored lenvatinib, was not statistically significant (14.5 versus 10.8 months, HR 0.60, 95% CI 0.29-1.26).

    Given the lack of a control group receiving molecularly targeted therapy alone, this trial cannot be used to inform a decision for locoregional plus systemic therapy versus systemic therapy alone. There are also no data combining TACE with modern immunotherapy-based systemic therapy.

  - Additional information is available from the Chinese phase III LAUNCH trial, described above, in which 338 patients with no prior locoregional treatment for HCC (87 percent HBV-related) were randomly assigned to lenvatinib monotherapy versus lenvatinib plus "on-demand" TACE [58]. Approximately 70 percent had PVTT at enrollment. In an interim analysis after median follow-up 17 months, median overall survival was significantly longer with TACE/lenvatinib (17.8 versus 11.5 months, HR 0.45, 95% CI 0.34-0.55), as was median PFS (10.6 versus 6.4 months, HR 0.43, p <0.001), and the objective response rate was also higher (54 versus 25 percent). In prespecified subgroup analysis, the survival benefit was more pronounced in those with PVTT (HR for death 0.31, 95% CI 0.23-0.41) than in those without PVTT (HR for death 0.67, 95% CI 0.43-1.05) although a p value for interaction was not provided. Grade 3 or 4 adverse events were more common with combined therapy, including ALT elevation, AST elevation, and hyperbilirubinemia. (See 'Lenvatinib alone or with TACE' above.)

Systemic chemotherapy — There are accumulating data on the responsiveness of HCC complicated by PVTT to initial systemic therapy:

- **Atezolizumab plus bevacizumab**

  - Scattered case reports note significant responses to atezolizumab plus bevacizumab (atezo/bev) in patients with HCC complicated by PVTT [116,117].

  - Additional information is available from the IMBrave150 trial, which demonstrated a survival benefit for atezo/bev over sorafenib alone [118]. (See "Systemic treatment for advanced hepatocellular carcinoma", section on 'Atezolizumab plus bevacizumab'.)

    Approximately 43 percent of those enrolled in the trial had PVTT (including some patients with Vp4 disease), and randomization had been stratified by the presence or absence of macrovascular invasion, among other factors. A later subgroup analysis indicated that treatment benefit was seen across all subgroups, including those with (median overall survival 14.2 versus 9.7 months, HR for death 0.68, 95% CI 0.47-0.98) and without PVTT (HR for death 0.66, 95% CI 0.47-0.92) [119].

    A later exploratory efficacy and safety analysis focused on a subset of 73 patients with HCC complicated by Vp4 PVTT who were enrolled in the trial and randomized to atezo/bev (n = 48) or sorafenib (n = 25) [120]. In a preliminary report, the benefits of atezo/bev in patients with Vp4 PVTT were of a similar magnitude and potentially clinically meaningful across all efficacy endpoints, although they were not statistically significant, likely due to the small numbers of patients (median overall survival 7.6 versus 5.5 months, HR 0.62, 95% CI 0.34-1.11; median PFS 5.4 versus 2.8 months, HR 0.62, 95% CI 0.35-1.09). Variceal bleeding occurred more often after atezo/bev (6 of 48 versus 0 of 25, 14 versus 0 percent).

- **Durvalumab plus** tremelimumab – In the HIMALAYA trial, which demonstrated a survival benefit for tremelimumab plus durvalumab versus sorafenib as initial therapy for advanced HCC, 103 of the 393 patients assigned to durvalumab plus tremelimumab had macrovascular invasion (26 percent) [121]. In preplanned subgroup analysis, treatment effects were generally consistent across all treatment groups including those with and without macrovascular invasion. (See "Systemic treatment for advanced hepatocellular carcinoma", section on 'Tremelimumab plus durvalumab'.)

- **Other immunotherapies** – Scattered reports on immune checkpoint inhibitor immunotherapy treatment for patients with HCC with macrovascular invasion have revealed that treatment has some efficacy, although questions remain as to whether

efficacy is as good in those without macrovascular invasion. As an example, in a retrospective analysis of 45 patients with advanced HCC treated with a variety of immune therapies, four of 19 patients with PVTT (29 percent) had a partial response or stable disease with nivolumab monotherapy; in the entire group of 45 patients, the disease control rate was 31 percent [122]. (See "Systemic treatment for advanced hepatocellular carcinoma", section on 'Nivolumab monotherapy'.)

- **Sorafenib** – Based on two landmark trials, sorafenib became the first systemic agent shown to improve overall survival in advanced HCC over best supportive care alone. The survival benefit is modest, approximately two months. (See "Systemic treatment for advanced hepatocellular carcinoma", section on 'Sorafenib'.)

  The following analyses have addressed sorafenib efficacy in patients with PVTT:

  - A prespecified subgroup analysis of the phase III SHARP trial of first-line sorafenib in advanced HCC (in which 38 percent of the enrolled patients had macrovascular invasion) indicated that the survival benefit with sorafenib was maintained in those with macrovascular invasion (median 8.1 versus 4.9 months), but the extent of vascular invasion was not described [123].

  - Data are also available from an exploratory subset analyses of the phase III Asia-Pacific trial, which demonstrated that the benefits of sorafenib relative to placebo were seen in patients with macrovascular invasion and/or extrahepatic spread (median overall survival 5.6 versus 4.1 months, disease control rate 31 versus 12 percent), but of a lesser magnitude compared with those without macrovascular invasion or extrahepatic spread (median overall survival 14.3 versus 8 months, disease control rate 53 versus 33 percent) [124].

  - In a combined analysis of both trials, 38 percent of the enrolled patients had macrovascular invasion, benefit for sorafenib was seen both in those with (median overall survival 184 versus 137 days, HR 0.69, 95% CI 0.53-0.89) and without (median overall survival 386 versus 303 days, HR for death 0.70, 95% CI 0.56-0.88) PVTT [125]. The extent of PVTT was not described.

  - On the other hand, several other analyses note short survival (approximately 6 months) in patients treated with sorafenib monotherapy (including two randomized trials in which the experimental arm was TARE, and two trials in which the experimental arm was sorafenib plus HAIC) in patients with HCC and PVTT [7,89,90,108,109,126-130]. This is especially true in patients with extensive PVTT, although the data are limited [7,126]. (See 'Locoregional treatments' above.)

- **Lenvatinib** – There are increasing numbers of reports of efficacy and safety of lenvatinib in patients with HCC complicated by PVTT, including involvement of the main portal vein [24,126,131-135].

  - Approximately 20 percent of the patients enrolled in the phase III REFLECT trial that demonstrated the noninferiority of lenvatinib to sorafenib for first-line treatment of advanced HCC had macroscopic vascular invasion, although patients with main trunk PVTT (Vp4) were excluded [136]. The effect of lenvatinib was similar across all predefined subgroups including those with macrovascular invasion, extrahepatic spread or both. (See "Systemic treatment for advanced hepatocellular carcinoma", section on 'Lenvatinib'.)

  - Benefit was also suggested in at least two retrospective reports:

    - In a retrospective analysis of 41 patients with HCC complicated by Vp4 PVTT (figure 2) lenvatinib resulted in a significantly higher objective response rate than sorafenib (54 versus 14 percent), and a longer median overall survival (not reached versus 187 days) [126]. No patient had to discontinue lenvatinib because of drug-related adverse effects.

    - The importance of underlying liver function was shown in another multicenter study of 61 patients with very advanced HCC (41 with tumor occupying more than one-half of the liver volume, and the remainder with Vp4 PVTT [133]), objective response rate in the group with PVTT was 27 percent among those with no worse than Child-Pugh class A cirrhosis, but there were no responders among those with Child-Pugh class B cirrhosis.

- **Other molecularly targeted agents**

  - In the phase III RESORCE trial, regorafenib was shown to improve survival over best supportive care in patients who progressed on initial sorafenib; 30 percent of those enrolled had macrovascular invasion [137]. In subgroup analysis, regorafenib reduced the risk of death both for patients without (HR 0.67, 95% CI 0.52-0.86) and with macrovascular invasion (HR 0.67, 95% CI 0.46-0.98).

  - In the phase III CELESTIAL trial, in which 707 patients with advanced and progressing HCC and no worse than Child-Pugh class A cirrhosis progressing after sorafenib had a significant survival benefit for cabozantinib or placebo, 129 of the 470 patients treated with cabozantinib had macrovascular invasion (27 percent) [138]. In a non-preplanned

subgroup analysis, benefit from the drug seemed comparable in those with and without macrovascular invasion.

- In the REACH-2 trial, which demonstrated benefit for ramucirumab after failure of sorafenib among patents with an initially high AFP level, 70 of the 197 patients treated with ramucirumab had macrovascular invasion [139]. In a preplanned subgroup analysis, benefit seemed limited to those without macrovascular invasion (HR for overall survival 0.60, 95% CI 0.42-0.87) and not those with macrovascular invasion (HR for overall survival 0.97, 95% CI 0.63-1.53).

  However, in a later combined analysis of this trial and the earlier placebo-controlled REACH trial (which did not limit eligibility to those with an initially high AFP level), a survival benefit favoring ramucirumab in those with an elevated AFP level was observed across all subgroups, including those with macrovascular invasion, and in multivariate analysis, there was no single factor that predicted a differential survival impact from ramucirumab [140].

Extrahepatic disease or otherwise ineligible for locoregional therapy — For patients who are ineligible for resection, transplantation, or liver-directed therapy because of underlying liver disease or the presence of extrahepatic spread, or for patients demonstrating progression on locoregional therapy, systemic therapy is an option if performance status (table 2) and underlying liver function are adequate.

The field of systemic therapy for HCC is evolving rapidly and modern therapies, including molecularly targeted agents and immunotherapy, have produced significant gains in overall survival relative to supportive care alone. (See "Systemic treatment for advanced hepatocellular carcinoma".)

The role of cytotoxic chemotherapy, which has modest efficacy for HCC, at best, has diminished with the advent of newer systemic therapy approaches. Cytotoxic chemotherapy has been removed from guidelines for advanced HCC by both the NCCN and European Society for Medical Oncology [20,141] given advances in molecularly targeted therapies and immunotherapy, with demonstrated better efficacy and tolerability. At some institutions, chemotherapy is still offered to select patients for third- or fourth-line therapy if not deemed optimal candidates for other approved therapies. (See "Systemic treatment for advanced hepatocellular carcinoma", section on 'Systemic chemotherapy'.)

The rapid evolution of immunotherapy and molecularly targeted therapy for advanced HCC has also led to several areas of ongoing uncertainty [23]:

- All of these systemic agents are expensive, and in almost all cases, the demonstration of benefit has been limited to those with well-preserved liver function (ie, no worse than Child-Pugh class A cirrhosis (table 3)). It is unclear if these agents offer cost-effective benefits to some patients with greater degrees of liver dysfunction (ie, well selected patients with Child Pugh class B disease). (See "Systemic treatment for advanced hepatocellular carcinoma", section on 'Fit patients with preserved liver function and functional status' and "Systemic treatment for advanced hepatocellular carcinoma", section on 'Less fit patients and those with Child-Pugh B cirrhosis'.)

- For patients who have access to all agents, and sufficiently preserved liver function, the best way to sequence the available systemic treatment options for advanced HCC has not been established.

These issues, as well as a detailed discussion on choice of regimen, are discussed in detail elsewhere. (See "Systemic treatment for advanced hepatocellular carcinoma", section on 'First-line therapy'.)

HEPATITIS B VIRUS REACTIVATION

Reactivation of viral hepatitis may occur in patients with HCC who are undergoing systemic therapy, so it is important to screen patients for evidence of hepatitis B virus infection and maintain antiviral medications as indicated. This topic is discussed elsewhere. (See "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

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".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more

sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Liver cancer (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Treatment algorithms** – Hepatocellular carcinoma (HCC) is an aggressive tumor that often occurs in the setting of chronic liver disease and cirrhosis. Treatment options depend on both the tumor extent and the underlying liver function.

  An overview of our general approach to treatment of HCC is shown in the algorithm (algorithm 1). Alternative algorithms are available (figure 1). While algorithmic approaches are useful for conceptualizing the various treatment options that are available for individual patients, they may not be applicable in all settings. (See 'Treatment algorithms' above.)

- **Importance of multidisciplinary care** – We strongly urge that patients with HCC (especially liver-localized HCC) be referred to specialized centers of excellence with multidisciplinary expertise so that the entire range of potentially available treatments can be offered, along with assessment, monitoring, and treatment of the underlying liver disease. (See 'Importance of multidisciplinary care' above.)

- **Potentially resectable disease** – Hepatic resection is a potentially curative therapy and the preferred treatment for eligible patients. There is no consensus on the parameters for selection of patients for hepatic resection and practice is variable. The ideal candidate has a solitary HCC confined to the liver that shows no radiographic evidence of invasion of the hepatic vasculature, with well-preserved hepatic function (Child-Pugh class A, (table 3)) and no evidence of clinically significant portal hypertension. However, resectability is highly subjective and these patients should be evaluated in centers of excellence with multidisciplinary expertise. (See 'Potentially resectable disease' above.)

  While thermal ablation is a less morbid procedure, for most patients, even those with small tumors, we suggest resection rather than ablation particularly if resection can be

done using a laparoscopic approach which reduces patient recovery time (**Grade 2C**). (See 'Resection versus ablation' above.)

Postoperative antiviral therapy improves outcomes after potentially curative treatment of HCC that is related to hepatitis B virus or hepatitis C virus (HCV), and is indicated for those with active viral infection. The benefit of any other form of adjuvant therapy remains unproven and not a standard approach. (See "Management of potentially resectable hepatocellular carcinoma: Prognosis, role of neoadjuvant and adjuvant therapy, and posttreatment surveillance", section on 'Postoperative therapy'.)

- **Unresectable, liver-isolated, no macrovascular invasion**

  - **Liver transplantation** – For patients without surgically resectable disease, liver transplantation is a potentially curative option. Expanded transplantation criteria and downstaging to achieve transplant eligibility are now widely accepted. Most patients will require bridging therapy prior to transplant because of time on the wait list. (See "Liver transplantation for hepatocellular carcinoma".)

  - **Ineligible for transplant** – There is no single best approach to these patients, and clinical practice is variable. Selection of treatment is influenced by the severity of underlying liver disease, the size and distribution of the intrahepatic tumors, the vascular supply, the patient's overall performance status and local expertise/availability of specialized techniques. We based our approach on the extent of disease burden within the liver (algorithm 1) (see 'Ineligible for transplant, no macrovascular invasion' above):

    - For most patients with limited intrahepatic tumor burden, we suggest liver-directed therapies (ablation, arterially-directed therapies, external beam RT) rather than initial systemic therapy, as long as they are suitable candidates (**Grade 2C**).

      If liver-directed nonsurgical therapy is chosen, current data do not support the addition of sorafenib, lenvatinib, or any immunotherapy-based combination to transarterial chemoembolization (TACE) or any other form of arterial embolization. (See 'Locoregional plus systemic therapy' above.)

    - For most patients with a large intrahepatic tumor burden, we suggest initial systemic therapy rather than locoregional therapy (**Grade 2C**). However, there is no consensus definition for the degree of "large intrahepatic tumor burden" at which point a patient would be considered "TACE-unsuitable" and better treated with systemic therapy. For most patients, we suggest atezolizumab plus bevacizumab

or, if there is a contraindication to bevacizumab, durvalumab plus tremelimumab, rather than molecularly targeted therapy (**Grade 2C**). Hepatic arterial infusion chemotherapy (HAIC, where local expertise is available) or TACE plus lenvatinib are alternatives to upfront systemic treatment, but these are not preferred approaches. (See 'Large intrahepatic tumor burden' above.)

- **Treatment at progression**

  - For patients with radiologic progression after resection or locoregional liver-directed therapy who have Child-Pugh class C cirrhosis (table 3) and for those with a poor functional status or extensive comorbidity, supportive care alone is appropriate. (See 'Treatment at progression' above.)

  - For patients who retain an adequate performance status and preserved liver function, options include systemic therapy or additional liver-directed therapy (depending upon tumor location). However, the relative benefit of these approaches is unclear.

- **Patients with portal vein tumor thrombus** – For patients with HCC complicated by portal vein tumor thrombus (PVTT), we utilize the extent of PVTT to select therapy (see 'Patients with portal vein tumor thrombus' above):

  - For most patients with extensive involvement of a lobar branch or the main portal vein (ie, Vp3 or Vp4 disease, (figure 2)), we suggest initial systemic therapy rather than locoregional therapy (**Grade 2C**). For most patients, we suggest an immunotherapy-based regimen such as atezolizumab plus bevacizumab, or for those with a contraindication to bevacizumab, durvalumab plus tremelimumab rather than molecularly targeted therapy (**Grade 2C**). (See 'Systemic chemotherapy' above.)

  - HAIC with or without sorafenib (where local expertise is available) or TACE plus lenvatinib are alternatives to upfront systemic treatment, but these are not preferred approaches.

  - For patients with lesser degrees of PVTT (ie, Vp1 or Vp2, (figure 2)), either locoregional therapy or systemic therapy are acceptable options, and decision-making must be individualized.

- **Extrahepatic disease or ineligible for liver-directed therapy** – For patients who are ineligible for resection, transplantation or liver-directed therapy because of underlying liver disease or the presence of extrahepatic spread, or for patients demonstrating

progression on locoregional therapy, systemic therapy is an option if performance status (table 2) and underlying liver function are adequate. (See 'Extrahepatic disease or otherwise ineligible for locoregional therapy' above.)

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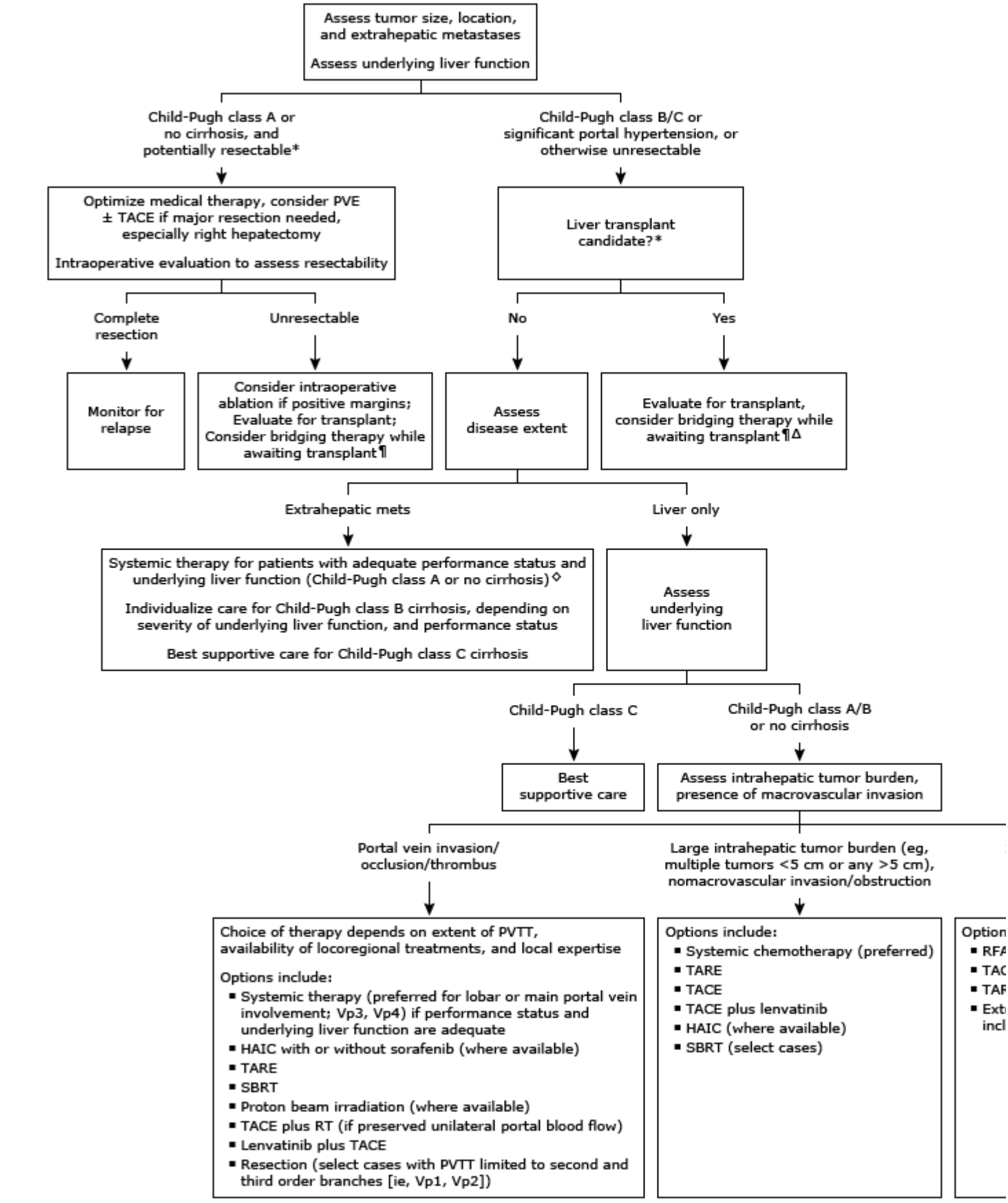
Topic 2489 Version 48.0

GRAPHICS

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.

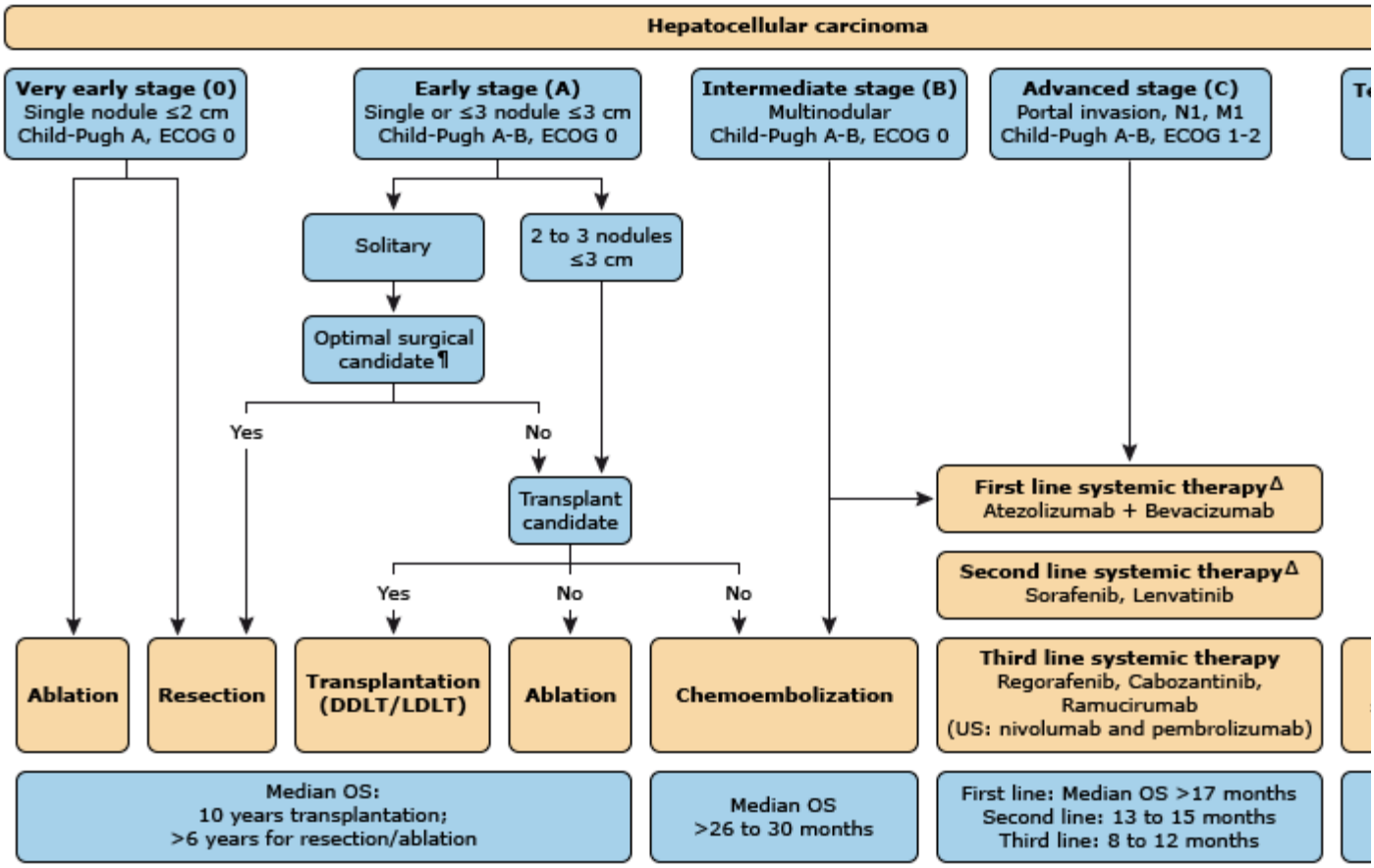
Δ In the United States, patients with underlying chronic liver disease (cirrhosis, hepatitis C virus infection) ar orthotopic liver transplant if they fulfill the Milan criteria (ie, solitary HCC ≤5 cm in diameter or up to three s which is larger than 3 cm, no evidence of gross vascular invasion, and 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

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

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.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Graphic 110835 Version 8.0

Karnofsky and Eastern Cooperative Oncology Group (ECOG) performance status measures

Karnofsky	
Score	**Definition**
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self, unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization is indicated, although death is not imminent
20	Hospitalization is necessary, very sick, active supportive treatment necessary
10	Moribund, fatal processes progressing rapidly
0	Dead

ECOG	
Score	**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
5	Dead

Graphic 57945 Version 11.0

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

Classification of the extent of portal vein tumor thrombus in hepatocellular ca according to the Japanese Liver Cancer Study Group

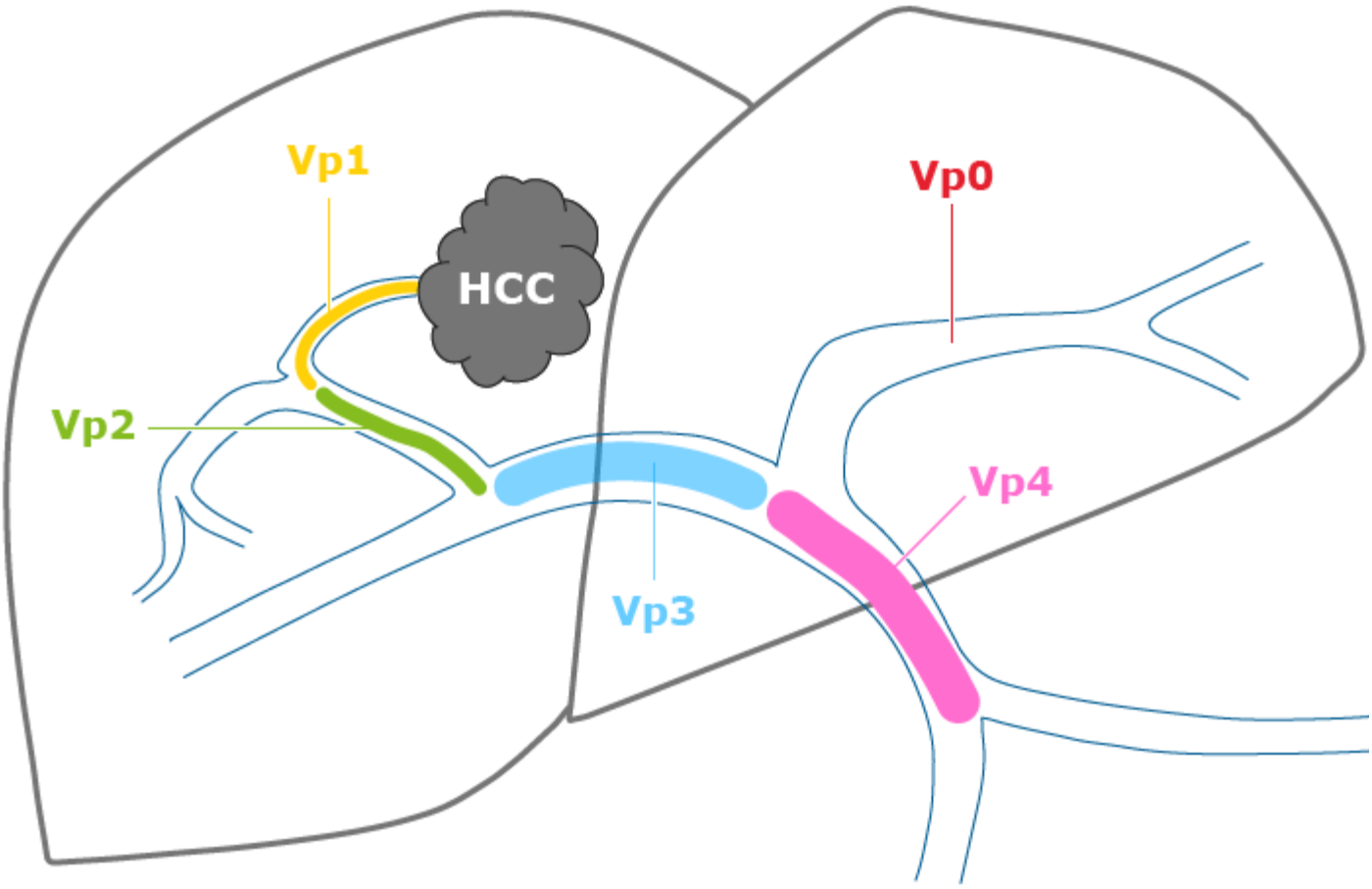

Figure describing the anatomical classification of portal vein tumor thrombosis as suggested by the Liver Ca Study Group of Japan (LCSGJ).

HCC: hepatocellular carcinoma; Vp0: no portal vein tumor thrombus; Vp1: segmental portal vein invasion; Vp right anterior or posterior portal vein; Vp3: right or left portal vein; Vp4: main trunk and/or contra-lateral po vein branch to the primarily involved lobe.

Graphic 138754 Version 1.0

American Liver Tumor Study Group modification of the TNM staging for hepatocellular cancer for the purpose of liver transplantation prioritization

T0	No tumor found
T1	One nodule, ≤1.9 cm
T2	One nodule, 2 to 5 cm; two or three nodules, all ≤3 cm
T3	One nodule, >5 cm; two or three nodules, at least one >3 cm
T4a	Four or more nodules of any size
T4b	T2, T3, or T4a, plus gross involvement of intrahepatic portal vein or hepatic vein, as indicated by CT, MRI, or ultrasonography
N1	Involvement of regional (porta hepatis) lymph nodes
M1	Metastatic disease including extrahepatic portal or hepatic vein involvement
Stage grouping	
Stage I	T1
Stage II	T2
Stage III	T3
Stage IVA1	T4a
Stage IVA2	T4b
Stage IVB	Any N1 or M1

TNM: tumor, node, metastasis; CT: computed tomography; MRI: magnetic resonance imaging.

Graphic 53242 Version 2.0

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

Contributor Disclosures

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. **Keith E Stuart, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Amit G Singal, MD** Consultant/Advisory Boards: AstraZeneca [HCC]; Bayer [HCC]; Boston Scientific [HCC]; Eisai [HCC]; Exact Sciences [HCC]; Exelixis [HCC]; Freenome [HCC]; FujiFilm Medical Sciences [HCC]; Genentech [HCC]; Gilead [Hepatitis C]; Glycotest [HCC]; GRAIL [HCC screening]; Roche [HCC]; TARGET RWE [HCC]; Universal Diagnostics [HCC]; Verve [NAFLD]. 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. **Richard M Goldberg, MD** Equity Ownership/Stock Options: Advanced Chemotec Inc [Pancreatic cancer]; Compass Therapeutics [Biliary tract and colorectal cancer]. Consultant/Advisory Boards: AbbVie [GI cancers]; Advanced Chemotherapy Technologies [GI cancer]; AstraZeneca [GI cancer]; Bayer [GI cancer]; Compass Therapeutics [GI cancer]; Eisai [GI cancer]; G1 Therapeutics [GI cancer]; GSK [Colorectal cancer]; Innovative Cellular Therapeutics [Colorectal cancer]; Inspirna [Colorectal cancer]; Merck [GI cancer]; Modulation Therapeutics [Lymphoma]; Novartis [GI cancer]; Sorrento Therapeutics [GI cancer]; Taiho [GI cancer]. Other Financial Interest: Taiho [Expert testimony GI 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.

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Conflict of interest policy

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