Evaluation and Management of Hepatocellular Carcinoma

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KEYWORDS
- Hepatocellular carcinoma • Evaluation • Management • Diagnosis • Treatment

KEY POINTS
- HCC is increasing in incidence.
- The role of HCC surveillance is to diagnose disease at a curative stage.
- Therapy for HCC is dependent upon the burden of tumor and degree of liver dysfunction.
- Potential curative options for HCC include hepatic resection, transplantation or ablation (in solitary lesion < 3 cm).
- Response to locoregional therapy, both radiographic and AFP decline, can be used to gain insight into tumor biology.

INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) is increasing in the United States and is predicted to continue to increase.1 Over the last several decades, the escalation in HCC has mirrored the increase in the incidence of hepatitis C virus (HCV)-induced cirrhosis, which carries the highest risk for the development of HCC, at an estimated 2% to 8% per year. The peak incidence of HCV-induced HCC is projected to occur in 2020. Despite an anticipated decline in HCV-induced cirrhosis and hence HCC, HCC related to nonalcoholic fatty liver disease is anticipated to increase.

There have been changing trends in the epidemiology of HCC in the United States, most notably with Hispanic men, who represent the fastest increase in the incidence of HCC, and a shift toward a younger age at diagnosis.2

Diagnosis at an incurable stage is associated with a dismal prognosis. Although there have been advancements in the treatment of HCC and a doubling of long-term survival, the overall 5-year survival remains low, at 18%, underscoring the need for novel therapeutic options.3

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The management of HCC is complicated by the superimposed morbidity/mortality related to cirrhosis, which is present in 80% to 90% of cases of HCC. Treatment of HCC is equally dictated by tumor burden, degree of liver dysfunction (Child-Pugh [CP] class), and the patients’ Eastern Cooperative Oncology Group (ECOG) performance status (Table 1). The Barcelona Clinic of Liver Cancer (BCLC) encompasses all these factors when making decisions regarding HCC therapy and is endorsed by the American and European associations (Table 2). More recently, a staging system from Hong Kong was published.

Given the complexities of caring for a patient with HCC, the vital necessity of a multidisciplinary approach cannot be overstated. Improvement in patient outcome, including more patients receiving curative therapies and prolonged overall survival (OS), has been reported in the setting of a multidisciplinary team.

In this article, the approach to patients at risk for the development of HCC and various treatment options are summarized.

RECOMMENDATIONS FOR HEPATOCELLULAR CARCINOMA SURVEILLANCE

The rationale for HCC surveillance is to diagnose at an early stage, when potential curative options are viable (resection, transplant, ablation). The recommendation for HCC surveillance is limited to a single randomized controlled trial (RCT) from China of 18,816 patients with hepatitis B that reported a 37% decrease in HCC mortality in those undergoing ultrasonography (US) + α-fetoprotein (AFP) every 6 months compared with the control group, despite low compliance in the surveillance group.

The decline in mortality among the surveillance group was related to detection of early HCC in 60% compared with 0% in the control group and a resection rate of 47% among those randomized to US + AFP versus 7.5% in the nonsurveillance group. It is not clear if these findings would be applicable to patients with cirrhosis in the United States. Nonetheless, an RCT of HCC surveillance is unlikely because of ethical concerns, and the feasibility of such a study has been reported to be remote, with only 0.5% of patients agreeable to randomization.

A meta-analysis, including more than 15,000 patients with cirrhosis, concluded that HCC surveillance led to earlier stage detection with improved curative treatment rates and OS. The results remained unchanged even after adjusting for lead time bias.

The screening interval is not determined by the risk for the development of HCC but rather the doubling time of HCC, which has been estimated to range from 1 to

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<th>Table 1</th>
<th>ECOG performance status</th>
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<tr>
<td>Grade</td>
<td>ECOG</td>
</tr>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work)</td>
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<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
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<td>5</td>
<td>Dead</td>
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19 months, with a median of 4 to 6 months. Semiannual screening has been reported to be superior to annual imaging in detecting HCC at an earlier stage. An RCT found no improvement in the detection of early tumors when screening was performed every 3 months compared with every 6 months.

The American Association for the Study of Liver Disease and European Association for the Study of the Liver (EASL) both advocate US every 6 months for patients with cirrhosis and those with hepatitis B without cirrhosis (men >40 years, women >50 years, Africans >20 years and at time of diagnosis if there is a positive family history). The EASL guidelines also recommend surveillance in HCV with stage 3 fibrosis. Surveillance is not recommended in decompensated cirrhotic patients who are not listed for transplantation, because they are unlikely to be candidates for resection or ablation. Similarly, those with substantial comorbidities that prohibit therapy are unlikely to derive a benefit from HCC surveillance. The cost-effectiveness of HCC surveillance has been shown, with curative options available for those with early stage disease.

US has the advantage of being noninvasive, inexpensive, and without radiation. The limitations of US are greatest among those with a more coarsened echotexture and in obese patients. In addition, results are dependent on the experience of the operator. Contrast-enhanced US (used in Europe) can aid in distinguishing regenerative nodules from malignant nodules; however, it is not available in the United State and is not anticipated to be approved by the US Food and Drug Administration, because of concern for cardiac toxicity. Furthermore, the use of contrast-enhanced US is not endorsed by guidelines, because of its inability to distinguish HCC from intrahepatic cholangiocarcinoma.

Since 2000, US technology has improved, allowing for the detection of smaller nodules, median 1.6 ± 0.6 cm. This development is reflected in studies that have reported improved survival among patients undergoing HCC surveillance in cohorts since 2000.

Computed tomography (CT) and MRI have been studied only as diagnostic tests. There are insufficient data to recommend cross-sectional imaging for surveillance purposes. However, a study examining the factors that affect US efficacy identified those with the greatest chance of failure of surveillance with US (HCC diagnosed exceeding Milan criteria or HCC detected after a negative US by CT or MRI performed for inadequate US quality or AFP >50 ng/mL), including those with features suggestive

| Effect of tumor number and presence of portal hypertension on 5-year OS and HCC recurrence |
|---------------------------------|-----------------|
| OS (%)                         | 5-y             |
| PHT CP A                       | 56              |
| No PHT CP A                    | 71              |
| Multiple HCC CP A              | 58              |
| Single HCC CP A                | 68              |
| Recurrence (%)                 | 5-y             |
| PHT CP A                       | 75              |
| No PHT CP A                    | 58              |
| Multiple HCC CP A              | 75              |
| Single HCC CP A                | 60              |

Abbreviation: PHT, portal hypertension.
of an aggressive HCC (AFP >200 ng/mL, infiltrating tumor, vascular invasion, or metastases) or patients with more advanced liver disease (leading to a more coarsened echo texture) or who are overweight.

 AFP is no longer supported by the current guidelines for surveillance because of high false-negative and false-positive results.\(^{21}\) AFP levels can be normal in up to 40% of patients with HCC. On the other hand, the presence of viral hepatitis, particularly in HCV, can lead to an increase in AFP levels in the absence of HCC. A persistently increasing AFP or disassociation of aspartate transaminase (AST) and AFP (increasing AFP level with no significant change in AST) is worrisome for underlying HCC.\(^{22}\) Despite the changes to the guidelines, many physicians continue to use AFP as part of a surveillance regimen. AFP should never be used alone for surveillance.

Other markers to improve the detection of early HCC have not been shown to be of benefit. The largest biomarker study comprising 836 patients failed to show lectin bound AFP (AFP-L3) or des-\(\gamma\)-carboxyprothrombin (DCP) to be more sensitive than AFP.\(^{23}\) A cutoff AFP level of 10.3 had the highest sensitivity for the diagnosis of very early/early HCC.

Education of physicians who care for patients at risk of HCC is required to improve the less than 20% of cirrhotics who are undergoing appropriate surveillance.\(^{24,25}\) Davila and colleagues\(^{25}\) reported that gastroenterologists/hepatologists as well as physicians affiliated with an academic institution are more likely to implement appropriate surveillance. A survey of the attitudes of primary care physicians (PCP) regarding HCC surveillance reported that the responsibility of surveillance is equal between the PCP and specialty physicians.\(^{26}\) The most common identified barriers to proper surveillance included a lack of knowledge of the current guidelines, difficulty discussing surveillance with patients, and competing clinical issues.

### Diagnosis of Hepatocellular Carcinoma

Once a lesion greater than 1 cm is detected on US, 4-phase CT, or contrast-enhanced MRI is required to make a diagnosis of HCC. Because of the difficulty and accuracy of liver biopsy (up to 40% false-negative results in lesions \(<\)2 cm), HCC diagnosis is frequently based on radiographic imaging.\(^{27}\) The classic descriptions of HCC imaging findings are intense contrast uptake in the arterial phase, followed by washout venous delayed phase. Biopsy is required if radiologic findings are not typical for HCC or cirrhosis is not present.\(^{28}\) Development of intrahepatic cholangiocarcinoma is also a risk in chronic liver disease and should be distinguished from HCC, because transplant is generally not recommended as a result of reported poor outcomes with high recurrence rates.

### Treatment of Hepatocellular Carcinoma

The recognized potentially curative options for HCC include hepatic resection, orthotopic liver transplant (OLT), or ablation for a lesion 3 cm or smaller. Selection criteria are critical to achieve the best possible outcomes.

**Hepatic Resection**

In the last 2 decades, surgical outcomes have significantly improved. This situation has largely been attributed to measures to decrease blood loss (maintaining a low central venous pressure of \(<\)5 cm H\(_2\)O during hepatic transaction, the Pringle maneuver [cross-clamping of the hilum], and laparoscopic surgery).\(^{29,30}\) RCTs have shown decreased morbidity with use of total parenteral nutrition and avoidance of drains.\(^{31}\)
The experience of the surgical team cannot be understated; an inpatient mortality of 10% has been reported in low-volume hospitals performing resection in the United States. The expected clinical outcomes in a CP A patient undergoing hepatic resection include less than 3% perioperative mortality, less than 10% transfusion requirement, and 5-year OS of greater than 50%.

The selection criteria used in the West for candidacy for hepatic resection have been the Barcelona criteria, which take into account clinically relevant portal hypertension and serum bilirubin levels. The 5-year OS status after resection was 74% in patients with a serum bilirubin level less than 1.0 mg/dL and hepatic venous pressure gradient (HVPG) less than 10 mm Hg compared with 25% in those not meeting these criteria. Surrogate markers used to predict an HVPG exceeding 10 mm Hg include the presence of esophageal varices, platelet count less than 100,000, or a spleen size greater than 12 cm on imaging. However, a lack of any of these findings does not necessarily preclude an HVPG greater than 10 mm Hg and therefore its measurement is still recommended. These criteria are for a solitary lesion with no upper limit of size; however, larger lesions (>5 cm) are more likely to have vascular invasion, and outcomes have been reported to be inferior, with 5-year OS of approximately 39%. Conversely, others have reported similar OS to smaller lesions.

The Model for End-Stage Liver Disease (MELD) score has also been shown to have prognostic value in potential resection candidates. A MELD of 8 or less predicts the best outcomes in patients with cirrhosis; higher MELD scores were associated with higher morbidity and lower OS.

The Makucchi criteria originated in Japan and have been used largely in the East to select appropriate candidates for resection. The extent of resection is based on the serum bilirubin level and a quantitative liver function test known as indocyanine green retention rate at 15 minutes (a normal liver has a retention of <10% at 15 minutes, whereas ≥40% at 15 minutes indicates that no resection is feasible, irrespective of how much liver removed). These criteria are not widely used in the United States.

Single institutions have devised their own criteria for resection, such as the University of Texas MD Anderson Cancer Center. A patient is deemed appropriate for a minor resection (<2 segments) if the patient is a CP A, with a bilirubin level of 2 mg/dL or less, no ascites, and platelet count greater than 100,000. For a major resection (>3 segments), the bilirubin level must be 1 mg/dL or less as well as meeting the other criteria for a minor resection.

In patients with compensated cirrhosis being considered for resection, CT and MRI volumetry are used to calculate the future liver remnant (FLR). An inadequate FLR is associated with postoperative complications and liver failure. Although there is no strict consensus on what volume constitutes a safe FLR, it is recommended that a remnant of 20% to 30% in normal livers, 30% to 40% in those with fibrosis or steatosis, and 40% to 50% in compensated cirrhosis be present after resection to sustain normal postoperative liver function. In those with a smaller predicted FLR, portal vein (PV) embolization (PVE) to occlude PV flow ipsilateral to the tumor to attempt to hypertrophy the remnant lobe has been used. An FLR hypertrophy of 5% or less after PVE is an indicator of poor regenerative capacity and is associated with higher postoperative complications and therefore a contraindication to resection. There are no RCTs examining the safety and efficacy of PVE before resection. Prospective trials have reported fewer postoperative complications and mortality without increased risk of HCC recurrence in patients undergoing a major resection with preoperative PVE compared with no PVE. The EASL guidelines have urged additional data be generated, specifically in the era of laparoscopic resection, before PVE can be endorsed as standard of care.
Others have challenged the notion of resection in patients in more than 1 lesion and in the presence of portal hypertension. The 5-year OS was significantly lower (see Table 2) among those with multiple lesions or presence of portal hypertension; however, these factors were not independent predictors of OS. Recurrence risk was significantly higher among those with multiple tumors.

Resection in the setting of macrovascular invasion has been considered a contraindication. However, in patients with branch PV thrombosis (PVT) and preserved liver function, resection may be a consideration after careful evaluation.

The risk of recurrent HCC is estimated to be approximately 70% at 5 years and the leading cause of mortality after resection. Nearly three-quarters of recurrences are caused by intrahepatic spread, with recurrence within 2 years of surgery. The remainder of recurrences occur later and are caused by de novo HCC as a result of the field defect of underlying cirrhosis. Factors that have been associated with a lower 5-year OS after resection include multiple nodules versus single, greater than 5 cm versus less than 5 cm, tumor margin 1 cm versus 2 cm, and higher median intraoperative blood loss. A meta-analysis has shown that an anatomic resection results in improved clinical outcomes compared with nonanatomic resection. Although an anatomic resection results in a smaller FLR, it allows for the removal of potential undetected tumor draining into the portal venules.

The National Comprehensive Cancer Network guideline recommends imaging every 3 to 6 months for 2 years, then, annually after surgical resection. In addition, if pretreatment AFP levels were increased, repeat serum AFP is recommended every 3 months for 2 years, then, every 6 months.

There are no proven adjuvant therapies to prevent HCC recurrence after resection. The STORM (Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma) trial, an international phase 3 trial designed to evaluate efficacy/safety of adjuvant sorafenib (400 twice a day) versus placebo after curative ablation or resection failed to show a benefit among the 1100 patients, of whom approximately 80% underwent hepatic resection (maximal tumor size 3.4 cm; 90% had a solitary lesion). There are data that suggest that the risk of HCC recurrence after resection is associated with HCV. With the advent of direct antiviral agents, this finding could play an important role in diminishing HCC recurrence among those with HCV.

Transplantation

The early experience with OLT for HCC was wrought with high HCC recurrence rates and thus poor OS (5 year <35%), leading to OLT being declared a contraindicated in HCC. The inception of the Milan criteria in 1996 (1 lesion <5 cm, 3 lesions with no one >3 cm, no vascular invasion, and no metastasis) revolutionized the role of OLT for early HCC. Excellent 5-year OS exceeding 70% has been reported in patients meeting the Milan criteria. OLT serves the dual purpose of removal of tumor and the underlying cirrhotic liver that predisposed to the development of HCC. The United Network for Organ Sharing (UNOS) allows a MELD exception for those meeting the Milan criteria starting at 22 points and increasing every 3 months in conjuction with repeat imaging to confirm that the tumor burden has not exceeded Milan criteria. Patients outside the Milan criteria are not granted prioritization, leading to the question of if the Milan criteria are too stringent. The obvious concern for expansion beyond the Milan criteria is the potential for negatively affecting posttransplant outcomes (with higher recurrence rates) and further straining the limited resource of organs available. More patients with HCC awaiting OLT with a MELD upgrade could incur harm to those awaiting OLT without HCC. A consensus statement on OLT for HCC...
recommended consideration for OLT in patients outside the Milan criteria if the dynamics of the wait list would not be negatively affected among other potential recipients without HCC.

Progression of HCC while awaiting OLT can lead to dropout; the risk at 1 year ranges from 15% to 30%.\textsuperscript{62} Recognized factors that increase the risk of dropout include tumor greater than 3 cm, AFP level greater than 200 ng/mL, waiting time exceeding 6 months, and lack of proven response to locoregional therapy (LRT).\textsuperscript{63} There are no RCTs that have addressed the role of LRT while awaiting OLT.

However, it is recommended to consider LRT in patients anticipated to wait longer than 6 months in the hopes of decreasing dropout.\textsuperscript{61}

Downstaging is defined as a treatment that intends to facilitate or make possible a surgical procedure that otherwise is too risky or unfeasible.\textsuperscript{64} There have been multiple reports, mostly limited to single-center experience of downstaging to OLT in patients who have on presentation exceeded the Milan criteria.\textsuperscript{64} Successful downstaging has been reported to vary from 40% to 90%. The heterogeneity of these results is caused by differences among these reports in terms of inclusion criteria (initial tumor size/number, AFP, tumor grade), type of LRT used, criteria defining response (ie, within Milan criteria based on total tumor size or taking into account tumor necrosis and only measuring viable tumor, decline in tumor markers; AFP/DCP) and enforcing a mandated period of observation after downstaging (3 or 6 months) before activation on the waiting list with a MELD upgrade to mitigate risk of HCC recurrence after OLT. The University of California, San Francisco group\textsuperscript{65} has reported encouraging results of 4-year OS of 92% in an initial cohort of patients enrolled in a downstaging protocol. In an updated analysis of 122 patients, there was no significant difference in posttransplant 5-year OS among those who were successfully downstaged to Milan criteria (N = 68) compared with those who met Milan criteria at time of presentation (80 vs 81%, \( P \) = not significant).\textsuperscript{66} Identified predictors of failure of downstaging were an initial AFP level greater than 1000 ng/mL and receiving more than 3 treatment sessions with LRT. In aggregate, the data suggest that there is a subgroup of patients who exceed the Milan criteria who have excellent posttransplant outcomes associated with successful downstaging procedures.

Patients with T1 lesions (solitary lesion <2 cm) are not granted a MELD upgrade for HCC. A common practice has been to closely observe solitary lesions less than 2 cm and wait until the lesion is 2 cm or greater before initiation of LRT to qualify for a MELD upgrade. However, this strategy incurs the potential risk of a lesion rapidly growing and exceeding Milan criteria. Mehta and colleagues\textsuperscript{67} examined the intention-to-treat outcome of watchful waiting in 114 patients with T1 HCC: 1.0 to 1.9 cm (median initial tumor diameter was 1.4 cm). Patients underwent imaging every 3 months. The median time for tumors to progress from T1 to T2 (1 lesion 2–5 cm or 2–3 lesions \( \leq 3 \) cm) was 6.8 months, compared with 5.1 months for a tumor to progress from T1 to T3 (N = 6, of which 2 patients developed advanced disease with PVT or metastatic disease). The factors associated with increased risk of tumor progression beyond the Milan criteria included rapid tumor growth (defined as >1 cm growth within 3 months) and an initial AFP level greater than 500 ng/mL. Overall, the risk of progressing beyond T2 in an initial T1 lesion without LRT was less than 10%. However, in those patients with an initial AFP level more than 500 ng/mL or rapid tumor growth, early LRT is recommended, even if the tumor is not yet at a T2 status.

Living donor liver transplant (LDLT) offers a timely transplant and hence would be anticipated to decrease dropout and simultaneously expand the donor pool. The number of LDLT (not limited to HCC) performed in the United States has remained low, with only a few hundred per year.\textsuperscript{68} Donor safety is a major concern; donor death has been
reported to be approximately 0.5%, morbidity 38%, with most complications not being life threatening or altering.69 Also fast tracking to transplant with an LDLT has led to concern for an inadequate observational period to gain insight into the biological behavior of the tumor such that a limited waiting time to transplant in an aggressive tumor may lead an increase in HCC recurrence after OLT.70 No significant difference in HCC recurrence has been found between LDLT and deceased donor liver transplant (DDLT) when the same selection criteria are used.71 However, in A2ALL (Adult to Adult Living Donor Liver Transplantation Cohort Study), a higher rate of HCC recurrence after transplant was observed after adjusting for tumor characteristics among the entire cohort; however, in the MELD era this difference was no longer statistically significant.72 The difference in HCC recurrence may be attributed to not only difference in tumor characteristics (LDLT offers an option for OLT in those exceeding the Milan criteria), but also pretransplant HCC therapy and waiting time between LDLT and DDLT.

In a CP A patient with HCC, resection or OLT may both be possible treatment options. Although OLT is generally reserved for nonresectable lesions, this decision is influenced by center experience, cultural attitudes toward OLT, practice patterns, and organ availability. The pros and cons for each approach are highlighted in Table 3. Intention-to-treat analysis has shown a lower OS in transplant compared with resection caused by dropout while awaiting OLT.34 Salvage OLT is a transplant that occurs after resection as a result of either hepatic decompensation or recurrent tumor within the Milan criteria. The benefit of such an approach is it engenders the potential for greater availability of organs in those without HCC and negates the need for immunosuppression (if salvage OLT is never required). It is estimated that up to approximately 40% of patients with HCC recurrence after resection are not candidates for salvage OLT because of recurrence beyond the Milan criteria. Several studies73–75 have reported no significant difference between a primary OLT for HCC compared with salvage OLT. A meta-analysis76 that examined primary OLT versus resection followed by salvage OLT found a gain in life expectancy of only 7 months associated with primary OLT in CP A patients within the Milan criteria. Primary OLT was the preferable approach over resection when 5-year OS postprimary OLT exceeded 60%. Sensitivity analysis found a gain in life expectancy in listed patients without HCC with resection followed by salvage OLT when the there is a higher percentage of HCC patients listed for OLT and when waiting times are longer. Because of the shortage of organs available, such dynamics need to be taken into account to maximize outcomes for both those with HCC and non-HCC patients listed for OLT. Resection explant characteristics that have been reported to predict HCC recurrence include presence of microvascular invasion, greater than 3 cm, poorly differentiated tumors, satellite nodules, and cirrhosis.77 Those with 3 or more of these factors

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<th>Table 3</th>
<th>Comparison between hepatic resection and transplantation for HCC</th>
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<td><strong>Transplantation</strong></td>
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<td><strong>Pro</strong></td>
<td>Transplantation</td>
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<tr>
<td></td>
<td>Removes cirrhotic liver and treats HCC</td>
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<td>5-y OS &gt;70% (within Milan)</td>
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<td><strong>Con</strong></td>
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<td>Shortage of organs</td>
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<td>Dropout because of</td>
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<td>HCC progression</td>
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<td>Potential recurrence of original disease</td>
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were significantly more likely to recur beyond the Milan criteria. Such patients should be considered for transplant before recurrence, known as de principle transplant. The recognized limitation is ability to obtain an organ, because there is no HCC MELD upgrade given after resection. Discussion for LDLT may be the most appropriate in these situations in those who would otherwise be a transplant candidate.

No guidelines are in place for monitoring patients after OLT for HCC recurrence. Recommendations regarding frequency and duration of imaging have been suggested based on explant pathology: low (Milan + well/moderately differentiated, no VI) versus high (>Milan or poorly differentiated or + VI) risk. When possible, HCC recurrence should be treated with resection. LRT, or sorafenib can be used for unresectable lesion(s). The safety and efficacy of sorafenib in high-risk patients is being investigated in an RCT (NCT00997022).

**Locoregional Therapy**

LRT can be used for multiple purposes. LRT may be appropriate in patients who are not surgical candidates. The other role for LRT is as a bridge to OLT and to downstage a patient to OLT or resection. The various types of LRT are listed in Box 1.

The response to LRT (radiographic and AFP decline) has emerged as a selection criteria for OLT. The notion of ablate and wait allows for a period of observation to gain insight into the biological behavior of a tumor. A lack of response to transarterial chemoembolization (TACE), regardless of Milan status, was associated with significantly higher post-OLT HCC recurrence rates. In addition, a lack of response has been reported, with a greater chance of dropout independent of tumor size. AFP level closest to transplant is an independent predictor of OS after OLT. However, a decline in AFP level associated with LRT results in no identified increase mortality. These findings indicate that the AFP level should be considered in determining patients’ candidacy for OLT regardless of tumor size/number. Although not yet implemented, a UNOS consensus conference recommended that patients listed for OLT with HCC should not be granted an upgrade unless AFP level is less than 500 ng/mL.

**Ablative therapies**

Percutaneous ethanol injection (PEI) was first used in the 1980s to treat small tumors. Thermal ablative therapies including radiofrequency ablation (RFA) and microwave ablation (MWA) have largely replaced PEI because of superiority, with a need for fewer therapies and better local tumor control in tumors greater than 2 cm. Moreover, OS with thermal ablation were higher in a meta-analysis. Both RFA (thermal injury) and MWA (electromagnetic energy) induce coagulative necrosis and can be

<table>
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<th>Box 1</th>
<th>List of LRT</th>
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<tr>
<td>1.</td>
<td>Percutaneous ethanol ablation</td>
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<td>2.</td>
<td>Radiofrequency ablation</td>
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<td>Microwave ablation</td>
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<td>4.</td>
<td>Transarterial chemoembolization</td>
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<td>5.</td>
<td>Drug-eluting beads</td>
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<td>6.</td>
<td>Radioembolization</td>
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<td>7.</td>
<td>Stereotactic body radiation therapy</td>
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performed via percutaneous, laparoscopic, or open laparotomy approach. General anesthesia is usually required. The size of the tumor is the best predictor of response. Complete response is reported in 90% of tumors less than 2.5 cm, whereas less than 50% achieve complete response when greater than 5 cm. Many factors influence the decision for ablative therapy, including tumor size, number, location (near organs or large blood vessels, which can create heat sink and decrease response). An advantage of MWA is less reported heat sink, and it may be more appropriate for use near large blood vessels. For lesions greater than 3 cm, RFA + TACE may lead to improved OS at 5 years compared with RFA alone, whereas in lesions less than 3 cm there seems to be no significant benefit of combination therapy.

RFA is an alternative to hepatic resection in solitary lesions less than 3 cm. An RCT of hepatic resection versus RFA for patients meeting the Milan criteria showed superior OS at 5 years and less recurrence among those who had resection. A subanalysis in those with a solitary lesion less than 3 cm did not alter these results. However, RFA is less invasive, requires shorter hospitalization, and is associated with less morbidity and cost. A meta-analysis showed RFA to be the treatment of choice in patients older than 75 years, because there was less mortality compared with resection.

**Intra-arterial therapies**

TACE is the most common LRT used in the treatment of HCC, largely because of an RCT showing improved OS compared with no therapy in patients with preserved liver function with intermediate HCC (BCLC B). The hypervascular nature of HCC is the rationale for injection of chemotherapy emulsified in lipiodol (delivery agent) with particles to embolize the feeding hepatic artery supplying the tumor inducing hypoxemia and subsequent tumor necrosis. Postembolization syndrome with symptoms of abdominal pain, fever, nausea, and vomiting is common. Ischemic hepatitis with hepatic decompensation can result in those with compromised blood flow in the PV because of PVT, hepatofugal flow, or presence of a transjugular intrahepatic portosystemic shunt. Although there are reports of TACE being feasible in branch PVT, main PVT is an absolute contraindication for TACE.

Drug-eluting beads (DEBs) offer an advantage over conventional TACE by delivering maximal and sustained intratumoral concentrations of doxorubicin and minimizing toxicity as a result of lower systemic absorption. DEBs also enable standardization (generating a consensus statement), which has been difficult to achieve with conventional TACE. A bead size of 100 to 300 μm is recommended to achieve maximal chemotherapy delivery and embolic effect. There are reports of DEBs in the presence of PVT.

PRECISION, an international RCT of DEB versus TACE, failed to meet the primary end point of radiographic response (EASL) at 6 months. However, improved radiographic response with DEBs was observed in those with ECOG 1, bilobar disease, CP B, or recurrent disease, along with significantly less serious side effects/liver toxicity compared with conventional TACE. Encouraging results with DEB from a prospective trial reported an OS of 48 months in CP A patients. DEBS has shown significantly higher rates of necrosis on explants and improved 3-year recurrence-free survival after OLT compared with conventional TACE.

Transarterial radioembolization (TARE) is another form of intra-arterial therapy. Microspheres impregnated with yttrium 90 (Y90) are injected into the hepatic artery. Because of the hypervascular nature of HCC and the small size of the microspheres, 25 to 30 μm, Y90 is preferentially delivered to the capillary bed of the tumor, leading to high intralesional radiation and minimization of radiation to nontarget surrounding
tissue. Before administration of Y90, a staging angiogram is performed to identify aberrant anatomy that may require coil embolization to prevent nontarget delivery of microspheres, correct catheter position, and determine degree of pulmonary shunting via a technetium 99 macroaggregated albumin scan. The amount of radiation is calculated via dosimetry.\textsuperscript{105} If the degree of shunting is too high (>30 Gy with single injection and cumulative dose of >50 Gy), therapy may not be performed or alternatively the dose of radiation can be lowered according to the degree of shunting. Within 7 to 10 days, the patient returns for administration of Y90; both procedures are outpatient. Same day administration is being performed in some centers.

Unlike chemoembolization, Y90 is not macroembolic; and therefore; the patency of the hepatic artery is maintained. The use of Y90 has been shown to be safe in patients with PVT (bland or tumor).\textsuperscript{106–109} OS is affected by both the CP class and locations of PVT (branch vs main) (Table 4). Another consideration is an emphasis on delivering intra-arterial therapies in a selective/superselective manner to minimize injury to surrounding tissue. It has been suggested that TACE should not be performed if greater than 2 segments are encompassed in the treatment field, generally larger tumors.\textsuperscript{110} In such cases, TARE has been advocated.

The other area in which Y90 has shown clinical promise is in downstaging. In a retrospective analysis,\textsuperscript{111} Y90 led to downstaging to T2 in 58% versus 31% with TACE ($P = .023$), and disease progression at 1 year was significantly lower among the Y90 cohort, 15% versus 32%, $P \leq .05$. Downstaging to resection has been coined radiation lobectomy. Lobar therapy with Y90 can lead to both treatment of the tumor and simultaneous hypertrophy of the FLR, thereby permitting resection in some patients who may have not otherwise been candidates because of concern for a small liver remnant.\textsuperscript{112} Although hypertrophy can be seen within 1 month after Y90, the degree of hypertrophy correlates with the time elapsed since treatment, with a median FLR increase of 45% from baseline at 9 months.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Impact of PVT on OS and TTP</th>
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<tbody>
<tr>
<td>Salem et al</td>
<td>OS Median (95% CI)</td>
</tr>
<tr>
<td>CP A: 0 PVT, 0 mets (N = 81)</td>
<td>22.1 (17.2–32.5)</td>
</tr>
<tr>
<td>Branch (N = 19)</td>
<td>16.6 (8.8–24)</td>
</tr>
<tr>
<td>Main PVT (N = 16)</td>
<td>7.7 (3.3–13.2)</td>
</tr>
<tr>
<td>CP B: 0 PVT, 0 mets (N = 65)</td>
<td>14.8 (11.8–29.1)</td>
</tr>
<tr>
<td>Branch (N = 27)</td>
<td>6.5 (5–8.5)</td>
</tr>
<tr>
<td>Main PVT (N = 30)</td>
<td>4.5 (2.9–6.6)</td>
</tr>
</tbody>
</table>

Abbreviations: mets, metastasis; NC, not calculable; PD, progression of disease; TTP, time to progression.

There are no published RCTs of TACE versus Y90. The comparison between the 2 treatment modalities is limited to retrospective analysis.\textsuperscript{113,114} Although OS was similar between TACE and Y90 (overall or in BCLC B), there were noted differences from a patient prospective, which may affect patients’ treatment decision. Y90 patients required no hospitalization, less abdominal pain, fewer treatment sessions, and improved quality of life.\textsuperscript{115}

**Systemic Therapy**

Sorafenib, a multityrosine kinase inhibitor, remains the only approved systemic therapy for HCC. Two RCTs (SHARP [Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol] and the Asian-Pacific group) reported improved OS in CP A advanced HCC compared with placebo.\textsuperscript{116,117} An interim analysis of the GIDEON (Global Investigation of Therapeutic Decisions in HCC and of its Treatment with Sorafenib) trial,\textsuperscript{118} a prospective observational trial of patients treated with sorafenib, highlighted that OS is influenced by CP status: CP A: 10.3 versus CP B 4.8 months. A survival advantage was reported in a small retrospective study in CP B patients treated with sorafenib compared with best supportive care.\textsuperscript{119} The safety and efficacy of sorafenib in CP B patients is being examined in an ongoing RCT, Sorafenib in First-line Treatment of Advanced B Child Hepatocellular Carcinoma or BOOST trial (NCT01405573).

CP A patients with PVT are potential candidates for sorafenib or TARE. The role of combining TARE + sorafenib lacks data; several trials are ongoing.

For those who progress or are intolerant to sorafenib, there is an unmet need. RCTs of other tyrosine kinase inhibitors (sunitinib, brivanib, linifanib) compared with sorafenib have not shown improvement over sorafenib.\textsuperscript{120–123} One agent has shown clinical promise. Tivantinib, an oral MET inhibitor, significantly improved time to progression (TTP) (11.7 vs 6.1 mo.; \(P = .03\)) and OS (7.2 vs 3.8; \(P = .01\)) in patients with high tumor MET expression on biopsy compared with placebo.\textsuperscript{124} The most common grade 3 or higher adverse events in the phase 2 trial were neutropenia and anemia, leading to dose alteration from 360 mg to 240 mg. A phase 3 RCT (NCT01755767) is under way to confirm if this agent is a viable second-line therapy. Several other agents are under investigation alone (SGI-110 NCT01752933) or in combination with sorafenib (everolimus NCT01005199), temsirolimus (NCT01687673), pravastatin (NCT01487292).

The use of sorafenib in the pretransplant setting is limited and has conflicting results.\textsuperscript{125,126} A pilot RCT of 20 patients (Y90 ± sorafenib) awaiting OLT found no benefit of sorafenib added to Y90 in terms of explant pathology or clinical outcomes.\textsuperscript{127,128} However, there was an increased risk of biliary complications and acute cellular rejection within 30 days in the sorafenib group. These findings suggest that sorafenib before OLT should be used only in the context of a clinical trial.

**Combination locoregional therapy with systemic therapy**

The rationale for combining sorafenib with LRT is to blunt a flare of angiogenesis and hence lead to slower progression of tumor. Three RCTs of conventional TACE or DEB ± sorafenib have reported conflicted results.\textsuperscript{129–131} A meta-analysis of 6 studies (which did not include the unpublished SPACE trial) concluded that the combination of sorafenib + TACE improved OS and TTP.\textsuperscript{132} Additional research is warranted to confirm this benefit.

**Hepatocellular Carcinoma Prevention**

HCC is the number 1 cause of mortality among patients with cirrhosis. Patients should be educated on measures to potentially prevent the development of HCC. All patients
should be counseled on alcohol abstinence, smoking cessation, maintaining a normal body mass index, and hepatitis B virus (HBV) vaccination. Data support intake of coffee to prevent HCC; however, decaffeinated coffee and other caffeinated beverages have not been shown to have a protective effect on HCC development. Further research is required to determine the effect of low vitamin D levels on the risk of HCC.

SUMMARY

The incidence of HCC is increasing in the United States. HCV carries the highest risk factor for development of HCC. Diagnosis at an early stage is crucial for survival benefits. Major guidelines recommend US surveillance every 6 months for patients with HCC risk factors. HCC diagnosis is based on typical findings on CT or MRI. Biopsy is required if imaging findings are not typical or noncirrhotic. The Barcelona treatment strategy is widely accepted in the West. Hepatic resection, liver transplant, and ablation are the main curative treatment options for early stage HCC. LRT can be used for patients with HCC who are not surgical candidates, downstaging for surgical treatments, or bridging therapy for OLT. Sorafenib is the only approved systemic therapy for HCC. Although there have been advancements in the treatment of HCC and a doubling of long-term survival, diagnosis in advanced stages has a low 5-year OS, at 18%, underscoring the need for novel therapeutic options.

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