The diagnosis and treatment of hepatocellular carcinoma (HCC) have witnessed major changes over the past decade. Until the early 1990s, HCC was a relatively rare malignancy, typically diagnosed at an advanced stage in a symptomatic patient, and there were no known effective palliative or therapeutic options. However, the rising incidence of HCC in several regions around the world coupled with emerging evidence for efficacy of screening in high-risk patients, liver transplantation as a curative option in select patients, ability to make definitive diagnosis using high-resolution imaging of the liver, less dependency on obtaining tissue diagnosis, and proven efficacy of transarterial chemoembolization and sorafenib as palliative therapy have improved the outlook for HCC patients. In this article, we present a summary of the most recent information on screening, diagnosis, staging, and different treatment modalities of HCC, as well as our recommended management approach.

**Diagnosis of Hepatocellular Carcinoma**

Cirrhosis is the strongest and the most common known risk factor for hepatocellular carcinoma (HCC), particularly cirrhosis related to hepatitis C virus (HCV) and hepatitis B virus (HBV) infections.\(^1-3\) In addition, HBV acquired in the perinatal period and early childhood is associated with increased risk of HCC even in the absence of cirrhosis.

**Clinical Features**

Patients with HCC present with one or more of several clinical features including right upper quadrant pain, weight loss, and/or worsening liver enzymes in a patient known to have cirrhosis. Rare presenting features include acute abdominal catastrophe from rupture of HCC with intraabdominal bleeding or extra hepatic manifestations (eg, hypercalcemia, hypoglycemia, thyrotoxicosis).\(^4-5\) Anemia is present in more than half of cases, although rarely erythrocytosis can be seen because of extrarenal synthesis of erythropoietin.\(^6\) In addition to signs of cirrhosis (eg, jaundice, palmar erythema, gynecomastia) and portal hypertension (eg, ascites, varices), a hepatic bruit could be detected in 10%-20% of patients with HCC.\(^7\) With the increased awareness of HCC, more asymptomatic patients are being diagnosed as part of active surveillance. Unfortunately, the majority of patients still present with signs and symptoms suggestive of liver decompensation and/or tumor spread.

**HCC Screening**

HCC screening is recommended in high-risk patients (Table 1). In a randomized controlled trial of nearly 19,000 HBV-infected patients in China, it was shown that HCC surveillance with testing of serum alpha-fetoprotein (AFP) and performance of abdominal ultrasound (US) at repeated 6-month intervals improves survival.\(^8,9\) Although adherence to surveillance was relatively low (<60%), a 37% reduction in HCC-related mortality was reported. A similar, randomized clinical trial study in China, however, reported that surveillance for HCC is not beneficial in the absence of curative therapies after the cancer was diagnosed.\(^10\) In addition, several nonrandomized trials, as well as observational studies, have observed a survival benefit in those identified with small and early tumors.\(^11\)

AFP and liver US are the most widely used tools for HCC surveillance. Based on the estimated HCC doubling time, the recommended surveillance interval is 6 months,
although a 1-year interval may be equally effective. The performance of US depends on the experience of the examiner, the technology used, the body habitus, the presence of cirrhosis, and the size of the tumor. Recent studies generally indicate a >60% sensitivity, and >90% specificity. The sensitivity of US to detect tumor nodules in cirrhotic livers is particularly low. The serum AFP level of 20 ng/mL commonly used as the upper limit of normal has low sensitivity (25% to 65%) for detecting HCC and is therefore considered inadequate as the sole screening test. Patients with chronic liver disease, especially those with a high degree of hepatocyte regeneration (eg, HCV), can express elevated serum AFP in the absence of malignancy. Other tests such as des-γ carboxy prothrombin and lectin-bound AFP (AFP-L3) are available, but there are no reliable prospective data on their effectiveness in HCC screening.

The cost-effectiveness of HCC surveillance strategies using both AFP and US have been evaluated in retrospective studies as well as mathematical models, and generally reported surveillance for HCC in patients with compensated cirrhosis might be associated with a modest gain in quality adjusted life years at acceptable costs. One study also reported that the effectiveness of surveillance depends mostly on the outcomes and costs of HCC treatments. In patients undergoing HCC screening while awaiting liver transplantation, screening with computerized tomography (CT) is associated with the greatest gain in life expectancy and is possibly cost-effective in this setting.

Therefore, current guidelines advocate the use of US at 6–12 months frequency to screen for HCC in high-risk patients. The use of AFP alone is strongly discouraged, and its use in addition to US is controversial. High-risk patients include virtually all patients with cirrhosis and some HBV-infected patients irrespective of cirrhosis (>40 years in men and >50 years in women).

### Diagnostic Imaging

Once a screening test is abnormal or there is a clinical suspicion that a patient may have HCC, imaging is very important for the diagnosis and staging of this tumor. The most reliable diagnostic tests are triple-phase helical CT and triple-phase dynamic contrast enhanced magnetic resonance imaging (MRI), whereas hepatic angiography has fallen out of favor in most practice settings. HCC derives its blood supply predominantly from the hepatic artery, whereas the remainder of the nontumorous liver receives both arterial and portal blood. The hallmark of HCC during CT scan or MRI is the presence of arterial enhancement followed by delayed hypointensity of the tumor in the portal venous and delayed phases, ie, washout (Figure 1). The presence of arterial enhancement followed by washout has a sensitivity and specificity of 90% and 95%, respectively. However, 71% of patients with HCC will have arterial enhancement and washout on more than one test, whereas the rest do not have these features and, therefore, will require liver biopsy for the diagnosis of HCC. There have been at least 4 studies that have compared the accuracy of CT and MRI for HCC diagnosis, using the explanted liver as the gold standard. These show that MRI is slightly better in the characterization and diagnosis of HCC when compared with CT scan (Table 2). The performance of CT and MRI is affected by the size of the lesions. For example, in tumors larger than 2 cm, MRI is reported to have an accuracy >90%; however, in tumors smaller than 2 cm, this level is reduced to 33%.

Currently, AFP serum levels above 200 ng/mL are highly specific for HCC diagnosis in patients with cirrhosis and coinciding radiologic evidence of focal hepatic lesions. However, the sensitivity of AFP is much lower because it has been reported that only one third of patients with HCC have AFP levels higher than 100 ng/mL.

### Diagnostic Approach to HCC

A diagnostic approach to HCC has been developed based on the literature and expert consensus and incorporates serology, cytohistology, and radiologic characteristics. Diagnosis of HCC can be confidently established if (1) a focal hepatic mass >2 cm is identified on one imaging technique wherein characteristic contrast enhancement features on the arterial phase with venous washout on an MRI or CT can be demonstrated; (2) a focal hepatic mass with atypical imaging findings (no arterial enhancement with washout), or a focal hepatic mass detected in a noncirrhotic liver, should undergo a biopsy.

Noninvasive diagnosis of HCC is best limited to patients with cirrhosis and to patients with a focal hepatic mass >2 cm. On the other hand, the recommended diagnostic approach for tumors ≤2 cm or tumors that do not meet above criteria is such that (1), when nodules within 1–2 cm on screening of a cirrhotic liver are typical of HCC (hypervascular with washout) on 2 imaging modalities, the lesion should be treated as HCC. In an atypical lesion where the
vascular profile is not consistent among techniques, a biopsy of the lesion should be considered. (2) Nodules smaller than 1 cm should be followed with US at 3- to 6-month intervals. If, over a period of 2 years, growth has not been observed, a return to routine surveillance at 6-month intervals is suggested.35

Percutaneous liver biopsy under radiologic guidance have sensitivities and specificities of 90% and 91% for US and 92% and 98% for CT scan guidance, respectively.36 A negative biopsy result, although highlight suggestive, does not completely rule out malignant disease, and the nodule should be further studied at 3- to 6-month intervals until the nodule disappears, enlarges, or displays diagnostic characteristics of HCC. If the lesion enlarges but remains atypical for HCC, a repeat biopsy is recommended.36

Treatment of HCC

The management of HCC involves multiple disciplines including hepatology, surgery, diagnostic and interventional radiology, oncology, and pathology. One has to consider several patient and tumor factors including the severity of underlying liver disease, tumor bulk, and associated comorbidities as well as several practice-setting factors including availability and expertise in surgical resection, transplantation, and ablative therapies.

Staging of HCC

A precise staging of the disease may help decide on prognosis as well as choice of therapy with the greatest survival potential. There are several prognostic scoring systems including Barcelona-Clinic Liver Cancer (BCLC), Cancer of the Liver Italian Program, the Chinese University Prognostic Index and Japanese Integrated Staging. They use different permutations of variables related to the severity of liver disease, number and size of tumor nodules, and cancer spread (Table 3). Although there is no one universally accepted HCC staging system, many have adopted the BCLC group’s proposal of 5 stages, further validated in a large North American expe-
The BCLC staging and prognostic system accounts for variables related to tumor stage, physical and liver functional status, and cancer-related symptoms and also provides a link to a treatment algorithm. Patients in stage A can undergo resection, transplantation, or ablation. Child–Turcotte–Pugh (CTP) class, which provides an assessment of the synthetic function, may serve complementary to the BCLC staging in providing a more refined treatment algorithm. The Okuda classification takes into account radiologic tumor size and liver function (ascites, total serum bilirubin, and serum albumin) is helpful in identifying patients with advanced HCC but may be less adequate for staging patients with early or intermediate stage disease. Another commonly used staging system is the Cancer of the Liver Italian Program (CLIP), which uses a mathematical score based on the CTP, tumor morphology, AFP, and presence of vascular invasion; however, it does not adequately assess populations undergoing radical therapies, such as resection or transplantation.

Despite some degree of overlap, several stages of HCC can be identified, and each has different clinical features as well as treatment and prognosis (Figure 2). Very early HCC is currently very difficult to diagnose, presenting with a single HCC lesion.<sup>37,38</sup> The BCLC staging and correlation with Okuda Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>PS:</th>
<th>Tumor stage:</th>
<th>Okuda:</th>
<th>pH:</th>
<th>Bilirubin:</th>
<th>Classification:</th>
</tr>
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<tbody>
<tr>
<td>A1</td>
<td>0</td>
<td>Single</td>
<td>I</td>
<td>No</td>
<td>Normal</td>
<td>Very early</td>
</tr>
<tr>
<td>A2</td>
<td>0</td>
<td>Single</td>
<td>I</td>
<td>Yes</td>
<td>Normal</td>
<td>Early</td>
</tr>
<tr>
<td>A3</td>
<td>0</td>
<td>Single</td>
<td>I</td>
<td>Yes</td>
<td>Altered</td>
<td></td>
</tr>
<tr>
<td>A4</td>
<td>0</td>
<td>3 × &lt;3 cm</td>
<td>I–II</td>
<td>Yes</td>
<td>Altered</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>&gt;5 cm or multinodular</td>
<td>I–II</td>
<td>Yes</td>
<td>Altered</td>
<td>Intermediate</td>
</tr>
<tr>
<td>C</td>
<td>1–2</td>
<td>Vascular invasion</td>
<td>I–II</td>
<td></td>
<td></td>
<td>Advanced</td>
</tr>
<tr>
<td>D</td>
<td>3–4</td>
<td>Any stage</td>
<td>III</td>
<td></td>
<td></td>
<td>Terminal</td>
</tr>
</tbody>
</table>

CLIP Staging<sup>b</sup>

<table>
<thead>
<tr>
<th>Points:</th>
<th>CTP:</th>
<th>Tumor morphology:</th>
<th>AFP:</th>
<th>Portal vein thrombosis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>A</td>
<td>Uninodular ≤50% of liver</td>
<td>&lt;400 ng/dL</td>
<td>No</td>
</tr>
<tr>
<td>1</td>
<td>B</td>
<td>Multinodular ≤50% of liver</td>
<td>≥400 ng/dL</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>C</td>
<td>Massive &gt;50% of liver</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CLIP, Cancer of the Liver Italian Program; PH, portal hypertension; PS, performance status; PT, prothrombin time; INR, international normalized ratio.

<sup>a</sup>Median survival without therapy: Stage I: 8.3 years, Stage II: 2 years, Stage III: 0.7 years.

<sup>b</sup>The median survival is 36, 22, 9, 7, and 3 months for total CLIP points of 0, 1, 2, 3, and 4 to 6, respectively.
Patients with compensated cirrhosis and without HCC-related symptoms or vascular invasion that are outside of the criteria of very early or early stage correspond to the intermediate stage HCC. In this group, transarterial chemoembolization (TACE) leads to a 23% improvement in the 2-year survival compared with conservative therapy.

Patients with mild cancer-related symptoms and/or vascular invasion or extrahepatic spread are considered as advanced stage (BCLC stage C). TACE may increase survival in well-selected candidates. However, a recently completed randomized trial showed that soranefib improved the overall survival for patients at the BCLC stage C compared with placebo. This therapy is likely to become the main option for patients at this stage.

Patients with advanced stage present with cancer symptoms, related to progressed liver failure, tumor growth with vascular involvement, extrahepatic spread, or physical impairment (performance status \(< 2\)). Trials of tamoxifen,\textsuperscript{42-44} octreotide,\textsuperscript{45} interferon,\textsuperscript{46} or antiandrogenic therapy\textsuperscript{47} have shown no clear benefit for these agents.

Unfortunately, patients who present with or have progressed into terminal stage have a 1-year survival less than 10%. This group does not benefit from treatments mentioned above. Therefore, to prevent unnecessary suffering, the patient should receive symptomatic treatment.

**Treatment Modalities**

A summary of the main treatment modalities, their indications, and reported outcomes is shown in Table 4.

**Surgical resection.** Hepatic resection is the treatment of choice for HCC in noncirrhotic patients because of the fact that the residual liver has well-preserved hepatic reserve. This group, however, accounts for less than 5% of patients in Western countries but nearly 40% in HBV-endemic Asian countries.\textsuperscript{14} HBV has several cancer-promoting actions including insertional mutagenesis and p53 inhibition that explain its potential to induce HCC in noncirrhotic liver.\textsuperscript{48} Patients with HCC and concomitant cirrhosis are not suitable for resection because of the potential for hepatic decompensation after surgical resection. Hepatic resection for HCC in patients with cirrhosis, therefore, requires careful selection. A fundamental problem is not only the stage of cirrhosis but also the diminished regenerative reserve at the cirrhosis stage. Hepatocyte regeneration decreases at the cirrhosis stage, which has been linked to telomere shortening, senescence, and DNA damage checkpoint activation.\textsuperscript{49} The development of molecular markers indicating the regenerative reserve of hepatocytes may help to better select HCC patients with underlying cirrhosis for surgical resection in the future.

Historically, the selection of candidates was based on the CTP classification; however, this often does not account for some of the symptoms of advanced liver disease. A normal bilirubin concentration and the absence of significant portal hypertension are probably the best predictors of excellent short- and long-term outcomes.\textsuperscript{50} Significant portal hypertension can be inferred from signs of esophageal varices and platelet counts below 100,000/mm\(^3\) related to splenomegaly or can be determined by indirect portal pressure measurements (hepatic venous pressure gradient \(< 10\) mm Hg). The 5-year survival is less than 30% in patients with elevated bilirubin (\(> 1\) mg/dL) and portal hypertension.

In patients with cirrhosis, 5-year recurrence rates following resection exceed 50%.\textsuperscript{14,34} Utilization of tools such as comparative genomic hybridization, integration pattern of HBV, DNA fingerprinting using loss of heterozy-
Several variables affect the risk of recurrence following resection: these include tumor size, number of tumors, vascular invasion, and the width of the resection margin. The recommended upper limit of tumor size for consideration of resection has been argued, noting that there is a significant difference in the 5-year recurrence rates in patients with tumors >5 cm that is considerably greater than those with <5 cm (43% vs 32%, respectively).54 Similarly, multinodular tumors have been determined to have an increased tendency to recur.55 A large study of 1000 HCC patients reported a 5-year survival after resection of single tumors to be 57% and 3 or more nodules to be 26%.56 Resectable tumor-free margins vary on a case-by-case basis to balance tumor removal to reduce recurrence with preservation functioning liver parenchyma to allow survival. A recent prospective randomized trial compared wide (~2 cm) and narrow (~1 cm) resection margins for solitary HCC.57 Although recurrence rates remained high in both groups, the overall survival rates were higher for the wide margin group.

Liver transplantation. Liver transplantation, in theory, is the optimal therapeutic option for HCC; it simultaneously removes the tumor and underlying cirrhosis thus minimizing the risk of HCC recurrence. Earlier selection criteria for liver transplantation were broad, leading to poor results with recurrence rates of approximately 50% and 5-year survival rates of <40%.58,59 The currently recommended United Network for Organ Sharing (UNOS) criteria (1 lesion ≤5 cm or maximum 3 lesions <3 cm in diameter) have shown tremendous promise, with reported 5-year survival rates of >70% and recurrence rates of <15%.59–61 The tumor burden criteria for transplantation for HCC as established by the UNOS are largely accepted. Expanded selection criteria (a single lesion of ≤6.5 cm or up to 3 lesions, none of which are larger than 4.0 cm, with a maximum combined tumor bulk of ≤8.0 cm), have been proposed by University of California in San Francisco.62 Liver transplantation in such candidates has been associated with outcomes similar to those who are within the UNOS criteria. However, given the large number of HCC cases considered for liver transplantation, the struggle is to keep a balance between HCC and non-HCC recipients.

The UNOS oversees liver allocation in the United States. Based on the radiologic diagnosis of the number and size of lesions, Model for End-Stage Liver Disease (MELD) exception points are awarded for HCC, with the expectation that liver transplantation is accomplished in a reasonable period of time. The exception points for HCC are based on the 3-month pretransplantation mortality rates. For solitary lesions ≥2 cm and <5 cm, as well as up to 3 lesions, each <3 cm, patients currently receive a MELD score of 22, unless their calculated MELD score is otherwise greater. For each 3-month interval that they remain on the wait list, a greater number of exception points are awarded based on an expected increase of 10% for the 3-month pretransplantation mortality rate (eg, extension No. 1: 25 points for 25% mortality; extension...
No. 2: 28 points for 35% mortality, . . .). The challenges encountered in HCC pertain to the degree of MELD exception points that should be assigned to HCC patients so that the number of transplantations done for HCC patients are reasonable relative to other indications, that there is an acceptable and comparable mortality from all indications while awaiting transplantation, and that the outcomes are similar after transplantation.

The role of downstaging of tumors that are outside of conventional UNOS criteria for OLT has been explored. Downstaging is HCC-directed therapy that aims at reducing the size and/or number of HCC lesions. Studies have shown that successful tumor downstaging can be achieved in up to 70% of the patients treated in a protocol with one or more therapeutic modalities including TACE, radiofrequency ablation (RFA), or percutaneous ethanol injection (PEI). Subsequently, successful liver transplantation was accomplished in nearly half of these patients. Although encouraging, longer follow-up is needed to assess further the risk of HCC recurrence after OLT before downstaging can be recommended and adopted. The role of salvage liver transplantation after initial resection of HCC is less clear. Overall, suboptimal outcomes have been observed with this strategy compared with primary liver transplantation for HCC.

Given the shortage of donors and in attempts to shorten the waiting time for cadaveric liver transplantation, living donor liver transplantation (LDLT) has been shown to be an alternative to cadaveric liver transplantation, with approximately 3000 cases done worldwide for all indications. LDLT is a complex procedure that is associated with a morbidity of 20%-40% and a donor mortality of 0.3%-0.5%. With that, consideration of ethical, societal, and legal issues are vital to successful implementation of LDLT for HCC treatment. A recent retrospective analysis of a United States experience noted that the disease-free survival following LDLT was lower than that of cadaveric liver transplantation. LDLT recipients had a higher rate of HCC recurrence within 3 years than deceased donor OLT recipients, 30% vs 0%, respectively. However, there was no difference in mortality or the combined outcome of mortality or recurrence. Thus, the role of LDLT, particularly for those outside of ideal criteria, needs further evaluation.

**Percutaneous ablation.** Minimally invasive percutaneous treatments are the best treatment alternatives for early HCC patients who are not eligible for surgical resection or transplantation. The most widely utilized methods to induce tumor necrosis are PEI and RFA. Other, less utilized methods include the injection of acetic acid, boiling saline, cryotherapy, microwave therapy, and laser therapy.

PEI consists of injecting absolute ethanol directly into the HCC lesions. PEI performed under US guidance achieves complete tumor necrosis in 70%-80% of solitary HCC ≤3 cm and in almost 100% in tumors less than 2 cm. Tumor necrosis is less likely to be achieved in large tumors; 70% necrosis is reported for tumors between 2 and 3 cm and 50% necrosis for HCC between 3 and 5 cm. It is a well-tolerated, inexpensive procedure with few adverse effects. In nonrandomized studies of patients with small HCC, PEI has been shown to carry the same overall survival and recurrence-free survival as surgical resection. In a large series of 3225 patients with solitary tumors <3 cm reported by Ryu et al, there were no significant differences in survival between resection and PEI. The best survival for PEI has been shown for tumors <3 cm and <3 lesions.

RFA, which has largely replaced PEI, provides more complete ablation with fewer sessions than PEI (Figure 3). The efficacy of RFA in ablating tumors <2 cm is similar to that of ethanol; however, in tumors >2 cm, efficacy is better than with ethanol.

Several recent randomized trials compared RFA and PEI in treating patients with small HCC <4 cm (Table 5) and demonstrated the superior efficacy of RFA in terms of less operator variability, lower local recurrence, and longer overall as well as disease-free survival. Local tumor control was reported to range between 90% and 96%, with a mean of 1.1-2.1 sessions for RFA vs 4.8-6.5 for ethanol injection. Local recurrence rates have ranged between 8% and 14% at 2-3 years in patients treated with RFA compared with 22%-34% in those treated with PEI. Overall survival rates for patients treated with RFA were 100% and 98% for 1 and 2 years, respectively, compared with 96% and 88%, respectively, in the PEI trials. Recurrence-free survival rates at 1 and 2 years were 86% and 64% for the RFA group and 77% and 43% for the PEI group, respectively. Adverse events were generally similar for the 2 treatment groups. There has been a large experience reporting RFA safety even in those with lesions close to vascular structures. These data indicate that RFA leads to better local tumor and longer overall survival for patients with very early as well as early stage HCC. Therefore, RFA is the preferred method of local ablation for patients with tumors <4 cm. RFA should be considered for patients with very early stage HCC when resection cannot be applied and also for patients with early stage HCC who are not candidates for OLT and possibly for those with long waiting times >3 months.

There are at least 2 prospective, randomized controlled trials comparing RFA with surgical resection. Both found no significant differences in overall survival or recurrence-free survival and expectedly lower complication rates and lower hospitalization in patients treated with RFA. A recent Italian cohort study of 218 patients with HCC tumors ≤2 cm in diameter showed a sustained response in 97% during a median follow-up of 31 months and a 5-year survival rate of 68%. It seems that these 2
procedures offer similar efficacy, and the choice of therapy for very early stage HCC should depend on candidacy for surgery in terms of performance status, severity of portal hypertension, and feasibility of RFA in terms of tumor location.

Transarterial embolization/chemoembolization. TACE may offer palliative benefits for patients with intermediate stage HCC with 5-year survival rates after treatment exceeding 50%. TACE has been shown to improve survival in patients outside of the early stage criteria, especially in those who have not presented with cancer-related symptoms or vascular invasion. However, its safe and effective use is limited to patients with preserved liver function, absence of extrahepatic spread or vascular invasion, and no significant cancer-related symptoms. A European study revealed that only 12% of the 903 patients evaluated for HCC were suitable for TACE.

The basis of embolization is to induce ischemic tumor necrosis via acute arterial occlusion. Embolization may be done alone (transarterial embolization) or combined with selective intraarterial chemotherapy (TACE) such as doxorubicin, mitomycin, or cisplatin and a contrast agent, lipiodol.

TACE induces extensive tumor necrosis in 30% to up to 50% of those treated patients, but with fewer than 2% achieving a complete response. A meta-analysis of 7 randomized controlled trials comparing arterial embolization and/or chemoembolization as a primary treatment for HCC in comparison with conservative management and/or suboptimal therapies. Arterial embolization improved 2-year survival compared

![Figure 3. Percutaneous ablation of HCC using radiofrequency.](image)

### Table 5. Summary of Several Studies That Compared PEI and RFA for HCC Treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Tumor size</th>
<th>Complete necrosis rate (%)</th>
<th>Sessions (average number)</th>
<th>Survival difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Livraghi et al</td>
<td>86</td>
<td>&lt;3 cm</td>
<td>80 90</td>
<td>4.8 1.2</td>
<td>No</td>
</tr>
<tr>
<td>Lencioni et al</td>
<td>102</td>
<td>Milan criteria</td>
<td>82 91</td>
<td>5.4 1.1</td>
<td>Yes Recurrence free</td>
</tr>
<tr>
<td>Lin et al</td>
<td>157</td>
<td>&lt;4 cm</td>
<td>88 96</td>
<td>6.5 1.6</td>
<td>Yes</td>
</tr>
<tr>
<td>Shiina et al</td>
<td>232</td>
<td>Milan criteria</td>
<td>NA</td>
<td>6.4 2.1</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NOTE. The 1-year survival rates are reported from different studies and thus may not be used to compare directly the different therapeutic modalities.

PEI, percutaneous ethanol injection; RFA, radiofrequency ablation.
with that in control subjects (odds ratio, 0.53; 95% CI: 0.32–0.89).

In a large, prospective cohort study of 8510 patients who received TACE for unresectable HCC, the median survival was 34 months with 1-, 2-, 3-, 5-, and 7-year survivals of 82%, 47%, 26%, and 16%, respectively. There is currently little data to guide the choice of the chemotherapeutic agent or the retreatment schedule for TACE. The current evidence does not support the use of transarterial embolization without chemotherapeutic agent.

Transarterial embolization/TACE are associated with adverse events in approximately 10% of treated patients; these events include ischemic cholecystitis, nausea, vomiting, bone marrow depression, and abdominal pain. A postembolization syndrome is reported in >50% of patients treated with TACE and includes fever, abdominal pain, and moderate degree of intestinal obstruction. Treatment-related mortality is less than 5%.

TACE is clearly the first-line therapy for patients at the intermediate stage who exceed the criteria for liver transplantation (Figure 2). In addition, TACE can be performed in patients at the early stage in whom RFA cannot be performed because of tumor location (proximity to a gallbladder, biliary tree, or blood vessel) or medical comorbidities. TACE is also the first-line therapy for downstaging tumors that exceed the criteria for transplantation.

Other options. Radionuclide Yttrium-90, a pure β emitter, is a form of hepatic artery-directed therapy. Microspheres of approximately 25 μm in diameter containing Yttrium-90 are lodged via a catheter insertion into the lobar or segmental level of either hepatic artery and emit local radiation with limited exposure to adjacent healthy tissue. Currently, there are no data to suggest its superiority over ablative therapies.

Molecular Therapies

There are a growing number of clinical studies evaluating the efficacy of molecular therapies in HCC, alone or in combination with classical chemotherapy.

Angiogenesis inhibitors. Several studies (phase I, II, and III) are underway. Positive results have been obtained for therapies using Bevacizumab (vascular endothelial growth factor inhibitor) in combination with Gemcitabine and Oxaliplatin.

Growth-receptor signaling. Studies have been conducted targeting platelet-derived growth factor receptor, endothelial growth factor receptor, Raf, and other signaling pathways controlling cell proliferation. Positive results were reported for the use of Nexavar (Bayer Healthcare AG, Leverkusen, Germany) (sorafenib), an oral multikinase inhibitor, in patients with HCC. A phase III double-blind, randomized, placebo-controlled trial was designed to evaluate Nexavar in patients with advanced HCC (BCLC stage C) who had no prior systemic therapy. Six hundred two patients were randomized and enrolled at sites in the Americas, Europe, and Australia/New Zealand. The overall survival (46.3 weeks, 95% CI: 40.9–57.9, vs 34.4 weeks, 95% CI: 29.4–39.4, respectively, P = .058) and time to symptom progression (24 weeks, 95% CI: 18–30, vs 12 weeks, 95% CI: 11.7–17.1, respectively, P = .007) were significantly longer in patients administered Nexavar vs those patients administered placebo. Approximately 83% of the patients in the sorafenib trial had portal vein invasion and were classified as Barcelona stage C, with 20% having extrahepatic metastases. The 17% without portal vein invasion were patients who did not respond to TACE and were classified as Barcelona stage B in the study. Most patients had mild to moderate performance status. Therefore, it is reasonable to recommend sorafenib for patients with advanced stage or intermediate stage HCC with portal vein thrombosis. Promising results on progression-free survival have also been reported for Erlotinib, an inhibitor of endothelial growth factor receptor signalling.

Telomerase inhibition. Telomerase is active in >90% of human HCC, and it appears to be necessary for the immortal proliferation capacity of HCCs. Preclinical studies show that telomerase inhibition can impair proliferation of human HCC in nude mice. Phase I/II clinical studies are currently underway in patients with lymphoma. In addition to the above approaches, antibody treatment against HCC surface markers have been reported to lower recurrence rates after liver transplantation.

Another important factor to improve future therapies in HCC is the development of new markers to improve screening of cirrhosis patients for early lesions. Selection of HCC patients that could benefit from surgery or chemotherapy, or diagnosis of HCC. However, the utility of these tests remains unproven and will have to be tested in translational and clinical studies.

HCC Treatment: Effectiveness vs Efficacy

Population-based studies in the United States indicate that the overall 1- and 3-year survival rates for patients with HCC are approximately 20% and 5%, respectively (median survival of 8 months). These figures accommodate for a 20% improvement in survival that was observed between 1987 and 2001. To make a positive impact on the effectiveness of treating HCC, several steps have to be successfully accomplished so that more patients can be diagnosed at an early stage and receive timely potentially curative therapy. However, there seems to be a serious chasm between efficacy and effectiveness of treatment of HCC. A United States population-based study reported that, in 2963 patients 65 years and older diagnosed between 1992 and 1999 with HCC, only 13% received potentially curative therapy (transplant, 0.9%; resection, 8.2%; local ablation, 4.1%). Furthermore, only 34% of 513 patients with single lesions and 34% of 143 patients with lesions <3.0 cm received potentially curative therapy. There were geographic variations in the management of HCC that are at least as significant as clinical and tumor-related features in deter-
mining the extent and type of HCC therapy. Another United States population-based study of 1156 patients diagnosed between 1998 and 2002 with small nonmetastatic HCC in the United States found that liver transplantation yielded excellent overall survival, but only 21% of patients with localized HCC received a transplant. Marked geographic and racial variations were seen in the use of transplantation for HCC after controlling for other tumor and patient-related variables. For example, 25% of white patients, 21% of Hispanic patients, 17% of Asian patients, and only 13% of African-American patients received a transplant. Patients with HCC were 2.2 times less likely to get a transplant in the South and 3.3 times less likely in the Northeast compared with patients in the Western United States.

Transplantation patients with nonmetastatic HCC have excellent long-term survival, and this has been shown in single center as well as population-based studies. In summary, the evidence indicates marked underutilization of these interventions. Underutilization seems to follow some disturbing patterns in relation to ethnicity, poverty, and gender.

Several steps have to be taken to improve effectiveness of HCC therapy. These include provider and patient education on risk factors for HCC and methods of diagnosis, increasing the number of patients diagnosed in early or very early stage by better implementation of screening programs and optimizing screened patients for curative therapy (eg, drug and alcohol rehabilitation), improving access to specialized multidisciplinary treatment, and utilization of a validated staging system.

References


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