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Hepatocellular Carcinoma: Diagnosis and Treatment

ALEX S. BEFELER and ADRIAN M. DI BISCEGLIE

From the Division of Gastroenterology and Hepatology, Department of Internal Medicine, Saint Louis University School of Medicine, St. Louis, Missouri

Hepatocellular carcinoma is the most frequent primary malignancy of the liver and appears to be rising in incidence in the United States and other developed westerm countries. Imaging studies play a key role in diagnosis of hepatocellular carcinoma, and more and more commonly, patients are being diagnosed at an asymptomatic stage. The use of triphasic computed tomography scanning and improved magnetic resonance imaging equipment and protocols has led to greater sensitivity and specificity for these techniques in diagnosis of hepatocellular carcinoma. Accurate staging of hepatocellular carcinoma is important in determining prognosis and in helping decide the best treatment for each patient. No one staging system appears optimal, but important factors to be considered are the size of the tumor, severity of underlying liver disease, and the functional status of the patient. Liver transplantation has grown in importance as a treatment for hepatocellular carcinoma but may be limited by availability of donor organs and long waiting times. This situation may be improved by greater use of living donor liver transplantation. Hepatic resection remains an important treatment modality for hepatocellular carcinoma, particularly in the absence of cirrhosis. Tumor ablation by alcohol injection or radiofrequency ablation is associated with favorable outcomes and may be considered a potentially curative treatment. Early diagnosis of hepatocellular carcinoma remains a key goal in improving the poor prognosis of this form of liver cancer. Identifying hepatocellular carcinoma at an early stage is often associated with having better treatment options for patients with small, asymptomatic tumors.

Hepatocellular carcinoma (HCC) is the most frequent primary malignancy of the liver and accounts for as many as 1 million deaths annually worldwide. In some parts of the world it is the most common form of internal malignancy and the most common cause of death from cancer. It is less common in most parts of the developed Western world but appears to be increasing substantially in incidence. Because it usually occurs in the setting of chronic liver disease, the diagnosis of HCC is often made by gastroenterologists and hepatologists, who are also becoming more involved in the management of patients with this form of cancer.

El-Serag and Mason[1] have described an increase of about 80% in the incidence of HCC in the United States over the past 20–30 years and it is estimated that approximately 15,000 new cases occur each year.[1] The reasons for this increase are not altogether clear but it has been attributed to the emergence of hepatitis C and occurrence of hepatitis B–related HCC in immigrants from countries where hepatitis B is prevalent.

Diagnosis of HCC

Clinical Features

The classic clinical features of HCC include right upper quadrant pain and weight loss. Other clinical scenarios that suggest this diagnosis include worsening liver function in a patient known to have cirrhosis, acute abdominal catastrophe from rupture of a liver tumor with intra-abdominal bleeding, and some rare extrahepatic manifestations. More and more commonly though, patients are being diagnosed with HCC at an asymptomatic stage while they are being evaluated for liver transplantation or as part of routine screening in those with cirrhosis. Symptoms at initial presentation in a series of 461 Italian patients with HCC showed approximately: 23% were asymptomatic, 32% had abdominal pain, 9% malaise, 8% fever, 8% ascites, 8% jaundice, 6% anorexia, 4% weight loss, 4% hemorrhage, and 2% encephalopathy.[2]

Radiologic Features

Imaging studies play a key role in the diagnosis of HCC. There has been a steady evolution in the radiologic techniques used to diagnose HCC. More than 20 years

Abbreviations used in this paper: AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; CT, computed tomography; OLT, orthotopic liver transplantation; pTNM, pathologic TNM; RFA, radiofrequency ablation; UNOS, United Network for Organ Sharing.

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ago, radioisotope scans of the liver were used to show the presence of intrahepatic masses. However, these liver scans lack both sensitivity and specificity, particularly for small tumors. Angiography has been used to detect HCC because it is typically highly vascular and was a routine part of the evaluation before resection. Its sensitivity in detecting small tumors less than 2 cm in diameter has recently been questioned.[3] The role of angiography is now limited to the administration of therapies such as chemoembolization.

Ultrasound examination continues to play a role in detecting HCC and is able to detect very small lesions within the liver. More recent practice has focused on the use of spiral computed tomography (CT) and magnetic resonance imaging with multiphase contrast enhancement.

On ultrasound examination, HCC is usually detected as having different echogenicity from surrounding liver. For smaller tumors, HCC is typically hypoechoic but may be hyperechoic as it enlarges. The presence of a capsule may also be noted on ultrasound examination. Ultrasound has been assessed extensively as a screening tool for HCC. In this setting, it has been reported to have relatively high sensitivity and specificity. Its use in diagnosis has been largely replaced by CT and magnetic resonance imaging, but it remains useful in specific situations, such as assessment of vascular invasion by HCC. Tumor invasion in the portal vein can be distinguished from bland thrombus by the presence of pulsatile blood flow on color Doppler. Several new contrast agents are being evaluated as an aid to assess HCC by ultrasound examination. For example, Levovist (Schering, Berlin, Germany) has been useful in evaluating the effectiveness of alcohol ablation of HCC.

There have been several key developments in improving CT imaging of HCC. These include the use of spiral scanners that allow very rapid imaging of the liver after infusion of intravenous contrast agents. A second major improvement has been the adoption of better scanning protocols that take into account the increased vascularity of HCC. Thus, HCC derives its blood supply predominantly from the hepatic artery whereas the remainder of the liver receives both arterial and portal blood. HCCs therefore enhance early on during the infusion of contrast, in the arterial phase (the first 2–40 seconds after intravenous infusion of contrast). The liver parenchyma enhances during the portal venous phase, which takes place 50–90 seconds after infusing contrast. The term *triphasic CT scan* has been coined to describe this process including before contrast, arterial phase, and portal venous phase (Figure 1). Even with the best of equipment and techniques, a substantial number of tumor nodules go undetected. Miller et al.[4] have suggested that many HCC tumor nodules found on examination of explanted livers are not detected by CT examination before transplantation. Enhanced CT had a sensitivity of 68% and a specificity of 81% in their study.

Magnetic resonance imaging has become the diagnostic procedure of choice for HCC at some institutions. This has been made possible by significant recent advances in magnetic resonance imaging technology, including scanner hardware, software, and contrast agents. Typically, HCC is hypointense on T-1– and hyperintense on T-2–weighted images, but there is considerable variability in its appearance that may be attributed to foci of hemorrhage, accumulation of copper, glycogen, or areas of fatty change. Krinsky[5] compared magnetic resonance findings before transplantation with examination of the explanted liver and found that magnetic resonance imaging depicted only 11 of 20 hepatic neoplasms overall (sensitivity of 55%). Sensitivity was lowest in tumors less than 2 cm in diameter.[5]

Serum α-Fetoprotein

Measurements of serum α-fetoprotein (AFP) may be helpful in the diagnosis and management of HCC. AFP is elevated above 20 ng/mL in more than 70% of patients with HCC. However, AFP elevations from 10–500 ng/mL and even occasionally to 1000 ng/mL may be seen in patients with a high degree of necroinflammatory activity, such as with chronic viral hepatitis, who do not have HCC.[6] The sensitivity, specificity, and positive predictive value of AFP in 3 well-performed screening studies for HCC ranged from 39%–64%, 76%–91%, and 9%–32%, respectively.[7] The positive predictive value increases significantly when the AFP is greater than 400 ng/mL, but this is at the expense of a poor sensitivity. AFP is useful in monitoring response to treatment and detecting recurrence after treatment of HCC if the AFP was elevated before treatment.

Because of the low specificity of AFP, especially with higher cut-off values, measurement of various isoforms of AFP has been investigated to improve sensitivity and specificity. The best studied is Lens culinaris agglutinin A–reactive alpha-fetoprotein, which improves specificity but still has relatively low sensitivity in several retrospective case control studies.[8] The clinical utility for screening or diagnosis of the newer isoform tests for AFP have not yet been established in well-performed prospective studies.

Liver Biopsy

Histologic examination of liver tissue is an important element in diagnosing HCC and is commonly

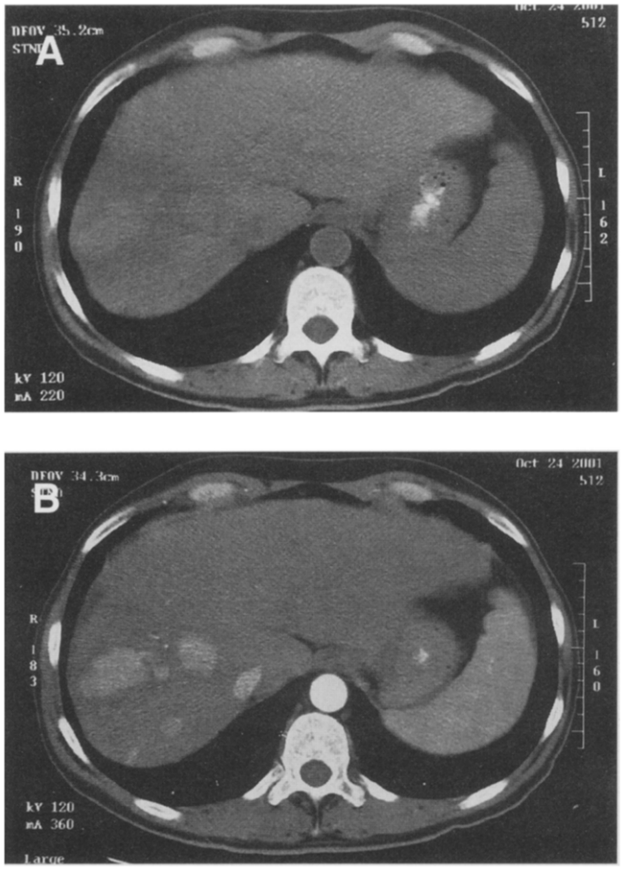

Figure 1. (*A*) CT of liver without vascular contrast. Right lobe of the liver shows only patchy inhomogeneity. (*B*) The same area of the liver during infusion of contrast (arterial phase). Several enhancing mass lesions can now be distinguished, ranging between 1.5–4 cm in diameter.

performed. However, the routine use of needle biopsy of HCC is controversial, particularly in patients with HCC who may be potentially cured by resection or liver transplantation. One possible risk of percutaneous needle biopsy is local spread of HCC along the needle track. This complication has been described in individual case reports but cannot be accurately quantitated. Preliminary evidence suggests local spread of HCC occurs in as many as 1% of cases after needle biopsy. Because of this concern, some physicians advocate not performing a needle biopsy before liver resection or transplantation for HCC. A biopsy procedure may not be needed if a large mass is found in the liver, perhaps associated with a markedly elevated level of AFP in serum, because the diagnosis is obvious. If therapies are being planned that involve some risk and possible toxicity, consideration should be given to a biopsy procedure to prove that HCC is present.

Biopsy procedures may be performed by any one of several methods. If the tumor is massive or spread extensively throughout the liver, a blind biopsy procedure may be performed and may be guided by palpation if a mass can be felt. More typically though, needle biopsy procedures are performed under radiologic guidance by using either ultrasound or CT. Open surgical biopsy procedures may sometimes be performed, particularly if HCC is suspected but the tumor cannot be located with precision by radiographic methods. The material obtained by fine-needle aspiration may be evaluated histologically, cytologically, or by using both methods in combination (Figure 2).[9] It may sometimes be difficult to distinguish well-differentiated HCC from benign hepatic masses such as macroregenerative nodules, adenoma, or focal nodular hyperplasia.

Staging of HCC

After making the diagnosis of HCC, the next step in the management of the patient is staging. The goal of

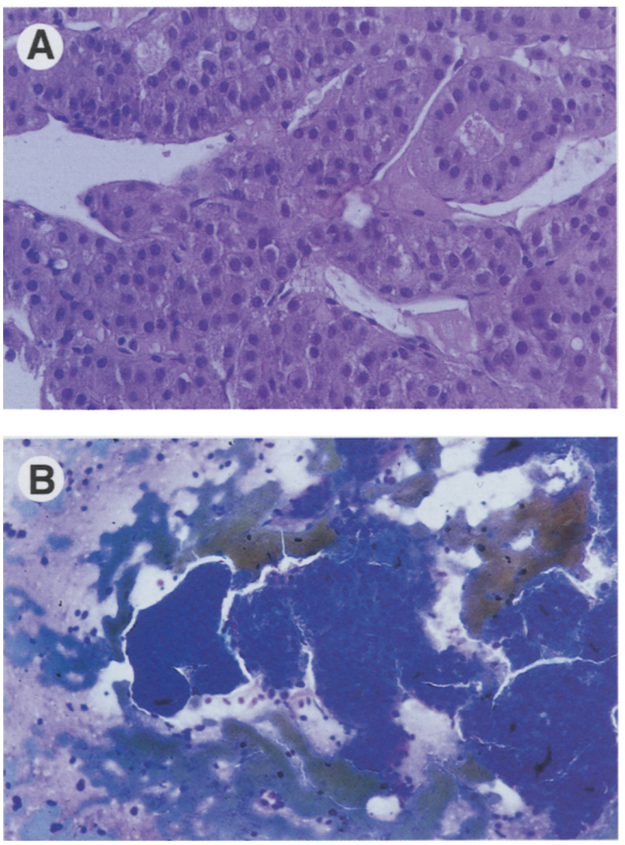

Figure 2. Liver biopsy of hepatocellular carcinoma. (*A*) Liver histology shows trabecular pattern of HCC (H&E, ×40). (*B*) Cytology specimen derived from the same tumor (Diff Quick, ×20). The cells show trabecular architecture, increased nuclear to cytoplasmic ratio, and abnormal nuclei. Bedside cytologic examination of material derived from fine-needle aspiration biopsy can be very useful to ensure that a guided biopsy needle is actually in the lesion before taking a larger core specimen for histologic examination.

Table 1. pTNM Staging System

Categories	Definitions
T	Primary tumor size, number, and location
T0	No evidence of primary tumor
T1	Solitary tumor ≤ 2 cm without vascular invasion
T2	Solitary tumor ≤ 2 cm with vascular invasion or multiple tumors in 1 lobe ≤ 2 cm without vascular invasion or solitary tumor > 2 cm without vascular invasion
T3	Solitary tumor > 2 cm with vascular invasion or multiple tumors in 1 lobe ≤ 2 cm with vascular invasion or multiple tumors in 1 lobe > 2 cm with or without vascular invasion
T4	Multiple tumors in more than 1 lobe or invasion of a major branch of portal or hepatic vein or invasion of adjacent organs other than the gallbladder or perforation of visceral peritoneum
N	Nodal metastasis
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	Distant metastasis
M0	No distant metastasis
M1	Distant metastasis
Stages	Stage according to the TNM categories
Stage I	T1N0M0
Stage II	T2N0M0
Stage IIIA	T3N0M0
Stage IIIB	T1N1M0 or T2N1M0 or T3N1M0
Stage IVA	T4, any N, M1
Stage IVB	Any T, any N, M1

cancer staging is to separate patients into different groups based on their predicted survival to help determine the most appropriate treatment modality. Patients within a particular stage should have a homogenous survival that is clearly different from the survival in other stages. HCC is different from other cancers because survival is not predominantly based on biology of the tumor, but also depends on underlying hepatic function. Additionally, most options for the treatment of HCC, except for orthotopic liver transplantation (OLT), result in a decrease in hepatic function. The currently available staging systems for HCC include: pathologic tumor-node-metastasis (pTNM), Okuda, Cancer of the Liver Italian Program (CLIP), and Barcelona Clinic Liver Cancer (BCLC).

The pTNM staging system is similar to that for other solid tumors and thus is limited by not taking into account the amount of underlying hepatic function (Table 1).[10] It therefore fails to accurately predict survival in patients undergoing hepatic resection for HCC.[11] In addition, an analysis of 58 patients who underwent OLT for HCC, which essentially negates the effect of underlying liver function, showed that there was no difference in rates of tumor recurrence for pTNM stages I–IV.[12] A multivariate analysis of 307 patients who underwent OLT for HCC suggested that moving macrovascular invasion of tumor and lymph node metastasis into stage IV would better stratify patients, though this proposal has not been assessed prospectively.[13] This proposal still does not take into account the tumor size limits suggested by the study by Mazzaferro et al.[14] (solitary tumor ≤5 cm in diameter or 3 tumors <3 cm), adopted by United Network for Organ Sharing (UNOS) and currently followed by most transplant centers in the United States.

The Okuda system was the first staging system to be widely used that included parameters that reflect the biology of the tumor and the underlying liver disease (Table 2).[15] This system is highly effective at identifying a subgroup of patients, Okuda stage III, who have a very poor prognosis and probably should be treated with supportive care only.[16,17] This leaves only 2 remaining stages, which may limit its ability to separate patients into clinically relevant groups. Okuda stages I and II are heterogeneous and include patients with good prognosis especially with liver transplantation and those with poor

Table 2. Okuda Staging System

Clinical parameters	Cut-off values	Points
Tumor size (cross-sectional area on imaging)	>50%	1
	<50%	0
Ascites	Present	1
	Absent	0
Serum albumin (mg/dL)	>3	0
	<3	1
Serum total bilirubin	<3	0
	>3	1
Number of points	Stage	
0	1	
1–2	2	
3–4	3	

Table 3. CLIP Staging System

Variables	Points 0	1	2
Child–Pugh class	A	B	C
Tumor morphology	Single nodule and <50% area[a]	Multiple nodules and <50% area[a]	Massive or >50% area[a]
AFP (ng/mL)	<400	≥400	
Portal vein thrombosis	No	Yes	

NOTE. CLIP score is the sum of points for the 4 variables.
[a]Cross-sectional area on imaging.

prognosis whatever treatment is given.[15,18,19] The analysis of Llovet et al.[20] of the natural history of nonsurgical patients randomized to no treatment was able to more effectively stratify patients than Okuda stage. The CLIP score was also more effective at stratifying patients as discussed later.

The CLIP staging system was developed based on the application of a stratified Cox proportion hazard model to a retrospective evaluation of 435 Italian patients with HCC (Table 3).[21] It has subsequently been validated in 196 Italian patients entered into a randomized controlled trial of tamoxifen, 154 consecutive Italian patients followed-up after diagnosis of HCC, and 662 Japanese patients retrospectively reviewed.[19,22,23] The CLIP score was shown to be superior to Okuda stage because it could better explain variability in survival especially within Okuda stage II but also in Okuda stage I.[21,22] The CLIP score, though mathematically more sound than Okuda and BCLC, is limited by not being adequately assessed in populations undergoing radical or curative treatment such as surgical resection or OLT. Some groups criticize the CLIP score because the stage for an individual patient does not appear to predict which treatment modality is best, but other groups suggest that the parameters used in the CLIP score are helpful in stratifying patients receiving various treatments for HCC.[24,25]

The BCLC staging system is based on the investigators' synthesis of several studies performed in groups of patients with homogeneous tumor characteristics, underlying hepatic function, and treatment modalities (Table 4).[17] This staging system is particularly useful in the clinical setting because it helps select treatment options. It appears to be very effective at selecting patients with early HCC (stage A) for aggressive treatment such as surgical resection, OLT, or local ablative therapy by using a synthesis of criteria from multiple studies of patients undergoing these treatments. It does not clearly indicate that Child-Pugh class C patients with small HCCs are candidates for OLT. Neither does it stratify patients into intermediate (stage B) or advanced stage (stage C), who are allocated to different types of treatment. Its proponents do caution that intermediate- and advanced-stage patients are best served by participating in randomized controlled trials of treatment, especially given the relatively good survival rate of untreated patients compared with several published treatment series.[20] A major limitation of the BCLC staging system is lack of external validation.

Thus, no one staging system is clearly superior to the others. Table 5 shows the median survival ranges obtained in 5 populations of recent patients with HCC. The BCLC seems best able to select early-stage HCC that should benefit from resection, OLT, or local ablation, perhaps with a modification to better capture Child-Pugh class C patients for the OLT group. The CLIP score may be more effective at stratifying patients who are not candidates for resection or transplantation. Okuda, CLIP, and BCLC are all effective at selecting patients with extremely poor prognosis who should only receive supportive care. The proposed treatment schedule according to the BCLC stage nicely synthesizes a treatment algo-

Table 4. BCLC Staging System for HCC

Stage	Performance status	Tumor stage	Liver function
Stage A: early HCC			
A1	0	Single, <5 cm	No portal HTN and normal bilirubin
A2	0	Single, <5 cm	Portal HTN and normal bilirubin
A3	0	Single, <5 cm	Portal HTN and elevated bilirubin
A4	0	3 tumors < 3 cm	Child–Pugh class A–B
Stage B: intermediate HCC	0	Large multinodular	Child–Pugh class A–B
Stage C: advanced HCC	1–2[a]	Vascular invasion or extrahepatic spread[a]	Child–Pugh class A–B
Stage D: end-stage HCC	3–4[b]	Any	Child C[b]

NOTE. Stage A and B: all criteria should be fulfilled.
HTN, hypertension.
[a]Stage C: At least 1 criteria should be fulfilled.
[b]Stage D: At least 1 criteria should be fulfilled.

Table 5. Range of Median Survival Among Patients With HCC, According to Stage by Various Systems

Staging system	Median survival (mo)				
	CLIP, 1998[21]	Llovet, 1999[20]	CLIP, 2000[22]	Ueno, 2001[23]	Farinati, 2000[19]
CLIP					
0	43	NA	36	69	31
1	32	NA	22	44	27
2	17	NA	9	26	13
3	5	NA	7	14	8
4	3	NA	3[a]	9	2
<5	1	NA	3[a]	5	2
Okuda					
I	33	32	23	46	30
II	12	6	7	16	13
III	2	NA	3	5	2
TNM					
I	NA	NA	NA	63.5	34
II	NA	40.4	NA	48.7	25
III	NA	17.4	NA	26.7	20
IV	NA	7.5–8.9[b]	NA	17.1	14

NA, not available.
[a]CLIP score 4–6.
[b]TNM IVA–IVB.

rithm, though stratification of intermediate and perhaps advanced stage according to CLIP may be beneficial in the design of randomized controlled trials (Figure 3).

Liver Transplantation

OLT is theoretically the best treatment for HCC because it results in the widest possible resection margins for the cancer, removes the remaining liver tissue that is at risk for the development of de novo cancer, and restores hepatic function. Unfortunately, the limited availability of donor organs with the resulting delay to transplantation makes OLT less effective and less available to individual patients. Living donor transplantation eliminates many of these obstacles if the patient has a suitable donor. OLT additionally results in an approximately 15% 1-year mortality rate overall for adults and thus may not be appropriate for early cancers that have a better prognosis.[26]

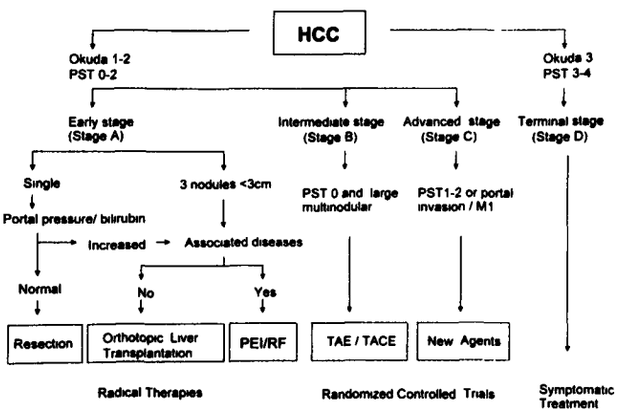

Figure 3. Treatment algorithm for HCC according to the BCLC staging system. Abbreviations: PST, performance status; PEI, percutaneous ethanol injection; RF, radiofrequency ablation; TAE, transarterial embolization; TACE, transarterial chemoembolization. (Reproduced with permission from Llovet et al.[17])

OLT is contraindicated if there is extrahepatic spread of tumor or if the tumor is greater than 5 cm in diameter, or if there are more than 3 tumors, or if multiple tumors are present and 1 of them is greater than 3 cm in diameter. Standard imaging techniques using helical CT or magnetic resonance imaging can often detect extrahepatic spread. Multiple early series of OLT for HCC contained significant numbers of patients with advanced tumors resulting in 3-year survival rates of 21%–47% and recurrence rates as high as 29%–54%.[27–30] These case series showed that tumor recurrence was strongly correlated to tumor size, number of nodules, and presence of vascular invasion. Figueras et al.[31] achieved 1-, 3-, and 5-year survival rates after OLT of 82%, 79%, and 75%, respectively, for solitary HCCs less than 5 cm in diameter or 2 tumors of smaller size. Mazzaferro et al.[14] reported a 75% 4-year survival rate if the HCC was less than 5 cm or 3 tumors less than 3 cm each. These survival figures after OLT are virtually identical to patients undergoing OLT without HCC and have been repeated at other centers.[12,32,33] These size criteria are used by most transplant centers in the United States and have been adapted by UNOS to provide an improved position of the organ allocation list.[26]

Unfortunately, as Llovet et al.[34] point out, most of the cited studies were performed during a time when the average waiting time for OLT was less than 6 months, whereas the most current UNOS data from 1998 indicates median waiting times with 95% confidence intervals of 517 (488,543) days.[34] As median waiting time increases from 6 months to greater than 1 year, the development of contraindications to transplantation or death increases from 23% to as high as 50%, usually because of progression of HCC.[35] A retrospective intention-to-treat analysis by the BCLC group comparing the 2-year survival of patients listed for transplant during 2 different time periods showed a decrease in survival from 84% to 54% as mean waiting time increased from 62 to 162 days.[35] The problem of long waiting times for patients with HCC may be ameliorated by the recently adapted Model for Endstage Liver Disease (MELD) system of liver organ allocation in the United States with its higher priority for patients with HCC.

Living donor transplantation eliminates the factor of waiting time and thus is theoretically to be preferred for patients with HCC when there is a long waiting time. According to UNOS data, 347 living donor liver transplants were performed during 2000, representing 6.5% of all liver transplants.[26] There are only limited data on survival after living donor liver transplantation but most series show comparable patient survival with that in cadaveric transplants.[36] A Markov model of living donor transplant vs. cadaveric transplant for early HCC showed substantial gains in life expectancy and cost effectiveness when the waiting list for OLT exceeded 7 months.[37] Another Markov model comparing intention-to-treat OLT vs. living donor transplant for Child-Pugh class A cirrhosis with 3.5-cm HCC showed substantial survival benefit for living donor transplant.[38] Although these simulation models are encouraging, long-term survival analysis of living donor transplant is not yet available.

The size limitations described by Mazzaferro et al. may be expanded.[14] Yao et al.[39] reviewed the survival of 70 consecutive patients undergoing OLT for HCC including 25% with either solitary tumors 5–6.5 cm in diameter or less than or equal to 3 nodules each less than or equal to 4.5 cm with total tumor diameter less than 8 cm. They showed overall survival rates of 90% and 75% at 1 and 5 years with no difference in survival rates of patients with the larger tumors compared with patients who met Mazzaferro et al. criteria. Sixty percent of their patients received chemoembolization within 24 hours of transplantation. This case series suggests modifications of the Mazzaferro criteria may be made, especially for patients who are close to the time of transplantation.

The role of adjuvant therapy, whether it is pretransplant local ablative therapy, chemoembolization, or chemotherapy or posttransplant chemotherapy, has not been assessed in randomized controlled trials. Comparative series also fail to convincingly show survival benefit for adjuvant therapy.[14,31,33,40–42] Many centers use some form of adjuvant therapy, especially if the waiting time to OLT is long. Randomized controlled trials are needed to determine which adjuvant therapy is most appropriate for which group of patients.

Given the organ donor shortage, resection of small HCCs in patients with intact hepatic function with salvage OLT for hepatic decompensation or recurrence of tumor may be an alternative treatment strategy. Majno et al.[43] compared this strategy with primary OLT for the treatment of small HCCs by using a Markov model and showed survival benefit for primary OLT at the expense of more donor organs used based on middle-of-the-road estimates for the transition variables. They suggested that the salvage OLT strategy may be superior if patients with low recurrence rates were chosen. Llovet et al.[34] point out that the estimate of 40%–80% salvage transplant rate is far above the reported rates in recent European series. They indicate that in clinical practice, salvage OLT for HCC is rare and may not be clinically relevant.[34]

There is no convincing evidence that the choice of primary immunosuppression (tacrolimus vs. cyclosporine) or withdrawal of steroids has any effect on survival after OLT for HCC or on recurrence of cancer.

Hepatic Resection

Liver resection treats HCC by surgically removing the portion of the liver involved with cancer. It is second only to transplantation in its ability to effectively eliminate the cancer, but has the disadvantage of not eliminating remaining portions of the liver at risk for malignant transformation and neither does it improve hepatic function. For patients without cirrhosis who have technically resectable cancers and no evidence of vascular invasion or spread outside of the liver, resection is the treatment of choice. Survival in the Bismuth et al.[44] series of 68 noncirrhotic patients who underwent liver resection for HCC with a mean diameter of 8.8 cm was 40% and 26% at 5 and 10 years, respectively. These results are much better than what one would expect for patients with cirrhosis, especially given the large size of the HCCs resected.

Unfortunately, noncirrhotic asymptomatic HCCs represent less than 5% of all HCCs found in Western patients.[35] Large series of liver resections for HCCs report

3- and 5-year survival rates between 38%–65% and 33%–44%, respectively.[25,28,45–47] The populations of patients in these series are heterogeneous, with varying stages of HCCs and severity of cirrhosis. Combining several case series of hepatic resection, Bruix[48] showed 5-year survival rates in excess of 50% if the patient met strict criteria. These patients were required to have solitary tumors less than 5 cm in diameter, with no evidence of vascular invasion or extrahepatic spread, and with either no evidence of cirrhosis or well-compensated Child–Pugh class A cirrhosis including no evidence of portal hypertension. Despite these strict criteria, recurrence of tumor resulting from either metastasis from the primary lesion or new tumors exceeded 50%.[48] The risk for decompensation after surgical resection with Child–Pugh class A cirrhosis is up to 50%.[49] Salvage transplant may be proposed for this group of patients, but is rarely performed in clinical practice.[34] Portal hypertension is the best marker of the increased risk for decompensation after resection in Child–Pugh class A patients, leading some investigators to advocate not performing resection in patients with portal hypertension.[48]

Surgical resection should be considered for all noncirrhotic patients who lack extrahepatic spread. Consideration of surgical resection for cirrhotic patients with HCC should be limited to Child–Pugh class A patients. Patients without portal hypertension are likely to have better outcomes. The choice of resection in other cirrhotic patients depends on the patient's candidacy for liver transplantation and the availability of OLT or living donor transplantation. The balance between these treatment options may shift with greater use of living donor liver transplantation.

Ablation

Ablation of malignant hepatic tumors has been performed for some time now, typically in patients in whom resection is not possible. Ablation may be accomplished by either chemical means (e.g., absolute alcohol or trichloroacetic acid) or physical means (e.g., cryoablation, radiofrequency ablation, microwave coagulation, or injection of hot saline). Alcohol ablation has been by far the most popular of these techniques and is associated with impressive success rates. More recently, however, radiofrequency ablation has been used more frequently. Other ablation techniques remain largely experimental.

Alcohol ablation is achieved by percutaneous injection of absolute alcohol under CT or ultrasound guidance. Approximately 8–10 mL is injected per session, though larger amounts can be used. The injection is begun at the distal end of the tumor and the needle is progressively advanced proximally so the whole lesion can be injected. The procedure is usually performed with conscious sedation. Serious complications of alcohol injection are rare. The most common problems are pain and a feeling of intoxication immediately after the procedure. Fever and pain may occur some days later associated with necrosis of the tumor. Almost all tumors smaller than 2 cm in diameter can be completely ablated in a single session. Larger tumors may require several sessions of ablation over a period of several weeks. The long-term outcome after ethanol injection is quite good. Castells et al.[49] compared patient survival in 30 patients with HCC treated with ethanol injection with that of 33 comparable patients undergoing surgical resection for HCC. Survival rates were comparable between the 2 groups (81% at 1 year and 44% at 1 and 4 years, respectively, with resection; and 83% and 34%, respectively, with ethanol).[49]

Recently, the use of radiofrequency ablation (RFA) has come to the fore and has become an established mode of therapy for HCC because of its ability to destroy HCC at 1 sitting. It is also relatively well tolerated and has few side effects. The principle of RFA includes introducing a needle into the tumor under radiologic guidance. An alternating current is then passed through the needle, resulting in heating (to near 100°C) around the tumor. When used for HCC, this results in destruction of an area up to 5 cm in diameter. An electrode pad is applied to that patient's skin and the needle electrode, an insulated cannula that contains as many as 10 individual hook-shaped electrode arms, is positioned within the tumor. Once the needle is positioned, the arrays are deployed. Power is then applied for several minutes until a power roll off occurs, indicating a precipitate drop in power output as tissue impedance increases markedly because of coagulative necrosis.

Risks involve bleeding from the puncture site, particularly if it is near the surface of the liver. As occurs with alcohol injection, fever, abdominal pain, and transient elevation of serum transaminases have been reported. Concerns have recently been raised about the risk for tumor seeding after RFA. Llovet et al.[50] found that as many as 12.5% of RFA-treated patients had biopsy-proven needle-track seeding 4 to 18 months later. This high rate of seeding has not been observed in other studies. In a series of 100 patients with HCC treated by RFA, local tumor recurrence developed in only 3.6% of patients followed-up for more than 12 months.[51] A recent comparison between ethanol injection and RFA recorded complete tumor necrosis in 90% of patients with RFA and 80% with ethanol injection.[52] Furthermore, the number of sessions required for complete ab-

lation is greater with ethanol injection. Long-term patient survival has not been adequately assessed yet after RFA. Local ablation through RFA or alcohol should be considered for small tumors that are not resectable by virtue of advanced liver disease or tumor location within the liver. Local ablation may also serve to control HCC while awaiting OLT. The choice between RFA and alcohol ablation may best be made when further data are available.

Chemoembolization

The success of chemoembolization relies on the fact that HCC derives its blood supply predominantly from the hepatic artery, whereas the surrounding liver receives both portal and arterial blood. Chemoembolization can be performed by using several different techniques. However, there are several general principles that apply to this form of therapy. First, it requires catheterization of the segmental hepatic artery supplying the tumor and performance of an arteriogram. Chemotherapeutic agents are then injected intra-arterially and the hepatic artery is then occluded by injection of material to obstruct flow. The theoretical benefits of this approach include delivery of a high concentration of chemotherapy to the tumor, a marked increase in contact time between the drugs and tumor cells, and high rates of first-pass extraction. Thus, the drugs are concentrated in the liver and tumor and systemic side effects are minimized.

The chemotherapeutic agent used varies between centers. Commonly used drugs include doxorubicin, cisplatinum, and mitomycin C. These agents are typically mixed with water-soluble contrast, as well as lipiodol (iodized poppyseed oil) to form an emulsion. Particulate embolization materials such as Gelfoam (Pharmacia and Upjohn, Kalamazoo, MI) and Ivalon (M-PACT Worldwide Inc., Eudora, KS) are injected at the end of the procedure to reduce arterial inflow and prevent chemotherapeutic agents being washed out. Extensive tumor necrosis can be achieved in more than 80% of patients. However, the potential side effects of chemoembolization are severe and include liver failure, severe pain, and formation of liver abscess.

A randomized controlled trial of chemoembolization vs. standard supportive therapy for unresectable HCC showed no enhanced survival in the chemoembolization group over a 4-year period.[53] Chemoembolization is relatively contraindicated when the tumor is diffuse throughout the liver, in the presence of liver failure (Child–Pugh class C), and with portal vein thrombosis. Chemoembolization is currently used most often as an adjuvant to other forms of therapy or in preparation for liver transplantation. Venook[54] reported on patients with HCC treated with preoperative chemoembolization and subsequent liver transplantation. Ten of their 11 patients with HCC who actually underwent transplantation remain free of recurrent cancer after a median of 40 months of follow-up.

Table 6. Chemotherapeutic Agents Reported to Have Objective Responses Against HCC

5-fluorouracil
Doxorubicin
Epirubicin
Etoposide
Cisplatin
Mitoxantrone
α Interferon
Tamoxifen
Capecitabine
Thalidomide
Octreotide

Chemotherapy

Chemotherapy is generally considered for use in patients with HCC not amenable to potentially curative therapy such as resection, transplantation, or ablation, and therefore its role is largely palliative. Varieties of chemotherapeutic agents have been tested against HCC. Few reliably are associated with antitumor responses (Table 6). Chemotherapy may be administered either systemically or regionally. Regional chemotherapy includes intra-arterial treatment, the results of which are similar to chemoembolization. Systemic chemotherapy is associated with low response rates (typically less than 25% objective responses) and dosing may be limited by cirrhosis often associated with HCC. Antiangiogenic agents hold considerable promise in the treatment of HCC because of the vascularity of this tumor. Thalidomide is an agent with both antiangiogenic and immunomodulatory actions that has been tested in patients with HCC. Researchers at the M.D. Anderson Cancer Center have found a 5% rate of partial response with 45% disease stability and only mild toxicity (Patt Y, personal communication, 2000).

Summary and Conclusions

HCC remains a major problem worldwide and appears to be increasing in developed Western countries. Recent advances in diagnosis include the use of 3-phase spiral CT scanning and progress in the use of magnetic resonance imaging. Better imaging has allowed more frequent diagnosis of HCC when tumors are still small. Smaller tumors are more amenable to potentially curative treatments, such as resection, ablation, and liver transplantation. Liver transplantation has become established

as an effective means of treating HCC, provided the tumors are not too big or too widespread. The use of OLT is limited by availability of donor organs, and living donor liver transplantation will probably come to the fore in the treatment of this cancer.

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Address requests for reprints to: Adrian M. Di Bisceglie, M.D., Division of Gastroenterology and Hepatology, Department of Internal Medicine, Saint Louis University School of Medicine, 3635 Vista Avenue, St. Louis, Missouri 63110.