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Management of Small Hepatocellular Carcinoma: A Review of Transplantation, Resection, and Ablation

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Abstract

Purpose and Design—The management of patients with early hepatocellular carcinoma has become increasingly complex. The most appropriate therapy largely depends on the functional status of the underlying liver. Here we review the modalities of transplantation, resection, and ablation in this patient population.

Results and Conclusion—In patients with cirrhosis and/or portal hypertension, and disease extent within the Milan criteria, liver transplantation is clearly the best option. This modality not only provides therapy for the cancer but also treats the underlying hepatic parenchymal disease. In patients with well-preserved hepatic function, on the other hand, liver resection remains the most appropriate and effective treatment. Hepatic resection is not constrained by the same variables of tumor extent and location that limit the applicability of transplantation and ablative therapies. In addition, patients whose disease recurs after resection are often still eligible for transplantation. Ablative therapies, particularly percutaneous radiofrequency ablation and transarterial embolization/chemoembolization, have been used primarily to treat patients with low-volume unresectable tumors. The question has increasingly been raised regarding whether ablation of small tumors (<3 cm) provides long-term disease control that is comparable to resection. Ablative therapies has also been used as a means of controlling disease in patients who are on transplantation waiting lists, although improved posttransplantation outcome using these techniques has yet to be proven prospectively. The major problem with assessing the efficacy of various treatment modalities in these patients is the heterogeneity of disease presentation, which often precludes the use of certain therapies and therefore makes the conduct of randomized control trial difficult.

Worldwide, hepatocellular carcinoma (HCC) is the fifth most common cancer, and it is the leading cause of cancer death in many areas. Although it is less common in the United States and other Western countries, the incidence of HCC is rising and is projected to further increase over the next two decades.¹⁻³ Patients with cirrhosis are at greatest risk for developing HCC, and globally, HCC incidence is closely linked with the incidence of chronic hepatitis infection. In particular, hepatitis C is a major underlying factor. In the United States alone, of the approximately 4 million people with chronic hepatitis C infection, as many as a third will go on to develop chronic liver disease. Once cirrhosis is diagnosed, the risk of a neoplastic change increases dramatically, to approximately 1% to 8% per year.⁴ Although the incidence of HCC is closely related to that of cirrhosis, there is some variability depending on geographic location, which in turn reflects differences in cause.⁵ In general, areas with high rates of hepatitis C infection will have higher rates of HCC arising in the setting of cirrhosis, in contrast to areas where hepatitis B is prevalent.

It is important to recognize that the presence of underlying hepatic parenchymal disease is critically important in determining both treatment options and outcome. Indeed, quite often, the extent of the underlying hepatic dysfunction may well be more important as cancer extent in dictating survival. Patients with advanced cirrhosis, with or without cancer, have substantial short-term mortality risk related to liver failure and the sequelae of portal hypertension. In one study that assessed survival related to liver disease stratified by Child-Pugh classification, 1-year mortality increased progressively from 0% to 20% to 55% in patients with Child-Pugh class A, B, or C cirrhosis, respectively.⁶ In addition, the extent of underlying hepatic dysfunction is a major determinant of the treatment options that can be pursued. Patients with a normal liver or with well-compensated cirrhosis are typically limited only by the extent of the malignant disease. In such patients, resection, transplantation, or ablative therapies are potentially available, depending on disease-related factors. By contrast, all of these options are not available to patients with severe cirrhosis; in particular, resection is contraindicated in patients with poor liver function. Indeed, in patients with severe underlying liver disease, even the most modest of interventions may precipitate hepatic failure.

Over the past several years, a number of changes have taken place in the management of HCC. First, surveillance programs are increasingly used in patients with cirrhosis or other risk factors for HCC.⁷ As a result, HCC is now increasingly detected at earlier stages. In addition, both liver transplantation and percutaneous ablative therapies have emerged as effective alternatives to hepatic resection, which had previously been considered the only potentially curative treatment option. As a result, the ideal treatment strategy for patients with early HCC, particularly in the setting of well-preserved hepatic function, has become increasingly controversial. To date, definitive prospective trials directly comparing these treatment modalities have not been performed. This is largely the result of wide heterogeneity in disease extent and underlying hepatic function, which makes the conduct of a prospective randomized trial difficult.

This review examines the indications for and the results of transplantation, resection, and ablation in patients with early HCC. For the purposes of the present discussion, early HCC will be defined as that falling within the Milan criteria: a solitary tumor ≤ 5 cm in size, or ≤ 3 tumors each ≤ 3 cm in size and no evidence of gross vascular invasion.⁸

LIVER TRANSPLANTATION

The early clinical experience with hepatic transplantation for HCC was poor, largely the result of the lack of appropriate patient selection. In these early series, recipients often had advanced disease, resulting in high rates of disease recurrence and poor survival.^{9,10} Because of the markedly lower survival rates in patients with HCC compared to other indications, liver transplantation for HCC was largely abandoned for several years. However, in 1996, Mazzaferro and colleagues reported much more encouraging results of transplantation when only patients with a limited malignant disease were targeted.⁸ In this seminal report, 4-year survival of 75% was identified, provided that patients had no more than a single tumor ≤ 5 cm in size or no more than three tumors, each of which was < 3 cm in greatest diameter, and provided there was no major vascular invasion. Since that report, several centers from around the world have confirmed the excellent long-term benefits of hepatic transplantation, provided that restrictive criteria are observed (Table 1).

The principle advantage of liver transplantation over other therapies is its treatment of both the tumor and the underlying hepatic parenchymal disease. Unlike resection, hepatic transplantation is not restricted by the underlying hepatic function because the entire organ is being replaced by removing all of the diseased liver; further, transplantation, unlike

resection, eliminates the risk of a iatrogenic tumor formation in other areas of the liver that are at risk. On the other hand, advanced underlying cirrhosis is associated with worse survival after transplantation, as demonstrated in a recent large population study of >4000 patients who underwent transplantation for HCC.¹¹

As a result of the improved results in many recent series, the United Network for Organ Sharing (UNOS) in the United States adopted the Milan criteria to establish priority for transplanting patients with HCC. In 2002, UNOS adopted the Model for End-Stage Liver Disease (MELD) for allocation of cadaveric donor livers. Within this system, patients with HCC that falls with the Milan criteria are given higher priority by virtue of their diagnosis of transplantable cancer. This change was in response to the frequent inaccessibility of cancer patients for donor livers, which often resulted in disease progression while on the waiting list.

Despite these changes, however, transplantation for HCC remains severely limited by organ availability. Although organ allocation that is based on the MELD system has reduced time on the waiting list for HCC patients, shortage of donor organs remains a major problem, and availability varies greatly, both by region and blood group.^{12,13} From the time of initial listing, the median time to transplantation in the United States can range anywhere from 9 to 12 months. In patients with malignant disease, such long waiting times are a problem because cancer progression is likely to occur and patients may then become ineligible for treatment. Indeed, this has been well documented in a number of prior studies showing dropout rates on the waiting list that range anywhere from 25% to nearly 40% at 1 year.^{12,14,15} In a more recent study, Pelletier and colleagues evaluated survival and waiting list removal rates on a national level in patients listed for transplantation between 1998 and 2006. In this study, which analyzed data from the Organ Procurement Transplant Network and included 4482 patients, 18% of the patients were removed from the waiting list because of tumor progression or death.¹¹

Disease progression while on the waiting list clearly affects the overall results of transplantation as a treatment modality. On the surface, the survival rates for transplantation in HCC patients are excellent—approximately 80% at 5 years in many series. However, when intention-to-treat analysis is used, dropouts from the waiting list due to death or disease progression clearly diminish long-term survival results. This point was illustrated by Llovet et al., who showed that 2-year survival decreased from 84% to 54% when all patients were included.¹⁵ Since then, other studies have documented that increasing the time on the waiting list leads to a larger proportion of patients who are ultimately ineligible for transplantation and leads to greatly reduced survival.¹⁶ In the recent study by Pelletier et al., median time to dropout from the waiting list because of tumor progression was 140 days.¹¹ As a result, 5-year survival decreased from 62% in those patients who received a new graft to 51% using an intention-to-treat analysis.

In an effort to improve these results and reduce the number of patients lost while awaiting transplantation, several strategies have emerged. One of these is the use of nonsurgical ablative therapies, such as radiofrequency ablation (RFA) or chemoembolization, as a means of providing some measure of disease control. Although these techniques are widely used, the evidence that they improve long-term survival after transplantation is lacking.¹¹ However, it has been shown that by means of these approaches, patients with disease outside of the Milan criteria can be effectively downstaged and the patient brought into transplant eligibility.¹⁷ This is a particularly noteworthy observation, especially considering that the 5-year survival of patients transplanted outside the Milan criteria is approximately 50% lower compared to patients whose disease met the criteria (32% vs. 61%, $P < 0.0001$).¹¹ Yao et al. recently reported a successful tumor downstaging in 43 of 61 patients by means of ablative

approaches, resulting in a posttransplantation 4-year survival of 92%.¹⁷ Similarly, Chapman et al., in a study of 76 patients, demonstrated successful downstaging in 24% of patients, with a posttransplantation survival of 94% at a median follow-up time of 19 months.¹⁸

In addition, live donor liver transplantation has been increasingly used in an effort to address the waiting list problem. Although this approach remains controversial, it clearly results in much shorter waiting times, but it remains to be demonstrated that the results that will be equivalent to transplantation that uses deceased donors. In a recent report from Fisher et al., patients who received live donor grafts, despite shorter waiting times, had a much higher 3-year recurrence rate compared to patients who received grafts from deceased donors (29% vs. 0%).¹⁹ The results from this and other studies suggest that the waiting list permits identification of patients with aggressive disease who would not benefit from transplantation.²⁰ Clearly, spending a lengthy time on the waiting list is unfavorable and leads to the death of patients who would otherwise benefit from a new liver graft. On the other hand, excessively rapid progression to liver transplantation will result in an inclusion of patients whose disease is inappropriate for this therapy.

HEPATIC RESECTION

Hepatic resection has been and remains the primary treatment for HCC in patients with limited disease. Resection has several advantages over transplantation. First, it is more widely applicable because there are no restrictions on tumor size or vascular proximity—variables that often preclude transplantation and ablation, respectively. In addition, there is no obligatory waiting time before proceeding with resection, as is the case with liver transplantation, and unlike ablative therapy, resection allows complete pathologic assessment of the specimen. Of course, the efficacy of partial hepatectomy depends on the ability to achieve a complete resection (R0) that leaves behind an adequate liver remnant. Like transplantation, disease extent is closely linked with outcome after resection, with the best results achieved in patients with solitary small tumors confined to the liver. In addition, resection is largely limited to patients with normal liver or Child-Pugh class A cirrhosis, and unlike transplantation, resection does not address the diseased precancerous liver remnant.

Underlying hepatic parenchymal disease remains a major obstacle to the safe conduct of major hepatic resection in patients with HCC. In patients with normal liver, regeneration after major hepatic resection occurs rapidly to replace the resected hepatocyte mass. After most major resections, transient hepatic dysfunction is common; however, this problem is greatly exacerbated in patients with cirrhosis, where regeneration is impaired and normalization of liver function is slow or may not occur at all. Patients with portal hypertension are in a particularly high-risk group. These patients have a high risk of major hemorrhage during the resection, while exacerbation of portal hypertension through increased flow through noncompliant vascular beds can lead to potentially catastrophic postoperative complications, including hepatic failure, uncontrolled ascites, and variceal bleeding. Indeed, complications resulting from liver failure and portal hypertension have represented the most common cause of postoperative mortality in this patient population.^{15,21,22}

In general, the Child-Pugh classification is a reasonably effective means of stratifying patient risk on the basis of underlying hepatic function and for selecting patients for resection. In most contemporary series, only patients with either normal hepatic parenchyma or those with Child-Pugh class A cirrhosis are candidates for major hepatectomy, while carefully selected Child-Pugh class B patients would be potentially eligible for limited resections. Additional preoperative assessments, aimed at better identifying the subgroup of Child-Pugh class A patients at increased risk, include the indocyanine green clearance test and the

measurement of portal pressure as determined by the hepatic venous pressure gradient. By means of the latter approach, Bruix et al. were able to identify a subgroup of Child class A cirrhotic patients with subclinical portal hypertension who, after hepatic resection, developed decompensated hepatic failure.²³ In this study, the hepatic venous pressure gradient seemed to be superior to indocyanine green clearance for risk stratification. Although both of these studies may have suggested some added predictive value, neither is used routinely in most Western centers. More recently, the MELD score has been shown to correlate with perioperative morbidity and mortality. Cucchetti et al. recently demonstrated that patients with MELD scores of <9 had no postoperative hepatic failure and very low perioperative morbidity after hepatic resection; this is in contrast to a 13% incidence of irreversible liver failure and a perioperative morbidity rate of 50% in patients with a MELD score of ≥ 9 .²⁴

In the 1980 s, the concept of preoperative portal vein embolization was introduced. By means of this technique, the portion of liver to be resected, usually the right lobe, was subjected to portal vein embolization, resulting in atrophy and contralateral hypertrophy.²⁵ By increasing the volume of the future liver remnant (FLR) before operation, the risk of postoperative hepatic failure would in theory be reduced. Since this initial report, several centers have reported experience with preoperative portal vein embolization, and the technique has been proven to effectively increase the volume of the FLR before operation. Although the lower limit of the FLR volume necessary to avoid postoperative hepatic failure remains uncertain, most centers consider patients with an FLR of 25% to 30% to be candidates for preoperative portal vein embolization. In patients with diseased liver, this number is clearly inadequate, and an FLR of $\leq 40\%$ would be considered a cutoff value. In 2003, Farges and colleagues published the results of a prospective study evaluating the role of preoperative portal vein embolization in patients with chronic liver disease undergoing right hepatectomy.²⁶ This study, which included 28 patients with underlying hepatic parenchymal disease, showed that preoperative portal vein embolization reduced postoperative morbidity and hepatic failure, although there was no effect on postoperative mortality.

The results of several large resection series are summarized in Table 2. In general, hepatic resection results in 5-year survival rates that range from approximately 30% to as high as 70%, with operative mortality rates typically of $\leq 5\%$. A report by Jaeck et al. is typical of many surgical series. In this study, which included nearly 1500 patients from 11 European centers, most patients had disease outside of the Milan criteria, including nearly half with tumors >5 cm in size, 40% with major vascular invasion, and 15% with multifocal disease. Despite this, the 5-year overall survival was nearly 40%.²⁷ In addition, the progressive safety of hepatic resection has also been documented, notably in a report from Hong Kong that cited 0% mortality in 110 consecutive resections for HCC.²⁸

When compared to liver transplantation, partial hepatectomy would seem to provide inferior results in terms of long-term survival. However, most surgical series reflect a population of patients with a wide spectrum of disease extent, which frequently extends beyond the Milan criteria. It is important to remember that the factors that preclude liver transplantation, namely tumors of large size, multifocal tumors, and major vascular invasion, are often included in series analyzing resection and are associated with early recurrence and shorter survival.²⁹ When patients with more limited disease are analyzed separately, the results obtained with resection are much more favorable, approaching those reported for liver transplantation. In a study from Poon et al. analyzing a series of Child-Pugh class A cirrhotic patients with HCC falling within the Milan criteria, those with solitary tumors had a 5-year survival of 68%.³⁰ Further supportive evidence in this regard is provided by a randomized, controlled trial by Shi et al.³¹ This report documented the outcome of 169 patients with

solitary HCC randomized to either wide or narrow resection margins. The 5-year survival of patients submitted to resection with wide margins was 75% and was 100% in patients with tumors ≤ 2 cm in size. A study by Cha et al. confirmed that hepatic resection in patients with disease within the Milan criteria yielded 5-year survival figures comparable to those attainable to liver transplantation, 69% vs. 31% in patients with disease that rendered them ineligible to receive a transplant. Of note, this study also showed that most recurrences were confined to the liver, and nearly all were within the criteria for liver transplantation.³²

In patients whose disease recurs after resection, and that disease within the Milan criteria, salvage liver transplantation is a potential treatment option. Indeed, Belghiti et al. reported that salvaged liver transplantation was a safe and effective alternative, providing short- and long-term outcomes equivalent to a group of patients submitted to primary liver transplantation. (i.e., without initial hepatic resection).³³ This is in contrast to a view put forth by Adam et al., who reported that salvage transplantation was associated with higher operative mortality and an increased risk of recurrence compared to primary liver transplantation.³⁴ A more recent study by Gaudio et al. seems to support the concept that the salvage liver transplantation is an effective treatment strategy.³⁵ An additional area of controversy in this debate is the number of patients who might be eligible for salvage transplantation. Although some studies have suggested this approach may be feasible and that up to 80% of patients experience recurrence after hepatic resection, others have reported that as few as 20% may benefit.³⁰

An extension of the concept of salvage transplantation is the use of resection as a planned bridge to hepatic transplantation.³⁶ This approach takes advantage of the detailed histopathologic data derived from the resected specimen to identify patients at high risk for cancer recurrence within the liver. This subgroup of patients would then be offered immediate listing for hepatic transplantation. Initial experience with this approach has suggested a potential benefit, but more data are required from larger series before this can be recommended for general adoption.³⁷

ABLATIVE THERAPY

Other alternatives to the treatment of HCC include nonresectional ablative treatment, the most common of which are RFA and transarterial embolization/chemoembolization (TAE/TACE). These approaches are methods for bringing about tumor necrosis and can be reasonably effective for relatively small tumors. However, both have important limitations. The efficacy of RFA, which is frequently used percutaneously, is greatly limited by tumor size and location. In a report from Mulier et al. of >5000 treated tumors, local recurrence (meaning cancer recurrence at the treated site) was 14% in tumors of ≤ 3 cm but increased to 25% in tumors that were 3 to 5 cm in size and was 58% in tumors that were >5 cm in size. Likewise, vascular proximity, or tumors close to major vascular structures, had a recurrence rate of 37%, compared to 3% for those that were not.³⁸ Despite these limitations, however, up to 80% tumor necrosis has been reported for tumors that are <2.5 cm in diameter.³⁹ In 2008, Livraghi et al. recorded results of a prospective multicenter analysis of percutaneous RFA with patients with solitary HCC of ≤ 2 cm. Treatment was successful in approximately 97% of patients. Overall survival of this entire cohort was 55% but was 68% in patients with tumors that were considered operable.⁴⁰ Chen et al. reported the results of a randomized, controlled trial comparing resection with RFA for tumors up to 5 cm in size. This study showed equivalent and overall disease-free survival between the two treatment arms.⁴¹ The results from these and other studies have led many to consider RFA as an effective alternative to resection in patients with small (<2 to 3 cm) HCC.

TAE and TACE are therapies that are commonly used in patients with unresectable HCC that is generally confined to the liver. This treatment exploits the fact that tumors beyond a fairly small size derive most of their blood supply from the hepatic arterial system. Hepatic artery embolization may be performed using bland particles that primarily serve to interrupt the arterial flow to the tumor (TAE); alternatively, chemoembolization (TACE) involves the administration of intra-arterial chemotherapy before obstruction of hepatic arterial flow. Embolization techniques, unlike percutaneous RFA, are not limited by tumor size or location. However, reasonably good hepatic function is necessary to avoid postprocedural hepatic failure.

Unlike RFA, TACE has been associated with lower rates of tumor necrosis. Nevertheless, efficacy of this approach has been shown compared to conservative management. In 2002, Llovet et al. reported the results of a prospective randomized trial comparing bland embolization with TACE and best supportive care. In this study, TACE was associated with better 2-year survival compared to TAE, although objective tumor response rates were equivalent between the two treatment arms; both treatment arms were superior to the conservative management group.⁴² Additionally, in a systematic review of randomized trials, TACE was shown to improve survival.⁴³ In selected patients with limited disease, combining TACE with RFA may offer more effective disease control than either of these modalities alone.⁴⁴

Both percutaneous RFA and hepatic artery embolization/TACE are used as a primary treatment in patients with advanced, unresectable HCC. Additionally, these approaches are used frequently to treat patients with limited HCC while they are on the liver transplant waiting list. Although these bridging techniques are commonly used with the aim of controlling disease in patients while they await a new graft, pretransplantation therapy has never been shown to improve overall disease-free survival after transplantation.^{45,46}

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TABLE 1

Selected series of liver transplantation for hepatocellular carcinoma published since 2000

Study	N	5-year survival	Mortality (%)
Iwatsuki (2000) ⁵²	344	49%	–
Tamura (2001) ⁵³	53	61%	–
Hemming (2001) ⁵⁴	112	57%	13
Jonas (2001) ⁵⁵	120	59%	1.7
Figueras (2001) ⁵⁶	307	63%	–
Yao (2001) ⁵⁷	60	75%	1.4
Todo (2004) ⁵⁸	316	69% (3-y survival)	–
Gondolesi (2004) ⁵⁹	36	45%	22
Zavaglia (2005) ⁴⁷	155	72%	11
Takada (2006) ⁶⁹	93	64%	–
Cherqui (2009) ⁴⁸	18 ^a	70% ^b	0
Lee (2010) ⁴⁹	78	68%	5.1
Coelho (2009) ⁵⁰	45	4 recurrences	0

^aSalvage transplantation after resection^bFrom time of transplantation

TABLE 2

Selected series of hepatic resection for hepatocellular carcinoma published since 2000

Study	N	5-year survival (%)	Mortality (%)
Zhou (2001) ⁶⁰	1000	63	1.5
Grazi (2001) ⁶¹	264	42	4.9
Yamamoto (2001) ⁷⁰	58	62	–
Poon (2002) ³⁰	135	70	3.7
Wayne (2002) ⁶²	249	41	–
Grazi (2003) ⁶³	308	42	4.9
Ercolani (2003) ⁶⁴	224	42	–
Hu (2005) ⁶⁵	154	–	–
Pawlik (2005) ⁶⁶	300	27	5
Wu (2005) ⁵¹	161 (1991–1996)	28.2	3.7
	265 (1997–2002)	34	0.4
Taura (2007) ⁶⁷	166	46	4
Yamashita (2007) ⁶⁸	59	71	–
Cherqui (2009) ⁴⁸	67	72	4.5
Lee (2010) ⁴⁹	130	52	0.8