Liver Transplantation for Hepatocellular Carcinoma: An Update

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Key Words
Liver transplantation, hepatocellular carcinoma, adjuvant therapy, living donors

Abstract
Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide and the most common primary hepatic malignancy. It arises on a background of hepatic cirrhosis in approximately 95% of the cases in the United States. A wide variety of treatment modalities have been applied in the treatment of HCC. Liver transplantation has emerged as the preferred treatment for patients with small HCC. Transplantation for patients whose tumors do not exceed the Milan criteria yields results equivalent to those of transplantation for non-HCC indications. Controversy now exists regarding the use of living donors, expansion of selection criteria, and role of adjuvant therapy. (JNCCN 2006;4:762–767)

For a patient with cirrhosis, the annual risk for developing hepatocellular carcinoma (HCC) is approximately 5%. Because the United States is in the midst of a hepatitis C epidemic, the number of people with cirrhosis is increasing. The successful treatment of HCC depends almost entirely on surgical therapies, in which liver transplantation is taking a larger role. Liver transplantation is an attractive alternative to other modalities for treating hepatocellular carcinoma, not only because it removes the diseased liver, but also because it provides the widest surgical margins and a low risk for hepatic failure. Of the patients undergoing liver transplantation in the United States, 10% to 15% have HCC.

Historical Perspective
In 1983, a National Institutes of Health consensus conference endorsed using liver transplantation to treat select patients with HCC. As liver transplant centers proliferated throughout North America and Europe, wider experience underscored a serious concern: the results of transplantation were disappointing for patients with HCC. Early series between 1985 and 1989 reported high rates of recurrence and 5-year survival rates of only 25% to 40%.

In 1991, Penn, relying on data submitted to the Transplant Tumor Registry by numerous transplant centers, reported that the overall 5-year survival was 18%. These reports arrived when the shortage of donor livers was beginning to drive waiting times for most patients beyond the 1 year mark, leading to an alarming increase in the risk for death for candidates awaiting transplantation. With 5-year survival probabilities exceeding 80% to 85% for patients undergoing liver transplantation for other types of disorders, advocates for providing liver transplantation to patients with liver cancer had to show improved results.

Investigators began focusing on 2 major strategies for improving results. One approach involved better patient selection through examining retrospective information about tumor staging and histologic grade, and the other included pre- and post-transplant treatment regimens designed to lessen the risk for recurrence and thereby improve overall survival.

Patient Selection: The Milan Criteria
Early reports suggest, and subsequent experience confirms, that the most favorable results with liver transplantation are obtained in patients with so-called “incidental hepatocellular carcinoma.” These are tumors that were not detected before liver transplantation but were discovered during careful examination of the resected liver. In the experience reported by Iwatsuki et al. in 1991, no patients in this category experienced tumor recurrence.
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during the follow-up period. This same report and data from other authors confirmed that the results for patients with known HCC, small tumors, and no vascular invasion were comparable to the results for patients without HCC. In 1993, Bismuth et al. reported favorable outcomes in patients with HCC smaller than 3 cm who underwent transplantation.

This study was followed in 1996 by the work of Mazzaferro et al. from Milan, who evaluated 48 patients with HCC whose tumors met the following criteria for transplantation eligibility: 1) a single tumor less than 5 cm in diameter or 2) 3 or fewer tumors, none larger than 3 cm. The actuarial survival rate at 4 years was 72%, and the disease-free survival rate was 83%. At pathologic review, 35 patients met the criteria and the remaining 13 exceeded it. The overall and recurrence-free survival rates in the patients who met the criteria were 85% and 92%, respectively, compared with 50% and 58% in those who did not meet the criteria. These “Milan criteria” are now widely used to select patients for transplantation and are used by the United Network for Organ Sharing (UNOS) in allocating livers for transplantation. Since that study’s publication, numerous other studies have confirmed that liver transplantation is the best treatment for small HCC.

Guidelines for Donor Organ Allocation in Liver Transplantation

The major limitation in using liver transplantation to treat HCC is the lack of donor organs. Donor organ allocation and distribution is directed by policies established by UNOS (Table 1). This organization is funded by the federal government, and polices are set by various transplantation professionals, transplantation recipients, donor families, and lay persons. The current allocation algorithm first assigns livers to the sickest patients in a defined geographic area. Currently, the Model of End-stage Liver Disease (MELD) system is used to stratify these patients. The MELD system takes into consideration the typical findings in patients with chronic liver diseases, such as bilirubin, coagulopathy, and creatinine, but is not designed to account for patients with HCC. Patients with HCC often do not have decompensated chronic liver disease, so the transplant community implemented a separate point system to provide these patients with access to organs before their disease progresses beyond eligibility for transplantation.

Table 1  UNOS Tumor Staging of Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>T0</th>
<th>Tumor not found</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>1 nodule &lt; 1.9 cm</td>
</tr>
<tr>
<td>T2</td>
<td>1 nodule 2.0–5.0 cm; 2 or 3 nodules all &lt; 3.0 cm</td>
</tr>
<tr>
<td>T3</td>
<td>1 nodule &gt; 5.0 cm; 2 or 3 nodules, at least 1 &gt; 3.0 cm</td>
</tr>
<tr>
<td>T4 A</td>
<td>4 or more nodules, any size</td>
</tr>
<tr>
<td>T4 B</td>
<td>T2, T3, or T4 A plus macrovascular invasion</td>
</tr>
</tbody>
</table>

Abbreviation: UNOS, United Network for Organ Sharing.

In an attempt to prevent continued tumor growth beyond the Milan criteria during the waiting period, UNOS allowed special consideration for patients with favorable hepatic tumors by allowing them to compete in a higher status category normally reserved for patients with severe liver dysfunction. A separate point system was then implemented for patients with HCC. Points were assigned based on predicted 3-month mortality for patients with stage I (15%) and II (30%) disease.

After the MELD system was introduced, the incidence of transplantation for HCC rose dramatically. These scores led to a 2.4-fold increase in the number of patients undergoing liver transplantation for HCC in the first year after the MELD system was implemented. In addition, most HCC patients (85%) underwent transplantation within 90 days of being listed. The system seemed to favor HCC patients disproportionately, and UNOS therefore made several adjustments to the point allocation for patients with HCC. Currently, only patients with stage II disease (single 2–5 cm HCC, or up to 3 tumors each < 3 cm) are eligible for point upgrades equivalent to a 90-day mortality risk of 15%.

Results of Liver Transplantation for HCC

A recent review of patients who underwent transplantation between 1996 and 2001 showed that the current 5-year survival rate after liver transplantation for HCC is 61.1%. With the introduction of the MELD system and better preoperative imaging techniques, these results will probably improve. The results with liver transplantation are superior to all other forms of treatment, including resection, radiofrequency ablation, ethanol injection, or chemoembolization. Specifically, patients with stage I and II disease, and
particularly those with severe underlying chronic liver disease, experience a survival benefit from transplantation compared with either resection or nonsurgical options. Patients with stage IV disease continue to have a poor prognosis with all treatment options, including transplantation.

The most challenging patients are those with stage III disease. The major factor in determining whether a patient will experience recurrence after transplantation is the presence or absence of vascular invasion. Unfortunately, this is often impossible to detect preoperatively, and tumor size is used as a surrogate marker. Patients with stage III disease are a heterogeneous group, particularly because patients with large (T3) tumors but no nodal disease are considered stage III. This has led some groups to question whether the Milan criteria are too restrictive and if these criteria exclude some patients with T3 tumors who could potentially benefit from transplantation. Yao et al.\(^1\) from the University of California at San Francisco retrospectively examined HCC explant data and showed that a modest extension of the Milan criteria (a single tumor no larger than 6.5 cm, or up to 3 tumors, each no larger than 4.5 cm with a total tumor volume of 8.0 cm or less) could achieve satisfactory long-term survival (5-year patient survival of 75%). A similar study from the University of Pittsburgh further supported this finding, showing that almost 50% of patients excluded by the Milan criteria would benefit from liver transplantation.\(^1\) Although these observational studies suggest that selected patients with tumors beyond the Milan criteria can undergo transplantation with acceptable results, other studies demonstrate poorer outcomes; therefore, caution must exercised before the current criteria are expanded.\(^1\)\(^4\) These extended criteria have not been adopted by UNOS, and organ distribution according to the Milan criteria remains in place.

Factors associated with a poor prognosis for patients undergoing liver transplantation for HCC include male gender, large tumor size, multiplicity, bilobar involvement, lymph node metastases, cirrhosis, and extrahepatic tumor.\(^1\)\(^2\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\) Histologic evidence of microvascular invasion may be one of the most important predictors of increased risk for tumor recurrence. Too often in practice, the more important histologic factors are determined only on careful examination of the explanted native liver days after the transplantation surgery.

Recurrent hepatitis C virus (HCV) infection after liver transplantation for HCC may also impact the outcome, because HCC is most commonly associated with chronic HCV infection, and reinfection of the allograft with HCV is inevitable after transplantation. Experts have suggested that long-term patient and graft survival after transplantation for HCV-related cirrhosis are worse than for other indications for transplantation. A study examining the UNOS database showed a 23% increased mortality rate and a 30% increased graft failure rate. However, a similar study using the National Institutes of Health database showed comparable survival between HCV and non-HCV patients who underwent transplantation.

### Pretransplant Locoregional Ablative Therapy

In 1983, Koo et al.\(^2\) recovered malignant tumor cells from the right atrium of patients undergoing hepatectomy for liver cancer. A decade later, Kar and Carr\(^3\) showed that patients with hepatoma can have as many as 1 billion tumor cells in their systemic circulation each day. The most common pattern of recurrence for hepatoma following liver transplantation was multifocal spread in the newly transplanted liver. The rationale for using pretransplant locoregional therapy was to decrease posttransplant tumor recurrence and, hence, patient survival. The use of neoadjuvant therapy, particularly transarterial chemoembolization (TACE), to attempt to sterilize or at least reduce the number of malignant cells in the circulation during the transplant procedure has received widespread attention during the past decade. Neoadjuvant therapy has been applied more recently to prevent tumor growth or spread during the wait-list period to keep patients eligible for transplantation (i.e., within the Milan criteria) as long as possible.

The theoretical advantages of pretransplant chemoembolization are attractive. Because most, if not all, of the blood supplied to HCC is arterial, the ischemia induced by arterial embolization makes the tumor more susceptible to the effects of the applied chemotherapeutic agent. Theoretically, one can also deliver higher doses of chemotherapeutic agents directly to the tumor than systemic use allows. However, randomized controlled trials document the beneficial effect of pretransplant adjuvant therapy in terms of either preventing dropout from the wait list or...
improving recurrence-free survival after transplantation in patients with T1 or T2 tumors.

In nonrandomized applications, several authors believe they have obtained improved survival with chemoembolization. In 1997, Majno et al. reported successful use of chemoembolization to downstage tumors that were larger than 3 cm in diameter. In some patients, they observed complete necrosis of the tumor. Patients with these responses who underwent subsequent transplantation experienced a significant improvement in tumor-free survival compared with patients who either experienced an incomplete response or did not undergo chemoembolization. More recent studies, however, have not shown a significant survival advantage for those patients undergoing TACE and liver transplantation.23,24 Tumor size seemed to be one of the most important prognostic factors among the patients in these reports; those who had a tumor larger than 5 cm in diameter experienced a 10 times greater incidence of recurrence than those with smaller tumors.

Several other modalities, including percutaneous alcohol injection, radiofrequency ablation, and internal radiation, have been applied either alone or in combination with TACE as pretransplant neoadjuvant therapy. The application of these modalities seems to be safe, but no prospective randomized data support the routine use of these techniques in patients with T1 and T2 tumors who are listed for transplantation. A recent study from the University of Pennsylvania could not show that patients with HCC who underwent pretransplant locoregional treatment had a survival benefit over those not treated.25 Our own data similarly could not document improvement in disease-free survival in patients undergoing neoadjuvant treatment.26

Because some patients with T3 tumors experience complete or partial response to neoadjuvant therapy, researchers question whether such patients who are downstaged to within Milan criteria will benefit from transplantation. A recent publication from the group in San Francisco was able to show good short-term survival in a group of patients with T3 tumors who were downstaged with multimodal therapy before undergoing transplantation. Although these data are encouraging, longer follow-up is required before firm conclusions can be made.27

The prognosis for liver allograft recipients treated for cancer is further affected by the need for long-term immunosuppression. In 1991, researchers at Pittsburgh examined the acceleration of growth rates among patients on antirejection medications with recurrent hepatoma.28 Despite continued advances in immunosuppressants in the subsequent decade, both cyclosporine and tacrolimus remain mainstays in modern maintenance protocols. Because both are potent inhibitors of interleukin-2 production, the mechanisms of natural tumor surveillance requiring natural killer cells and lymphokine-activated killer cells may be reduced among transplant recipients.29,30

Researchers have recently shown interest in using rapamycin for its antiproliferative effects with the hope that it will inhibit the growth of any residual tumor cells while still providing effective immunosuppression. The efficacy of adjuvant chemotherapy after liver transplantation has not been studied in a controlled fashion.

Living Donor Liver Transplantation

In addition to the general advocacy for increasing the available supply of cadaveric donor livers,21-23 many programs began examining the risks and benefits of using live volunteers to provide donor livers. Typically a family member will donate the right lobe of his or her liver. Using a statistical decision analysis technique that considered a cohort of hypothetical patients with compensated Child's cirrhosis and an unresectable 3.5-cm hepatoma, Cheng et al. showed that live-donor adult-to-adult liver transplantation offered a 4.5-year increase in tumor-free survival compared with waiting for cadaveric donor liver transplantation or no transplant. The advantage persisted in their model even in the face of varying severity of cirrhosis, age, tumor doubling time, tumor growth pattern, blood type, regional transplant volume, initial tumor size, and rate of cirrhosis progression. A similar experience was reported by Mount Sinai Hospital, where from 1998 to 2001 the average waiting time for a liver from a deceased donor was 414 days compared with 83 days for one from a living donor. Therefore, researchers have proposed that HCC is an ideal indication for living donor liver transplantation.34

Conclusions

Liver transplantation remains the best treatment for HCC in select patients with cirrhosis. This aggressive surgical procedure removes the liver tumor and replaces the cirrhotic liver. Limited surgical therapies,
such as resection, radiofrequency ablation, or percutaneous ethanol injection, must be considered in the context that the cirrhotic liver, with its continued propensity to develop new HCC, is left in place. As the full impact of the hepatitis C epidemic reaches its peak in the United States, the prospect of a similarly overwhelming population of patients with HCC should cause considerable alarm. Although HCC may best be prevented by more effective early treatment of viral hepatitis, the absolute number of patients with established cirrhosis who are at risk for developing cancer is likely to be staggering. Thus, assuming that transplantation offers the best chance of tumor-free survival for these patients, and with the supply of donor livers from cadaveric sources falling further behind the demand from all patients with liver disease (many with far better long-term survival prospects than those who have tumors), the burden on families, friends, and other volunteers to provide pieces of their livers should give everyone pause. The role of adjuvant therapies remains limited and may best be used to downstage patients so that they may qualify for liver transplantation.

References
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