Liver transplantation can provide long-term survival for well-selected patients with HCC and cirrhosis who are not candidates for tumor resection.

Liver Transplantation for Hepatocellular Carcinoma
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**Background:** The treatment of hepatocellular carcinoma (HCC) is challenging, but transplantation of the liver has emerged as one of the options in the therapeutic armamentarium against this disease.

**Methods:** This article reviews the changing criteria for patient eligibility for liver transplantation for HCC and presents an initial evaluation of institutional treatment outcomes for this treatment modality. A method for evaluating prognosis is also described.

**Results:** Patients are considered for liver transplantation if they meet the Milan criteria for eligibility or a UCSF-attributed expansion of these criteria that includes the “rule of 7,” whereby the sum of the size of the largest nodule plus the total number of nodules cannot exceed 7. Preliminary institutional experience suggests a tumor recurrence rate of 11% in 91 patients with HCC who received liver transplants between 1996 and 2008.

**Conclusions:** Liver transplantation offers an opportunity for long-term survival in patients with HCC and chronic cirrhosis whose tumor cannot be resected. Criteria for patient selection for this modality of treatment continue to be upgraded and refined.

**Introduction**

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide.1 Patients with hepatitis C and alcohol-related cirrhosis comprise the majority of cases of HCC in the United States,2 where the incidence is increasing. However, hepatitis B is the single most common cause worldwide.5 Liver transplantation emerged in the 1990s as a viable approach to treating HCC, following poor results in the 1980s.4 A landmark study from the Milan group reported survival at 4 years of 85%, with a recurrence rate of 8%.5 This experience was subsequently validated by other groups.6,7 The Milan criteria are now used worldwide to identify patients with HCC who have good prognosis after liver transplantation. The major criteria include a single tumor ≤ 5 cm, or up to 3 nodules ≤ 3 cm each, and with no macrovascular invasion. Liver transplantation offers the advantage that the malignancy is resected, and it is the only therapy addressing metachronous risk by eliminating the parenchymal liver disease that leads to HCC. Disadvantages of liver transplantation include a high perioperative risk, a life-long need for immunosuppressants, the side effects of those drugs, including those on tumor behavior following liver transplantation, and a large donor/recipient disparity.

**Wait List and Allocation Issues**

Patients initially meeting the Milan criteria could become ineligible due to tumor progression. This is particularly significant in regions of the United States where waiting times for liver transplantation are long. Pretransplant therapies are therefore utilized in an
attempt to reduce dropouts from the waiting list and to reduce recurrence rates following liver transplantation. These treatments include ablative therapies; radiofrequency ablation and transarterial chemoembolization are both widely utilized as a “bridge” to liver transplantation. The concept of tumor resection as a bridge is not practiced. Patients who have had a tumor resection have no priority for liver transplantation unless a recurrence arises. A patient who has a recurrence after tumor resection, has poor liver function, and meets the criteria for liver transplantation, however, could benefit from liver transplantation.

Since 2001, the transplant regulatory body in the United States — the United Network for Organ Sharing (UNOS) — has assigned an automatic Model End-stage Liver Disease (MELD) score to patients with HCC meeting the Milan criteria, based on the high mortality of these patients prior to transplant and the improved results following liver transplantation. Thus, HCC has become a prioritized condition under the MELD liver allocation system. Among the 104 liver transplantations performed in 2008 at our center, approximately 18% were for HCC. A patient with a MELD score of 22 in our center and in the southeastern part of the United States will have a mean waiting time to liver transplantation of only 3 months. Thus, the likelihood of dropout from the waiting list is low, and the likelihood of liver transplantation is high. This could translate to less vascular invasion, reduced recurrence following liver transplantation, and better outcomes. However, this has not been proven. Methods to expand the pool of donors for patients with HCC include the use of split liver transplantation, living donor liver transplantation, and expanded criteria of high-risk donors, including those with hepatitis C.

Expansion of HCC Criteria
A dilemma arises since some patients exceeding the Milan criteria have the potential for cure by liver transplantation. These patients are currently ineligible for liver transplantation, except in 2 of the 11 geographic regions in the United States, as defined by UNOS. Investigators at the University of California at San Francisco have proposed the UCSF criteria that consists of 1 lesion ≤ 6.5 cm, or 3 lesions with the largest lesion ≤ 4.5 cm and the total tumor burden ≤ 8 cm. Downstaging protocols at many institutions, including our own, have been implemented (Table). Furthermore, UNOS Region 3 (southeastern United States) has approved a downstaging protocol that includes prioritizing these patients by assigning them a MELD score of 22.

Tumor Resection vs Liver Transplantation
Less than 15% of patients with HCC are candidates for resection. Although hepatic resection is widely available, it should be offered early and should be limited to patients without portal hypertension in order to avoid postoperative hepatic failure. Five-year survival rates of 40% to 50% have been reported, but high recurrence rates of 40% to 70% represent the main cause of death. It has been hypothesized that increased hepatocyte regeneration after resection might help enhance hepatocarcinogenesis in the remnant. However, a more accepted theory is that recurrences are usually the result of multicentric carcinogenesis or intrahepatic recurrence via the systemic circulation.

Salvage Liver Transplantation Following Resection
This concept could be utilized at the time of tumor recurrence. Studies from Asia indicate that 80% of patients at the time of recurrence could be eligible for liver transplantation. However, this refers to patients with hepatitis B and also with the use of living donors, both rare events in the United States. The data are not reproducible in our large hepatitis C population with HCC, where tumor recurrence exceeds the Milan criteria in 60% of patients following resection. Therefore, in a cirrhotic patient with hepatitis C, resection may represent a loss of opportunity for cure since only a limited number of patients can subsequently undergo transplantation. If the tumor meets liver transplantation criteria, this approach should be considered. This is not to imply that cirrhotic patients with hepatitis C should never have a tumor resection. Resection and transplant patients differ in many aspects, including tumor stage, liver function, comorbidities, and psychosocial status. These two management modalities have not been compared directly.

Criteria for Inclusion
1. Single tumor ≤ 6.5 cm
2. Total tumor burden ≤ 8 cm
3. No vascular invasion

Criteria for Successful Downstaging
1. Decrease in tumor size and number to meet United Network for Organ Sharing (UNOS) T2 criteria or
2. Complete tumor necrosis without contrast enhancement to suggest residual tumor, equal to obliteration of tumor irrespective of tumor size

Criteria for Treatment Failure
1. Dropout due to tumor progression
2. Vascular invasion
3. Extrahepatic or lymphatic metastases

Criteria Prior to Placement on Waiting List Once Downstaged (Time-Out Period)
Once criteria for downstaging are met, a minimum of 3 months of follow-up is required before the patient is listed for liver transplantation along with new imaging that meets the criteria for successful downstaging
The Metroticket Project
The Metroticket project was introduced at the International Liver Transplant Society (ILTS) meeting in 2005 as a Web-based survey. In an attempt to gather a sufficient number of patients to allow for robust statistical analysis, the project collected data on more than 1,000 patients who exceeded the Milan criteria and received transplants. The Metroticket project has been endorsed by the European Liver and Intestine Transplant Association (ELITA) and the ILTS. The result of the project is the Metroticket calculator, which can be used to predict 5-year survival based on a patient’s morphological and biological characteristics (size of the total nodules, size of the largest nodule, and vascular invasion if available). The calculator also places a patient on the “HCC weather forecast chart”: the blue zone indicates good survival (a 5-year survival rate of 50%), and the red zone indicates poor prognosis (a 5-year survival rate of < 50%, which is considered unacceptable in liver transplantation for HCC). The Metroticket predicts survival beyond the Milan criteria, the upper limit of liver transplantation for HCC. The Metroticket calculator, which can be used to predict 5-year survival based on a patient’s morphological and biological markers. The most important pathological criteria are vascular invasion, grade, satellitosis, and α-fetoprotein (AFP). Poor histological grade is detrimental to liver transplantation. The diameter and number of nodules in correlation with grade were predictive of vascular invasion if tumors were > 5 cm.

Institutional Experience With HCC
At our institution, patients referred for the possibility of liver transplantation are prioritized. Imaging studies and clinical data are reviewed. The American Association for the Study of Liver diseases (AASLD) guidelines for diagnosis of HCC are followed. Ablative techniques are employed early in the evaluation process as a bridge to liver transplantation or as definitive treatment. Candidates for tumor resectional therapy are offered surgical resection. Patients being considered for liver transplantation undergo continued evaluation during the cancer treatment process. The severity of liver disease, the etiology and comorbidities, the ability to obtain immunosuppressants, and the social support systems are examined. Final candidacy is decided by a liver transplant patient selection committee. Patients with tumors of poor grade, diffuse tumor spread, macrovascular invasion on imaging, or microvascular or lymphatic invasion on pretransplant pathology are usually not accepted for liver transplantation.

A total of 754 patients underwent liver transplantation at our institution between December 1996 and June 2008, including 91 patients with the preoperative diagnosis of HCC. The overall tumor recurrence rate was 11%. No significant difference in overall posttransplant cancer recurrence was observed between well-compensated cirrhotic patients (n = 35, 8.5%) and decompensated cirrhotic patients (n = 56, 12.5%). A third group of incidental HCC discovered at pathological explant represented 5% of all liver transplant recipients. The recurrence rate for this group was 7.3%. Tumor recurrence in all cancer patients occurred at a median time of 13 months and was uniformly fatal. The short- and long-term survival, the effects of ablative treatments, and the morbidity of liver transplantation are being evaluated. These data are currently unpublished.

Conclusions
Liver transplantation offers an opportunity for long-term survival in HCC patients with underlying cirrhosis whose tumor cannot be resected. Resection and transplantation patients are dissimilar, and the two therapies have not been compared directly or in randomized trials. The outcome of liver transplantation in the well-compensated cirrhotic patient is not well known and is currently under study in our center.

Tumors ≤ 5 cm in diameter or 3 tumors each ≤ 3 cm and without vascular invasion are considered to be within the Milan criteria and are prioritized for transplant. Expansion of eligibility beyond the Milan criteria of ≤ 6.5 cm in size, or the “rule of 7,” is achieving acceptable outcomes and is now more widely accepted. A downstaging protocol at Tampa General Hospital has been developed. UNOS Region 3 (southeastern United States) has approved prioritizing successfully downstaged patients. The Metroticket calculator is a first step in prognostic tools. Additional parameters will be added in the future. Objective approaches will be needed for policies and prioritization when patients are being listed with UNOS on the national waiting list.

Recurrence of HCC following liver transplantation is a double failure. Multicenter clinical trials should be focused on morphological, pathological, and biological parameters to minimize failure. Transplantation for HCC is already being prioritized, but new policies are being implemented.

References


