Liver Transplantation for Hepatocellular Carcinoma: The Ochsner Experience

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Liver transplantation is now advocated for patients with early stage hepatocellular carcinoma (HCC) not amenable to surgical resection. In this article we review our experience with liver transplantation as treatment for patients with HCC and end-stage liver disease. Between April 1998 and May 2002, 36 patients with a diagnosis of HCC underwent liver transplantation at Ochsner Clinic Foundation. A retrospective analysis was performed examining pretransplant staging of disease, pathologic staging, disease recurrence, and patient survival. Cumulative 1- and 3-year patient survival rates are 80% and 61%, respectively. To date, none of our patients has developed evidence of recurrent cancer. Our data support liver transplantation as the treatment of choice for patients with unresectable early stage HCC.

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At the beginning of the 20th century, hepatocellular carcinoma (HCC) was thought to be extremely uncommon, but as we enter the 21st century, HCC has become the fourth most common cancer in the world, accounting for an estimated 1 million cases annually (1-3). In the United States, the incidence of HCC has risen more than 48% since 1993, an increase that has paralleled the dramatic rise in cirrhosis due to viral hepatitis (4-6). Cirrhosis, regardless of etiology, remains the most important risk factor for the development of HCC, accompanying up to 90% of HCC cases (6,7). Viral hepatitis (hepatitis B or C) is the other important risk factor for HCC development (6-8).

If untreated, even small HCC lesions are uniformly fatal, with survival dependent not only on the extent of tumor present, but also on the degree of hepatic dysfunction (9). In most cases, nonsurgical therapies, including percutaneous ablation, chemoembolization, radiation therapy, and chemotherapy, are palliative at best (5,10). Currently, surgical intervention offers the only chance for cure.

In the absence of cirrhosis, the mainstay of therapy is partial hepatic resection, with 1- and 3-year survival rates of 80% and 40%, respectively (6,11). However, tumor multicentricity, tumor location, or insufficient hepatic reserve due to cirrhosis precludes resection in the vast majority of patients (12). Liver transplantation offers hope for these patients with unresectable HCC. Transplantation not only radically excises the cancer but also removes the cirrhotic, tumorigenic liver. Normal liver function is restored and concerns about occult multicentric disease are eliminated (13-15).

As liver allografts are a scarce resource with the demand far outpacing the supply, current liver allocation policy for HCC restricts priority transplant listing to those patients with an early stage of disease (those with a favorable prognosis), who are not candidates for curative resection. In this article we describe our experience with liver transplantation in patients with end-stage liver disease and HCC.

METHODS

Patients

All adult patients with a histologically confirmed HCC in the explanted liver specimen (n=36) between April 1998 and May 2002 were included in this analysis. Patients with known HCC prior to transplant (n=22) underwent triple phase computerized tomography (CT) imaging of the chest and abdomen to assess the stage of the tumor. Each had HCC deemed unresectable due to tumor location, tumor multicentricity, or severity of underlying liver disease. Pretransplant surveillance consisted of serial (every 3 months) hepatic ultrasounds as well as alpha-fetoprotein (AFP) levels. Patients found to have HCC only after evaluation of the explanted cirrhotic liver were described as having incidental HCC (IHCC, n=14). All patients satisfied

standard liver transplantation listing criteria established by the United Network for Organ Sharing (UNOS).

Pretransplant patients were staged according to the American Liver Tumor Group Modified Tumor-Node-Metastasis (TNM) Staging Classification in compliance with UNOS regulation (Table 1). A pretransplant biopsy was not mandatory, but the lesion had to meet established imaging criteria for a diagnosis of HCC.

A single pathologist examined all explanted livers, and each patient was given a pathologic stage based on macroscopic and microscopic findings.

Operative Technique

Standard operative techniques for orthotopic liver transplantation were employed. Thirty-five patients received whole liver allografts while one patient received a right-lobe split-liver allograft. All patients underwent a thorough abdominal exploration at the time of transplant to assess for extrahepatic disease. In instances of known or suspected HCC, a wider margin of resection was performed to include the lymphatic tissue of the porta hepatis and gastrohepatic ligament. During the hepatectomy, manipulation of the liver was minimized. Enlarged or suspicious lymph nodes were sent for histologic evaluation by frozen section to rule out extrahepatic disease. The retrohepatic vena cava was completely resected in each case and veno-veno bypass was not used.

Immunosuppression

Immunosuppression consisted of either a triple drug regimen of corticosteroids, tacrolimus, and mycophenolic acid, or a steroid-free regimen of antithymocyte immunoglobulin induction with concomitant tacrolimus and mycophenolic acid. Maintenance immunosuppression was reduced to tacrolimus monotherapy by 3 months post-transplant in each case.

Post-Transplant Surveillance

Post-transplant surveillance for recurrent disease consisted of abdominal and chest CT scans performed every 6 months and serial AFP levels checked every 3 months. Recurrence was defined as CT evidence of a new tumor lesion with histologic confirmation.

Statistical Analysis

The survival curves of patients with and without HCC were generated using Kaplan Meier survival analysis with log rank test for comparison.

Table 1. American Liver Tumor Study Group modified tumor-node-metastasis (TNM) staging classification.

T1:	1 nodule < 1.9 cm
T2:	1 nodule 2.0-5.0 cm; 2 or 3 nodules all < 3.0 cm
T3:	1 nodule > 5.0 cm; 2 or 3 nodules, at least one > 3.0 cm
T4a:	4 or more nodules, any size
T4b:	T2, T3, or T4a plus gross intrahepatic portal or hepatic vein involvement as indicated by CT, MRI, or ultrasound
N1:	Regional (porta hepatis) nodes involved
M1:	Metastatic disease, including extrahepatic portal or hepatic vein involvement

Stage I	T1
Stage II	T2
Stage III	T3
Stage IV A1	T4a
Stage IV A2	T4b
Stage IVB	Any N1, any M1

Table 2. Patient characteristics.

Total Number of patients	36
Age (mean, [range])	52 (20-68)
Sex (M/F)	30/6
Hepatitis C	24
Hepatitis B	2
EtOH	3
Cryptogenic	4
Hemochromatosis	1
PBC	1
Autoimmune	1

Child Classification (Child-Pugh Score)	
A (5-6)	3
B (7-9)	11
C (10-15)	22
Known HCC	22
IHCC	14

EtOH = ethyl alcohol, PBC = primary biliary cirrhosis, HCC = hepatocellular carcinoma, IHCC = incidentally found (at pathologic examination) hepatocellular carcinoma.

Table 3. Pathologic Stage and Tumor Characteristics.

	No. of Patients		No. of Patients
Pathologic Stage		**Greatest Tumor Size**	
Stage I	8	<2 cm	13
Stage II	18	2-5 cm	20
Stage III	4	> 5-10 cm	3
Stage IV	6	> 10 cm	0
Tumor Number		**Vascular Invasion**	
1	24	micro	7
2-3	8	macro	3
4-5	3		
>5	1		

RESULTS

Patient Characteristics

In the time period studied, 36 patients with HCC (14 incidental and 22 with known HCC) received liver transplant allografts. Recipient characteristics are listed in Table 2. Age of recipients ranged from 20 to 68 years (mean 52.4 ± 9.7 yr). Men outnumbered women in our series by a ratio of 5 to 1. Underlying hepatitis C was present in 24 of 36 patients (67%) and was by far the most common cause of cirrhosis in our recipients.

Severity of cirrhosis was measured by Child classification and by Child-Pugh scoring (Table 2). Of 36 patients, 22 (61%) were classified as Child's C cirrhotics, 11 of 36 (31%) Child's class B, and 3 of 36 (8%) Child's class A.

AFP Levels and Tumor Stage

Peak pretransplant AFP levels were outside the normal range in 23 of 36 patients (64%). However, only 7 (19%) had AFP levels over 500 ng/ml. In the pretransplant period, 8 patients were classified as having Stage I disease, 13 Stage II, and 1 Stage IV disease. The remaining 14 patients had HCC lesions found incidentally at pathologic examination of the resected liver (IHCC). Ten patients underwent pretransplant transarterial chemoembolization therapy.

Pathologic staging and tumor data are listed in Table 3. Pretransplant imaging underestimated the extent of disease in 27 of 36 patients (75%). Three patients (8%) had macroscopic vascular invasion and 7 patients (19%) had microscopic vascular invasion.

Time on Transplant Waiting List

The overall mean time from transplant listing to transplantation was 109 days (median 41 days). However, mean waiting time for patients with known HCC was 72 days (median 35 days) versus a mean waiting time of 162 days (median 50 days) for those patients with IHCC. No patient with HCC was removed from the transplant list due to progression of HCC during the study period.

Cumulative Survival and Recurrent Disease

The total follow-up period ranged from 1 to 47 months (mean 20 ± 12 months). Among the 36 patients with HCC, 4 patients (11%) died within 1 month (1 intraoperative,

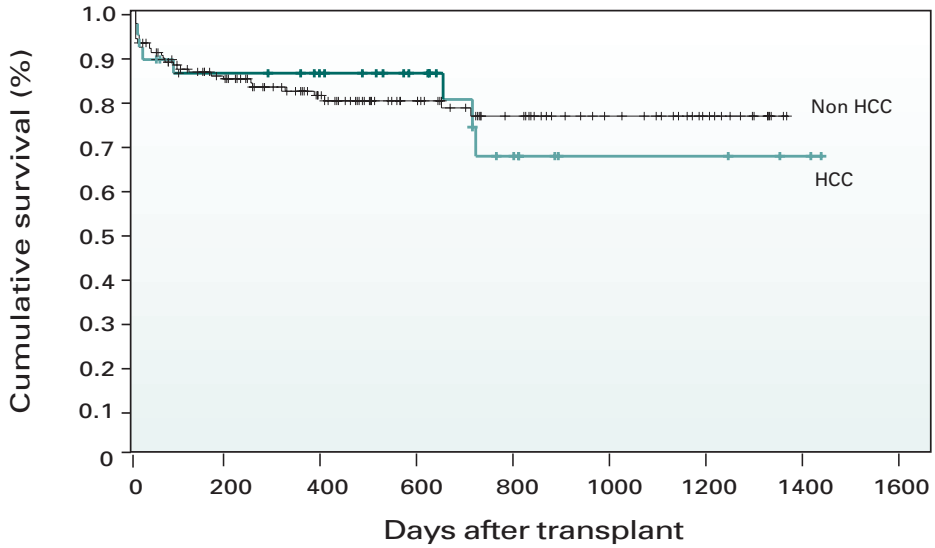

Figure 1. Kaplan Meier actuarial survival curves for liver transplant recipients with (HCC) and without (non-HCC) hepatocellular HCC.

1 from graft failure, 1 from myocardial infarction, and 1 from sepsis). Four patients subsequently died within 2 years (2 from liver failure due to recurrent hepatitis C, 1 from metastatic colon cancer, and 1 from myocardial infarction). Each was clinically free of HCC at the time of death.

The overall survival of patients with HCC was not statistically different from patients transplanted for nonmalignant disease (log rank test, Figure 1). One patient was recently noted to have increasing AFP levels (maximum 267 ng/ml), although multiple imaging studies did not reveal any lesions. Serial CT scans as well as AFP values remain normal in the remaining patients. Hence the actual disease-free survival at 1 year (excluding patients who died within 1 month of transplantation) is 100%. The small number of patients in our series precludes any meaningful regression analysis to determine whether staging or pretransplant chemoembolization was independently predictive of survival.

DISCUSSION

The epidemic of hepatitis C that began in the 1970s and 1980s has produced unprecedented numbers of patients with hepatitis C-related cirrhosis (6). In the United States, chronic active hepatitis C has become the most common etiology of cirrhosis necessitating liver transplantation, and it is the primary diagnosis of more than 50% of patients awaiting transplantation at our center. The two most important risk factors for developing HCC are viral hepatitis and cirrhosis (6-8). When both hepatitis C and cirrhosis are present, the estimated cumulative 5-year risk of developing HCC is 15% to 20% (6). Our experience is that 33% of patients undergoing liver transplantation for hepatitis C virus have concomitant HCC (16). With the current influx of patients with hepatitis C-related cirrhosis, we are likely to see increased numbers of patients with HCC.

Close surveillance is the key to identifying hepatocellular cancer in its early stages and should be done in all patients with cirrhosis. Serial AFP levels and hepatic ultrasound examinations are the usual screening modalities employed, though our data suggest AFP levels should not be used alone due to a lack of sensitivity. Despite normal AFP levels on serial measurements, several of our patients were found to have HCC. Hence an imaging study should be the mainstay of HCC surveillance, though the optimal testing frequency is not clear. Our policy is to screen cirrhosis patients every 3 months with both an AFP level and a liver ultrasound. Any patient with a suspicious lesion undergoes a triple phase CT scan. A solid lesion on ultrasound or CT scan in patients with cirrhosis is considered HCC until proven otherwise. This is especially true in patients with viral hepatitis. Lack of a size increase on serial imaging studies does not necessarily indicate a benign lesion. One patient with a solid lesion unchanged in size for 18 months on multiple CT scans was subsequently found to have HCC with macroscopic vascular invasion.

One question facing the clinician is whether to treat HCC with resection or transplantation. The ideal candidate for partial hepatectomy is one who is asymptomatic with normal or near normal liver function, who is without significant portal hypertension (17,18), and who has clearly resectable disease. Unfortunately, HCC in the United States most often occurs in the setting of well-established cirrhosis. As a result, only a small fraction of patients with HCC are ever candidates for partial hepatic resection due to insufficient hepatic reserve (6,12). Bismuth et al reported a 50% mortality rate when partial hepatic resection was performed in the setting of Child's class B or C cirrhosis (15). Therefore, partial hepatic resection should be avoided in those with advanced cirrhosis and these patients should be referred for transplantation.

There are concerns, however, with performing partial hepatic resection even in patients with Child's class A cirrhosis. Partial hepatic resection for HCC results in a high tumor recurrence rate. Three-year disease-free survival is reported to be only 18% after partial hepatic resection for early stage HCC and cirrhosis versus a rate of 83% for those treated with transplantation (15). The higher incidence of recurrent cancer observed in surgical resection patients is likely related to unrecognized tumor left within the remaining liver or the subsequent development of new tumor foci within the residual tumorigenic liver. Indeed, in our series, pretransplant imaging studies underestimated the extent of disease in 28 of 36 patients (78%). Also, the severity of underlying liver disease may be underestimated, resulting in hepatic decompensation after partial resection.

Liver transplantation offers patients with advanced liver disease a real hope for cure. Our results, which corroborate those published by other centers, suggest that liver transplantation for early-stage HCC yields survival rates similar to those achieved with transplantation for nonmalignant disease (13,19). HCC recurrence rates are lower after transplantation than after partial hepatic resection (11,15,20) and, unlike resection, transplantation can be applied to HCC patients irrespective of their level of underlying liver disease. Ninety-two percent of our patients were Child's class B and C cirrhotics, patients not considered candidates for partial hepatectomy. In addition, transplantation offers the advantage of eliminating the tumorigenic liver.

The choice of transplantation, however, raises several important concerns. One is that patients might develop inoperable disease or even die from tumor progression while waiting for an available allograft. Llovet et al reported a 23% patient dropout rate due to tumor progression with a median transplant list waiting time of 6 months (19). The survival benefit of chemoembolization, radio frequency ablation, or percutaneous ethanol treatment as a bridge to transplant is not fully established. However, we routinely perform chemoembolization in patients awaiting transplantation. We have

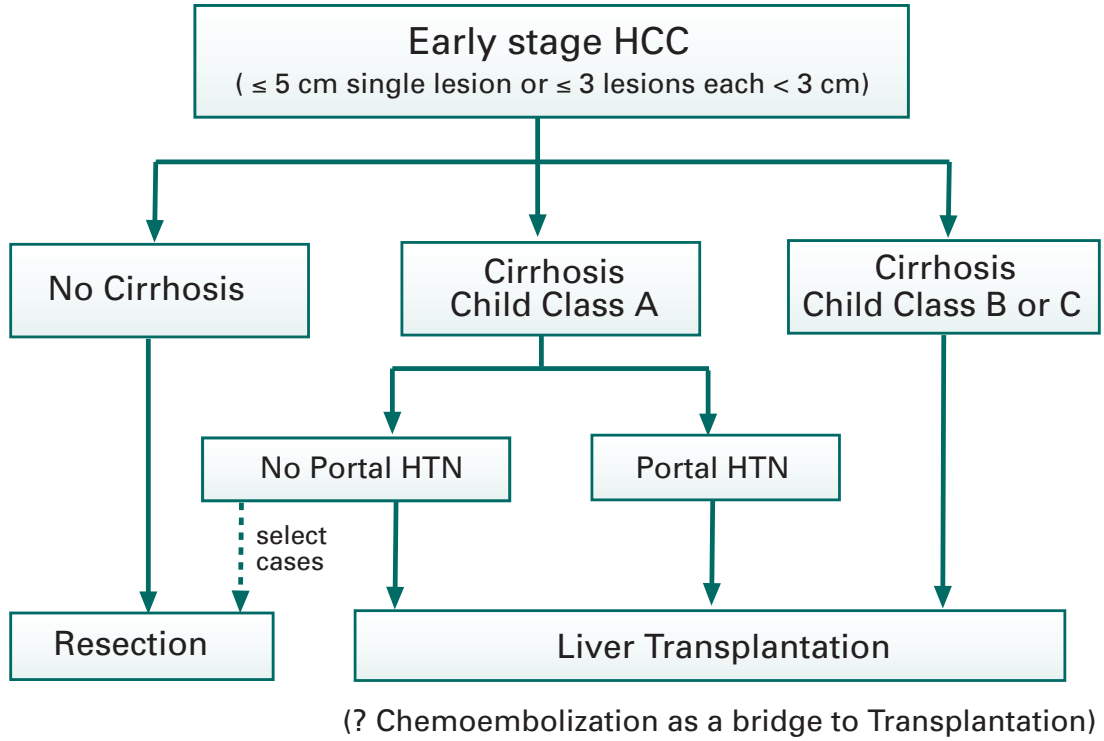

Figure 2. Proposed algorithm for treating early stage hepatocellular carcinoma (HCC). While not shown, patients without cirrhosis who have unresectable HCC due to tumor location are also evaluated for liver transplantation. HTN=hypertension.

not yet observed a survival advantage for these patients, though our analysis is limited by the small sample size. Potential for tumor progression should be an important consideration in centers with long waiting times. In the newly revised organ allocation policy based on MELD (Model for End stage Liver Disease), patients with cancer get a higher priority and hence this problem may be alleviated to some extent. In addition, living donor or split-liver transplantation should be actively pursued in such patients especially if the waiting time is likely to be prolonged.

The median waiting time at Ochsner was only 35 days for patients with known HCC and only 50 days for those with IHCC, times which are much shorter than the national average. No patient in our series was dropped from the transplant list due to progression of HCC. Only 6 of our 36 patients (16.7%) had waiting times longer than 6 months and 4 of these were in the IHCC group. This reflects both increased donor organ availability in our region and our aggressive approach to transplanting patients with HCC.

A second concern with treating HCC with liver transplantation is the impact of lifelong immunosuppression on recurrent hepatitis C. Two of our patients (5.6%) died within 24 months of operation of recurrent hepatitis C cirrhosis without evidence of recurrent HCC. Our current approach for treating HCC is outlined in Figure 2.

SUMMARY

Clearly, liver transplantation offers the best chance for cure of HCC, but to be effective it must be performed in a timely fashion. The limited supply of available cadaveric organs, however, cannot meet the needs of the ever-increasing list of patients awaiting transplantation for both malignant and nonmalignant liver disease. Living donor liver transplantation is always considered for patients with HCC, but living donor liver transplantation alone will not alleviate the disparity between liver allograft supply and demand. In this context, partial hepatic resection may be considered in patients with well-compensated disease after a comprehensive evaluation and after accepting both an increased risk of tumor recurrence and a risk of postoperative liver decompensation. As we continue to see more cases of HCC and learn more about the biology and natural history of this disease, new and creative surgical and nonsurgical management schemes will be required to better serve this growing patient population. Until then, our results support an aggressive policy of liver transplantation as the treatment of choice for patients with unresectable HCC.

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