Liver Transplantation for Hepatocellular Carcinoma: Long-Term Results Suggest Excellent Outcomes

MB Majella Doyle, MD, FACS, Neeta Vachharajani, BS, Erin Maynard, MD, Surendra Shenoy, MD, Christopher Anderson, MD, Jason R Wellen, MD, FACS, Jeffrey A Lowell, MD, FACS, William C Chapman, MD, FACS

BACKGROUND: Selected 5-year survival results after liver transplantation for hepatocellular carcinoma (HCC) have been reported to be 70%. Our hypothesis was that liver transplantation is effective for long-term cancer control for HCC.

STUDY DESIGN: A 20-year retrospective review of a prospectively collected database was carried out. Demographic data and patient survival were calculated.

RESULTS: There were 1,422 liver transplantations performed between January 1990 and April 2011. Of these, 264 had HCC and 157 (59%) were pretreated with transarterial chemoembolization. Recipient age was 55.9 (±7.9) years and 208 (79%) of patients were male. The underlying disease was hepatitis C virus in 155 (58.7%), hepatitis B virus in 16 (6%), alcohol in 21 (8%), and miscellaneous in the remaining 72 cases. The mean number of tumors was 1.8 (±1.7) and the mean largest tumor diameter was 2.3 (±1.3) cm in the explanted liver. One, 5, and 10-year patient survival was 88.5%, 69.1%, and 40.5%, respectively; disease-specific survival was 99.1%, 94.4% and 87.9%; and disease-free survival was 86.0%, 64.6%, and 40.1%. One, 5, and 10-year graft survival was 87.3%, 68.0%, and 41.8%. Nine (3.4%) patients required retransplantation; 75 patients (28.4%) have died, but only 10 of 75 (13.3%) died of recurrent HCC (3.7% of all HCC patients receiving a transplant) and 6 (8%) died of recurrent viral hepatitis. An additional 9 recipients developed recurrence (total HCC recurrence, n = 19 [7%]), 4 of whom died of causes other than HCC. The remaining 5 are disease-free post-treatment (mean 5.5 years after orthotopic liver transplantation).

CONCLUSIONS: Orthotopic liver transplantation offers an effective treatment strategy for HCC in the setting of cirrhosis, even in the setting of hepatitis C virus. Hepatocellular carcinoma recurrence is uncommon in properly selected patients and disease-specific long-term survival approaches 90%. (J Am Coll Surg 2012;215:19–28. © 2012 by the American College of Surgeons)

Hepatocellular carcinoma (HCC) is on the rise in the United States as well as worldwide and resection remains the standard first-line treatment strategy. However, in many patients this is not possible because cirrhosis precludes extensive resection. In addition, resection in the face of multifocal HCC has a poor prognosis, with recurrence rates between 80% and 100% in long-term follow-up.[1] Early series of liver transplantations for HCC reported 5-year survival of 30% to 40%.[2,3] Since then, liver transplantation has become a widely accepted treatment for patients with early-stage HCC and more selectively for downstaged patients with more advanced disease.[4,5] Patients eligible for liver transplantation in the United States include those within the Milan criteria[4] (ie, 1 tumor ≤5 cm or up to 3 tumors, with the largest ≤3 cm), currently defined on contrasted enhanced cross-sectional imaging. These patients receive 22 Model for End-Stage Liver Disease (MELD) exception points for transplantation priority.[6] Because of wait time variability throughout the United States, in some regions patients can wait from 6 months to 1 year, despite the 10% increase in MELD every 3 months on the waiting list.[6] Locoregional tumor therapies such as

CME questions for this article available at http://jacscme.facs.org

Disclosure Information: Authors have nothing to disclose. Timothy J Eberlein, Editor-in-Chief, has nothing to disclose.

Presented at the Western Surgical Association's 119th Scientific Session, Tucson, AZ, November 2011.

Received January 4, 2012; Revised February 23, 2012; Accepted February 23, 2012.

From the Department of Surgery, Section of Abdominal Transplantation, Washington University School of Medicine, St Louis, MO.

Correspondence address: William C Chapman, MD, FACS, Washington University School of Medicine, 660 S Euclid Ave, Campus Box 8109, St Louis, MO 63110. email: doylem@wustl.edu

ISSN 1072-7515/12/$36.00
http://dx.doi.org/10.1016/j.jamcollsurg.2012.02.022

Abbreviations and Acronyms

HBV = hepatitis B virus
HCC = hepatocellular carcinoma
HCV = hepatitis C virus
MELD = Model for End-Stage Liver Disease
NASH = nonalcoholic steatohepatitis
RFA = radiofrequency ablation
TACE = transarterial chemoembolization

transarterial chemoembolization (TACE) or radiofrequency ablation (RFA) are commonly used as a bridge to transplantation or to down-stage potential candidates.[7,8] Reports have shown that down-staged patients have survival similar to stage II recipients.[8] The aim of the current report is to review our center's 20-year experience with liver transplantation for HCC and to assess the long-term results of transplantation for this malignancy.

METHODS

This study was compiled after approval from our institutional review board and used a prospectively collected clinical database of our liver transplantation patients. For all liver transplant recipients, patient demographics, clinical details, outcomes, and recurrence data were obtained. Disease-specific and disease-free survival along with patient and graft survival rates were calculated and compared with survival rates of non-HCC patients who underwent liver transplantation between January 1, 1990 and April 30, 2011. We also examined differences in wait time, stage of HCC, and survivals in the pre-MELD allocation era (before February 2002) and the MELD era.

Diagnosis

In the 1990s, HCC was most commonly diagnosed on the basis of cross-sectional imaging with CT, with or without biopsy. However, with the advancement of cross-sectional imaging in the last decade, HCC is usually diagnosed without biopsy, with gadolinium-enhanced MRI or triphasic CT. Before transplant listing, every patient had a complete evaluation and presentation at multidisciplinary transplantation conference. At our center, patients who have been down-staged from outside of Milan criteria were considered for exception points after regional review board approval. Patients listed with HCC had interval imaging studies (usually with chest CT and abdominal MRI or CT) every 3 months to assess for new or progressive disease. During the evaluation, a bone scan is performed to rule out evidence of metastatic disease. Positron emission tomography scanning is not routinely performed.

Locoregional therapy

Before 1998, TACE was not routinely performed at our center. Since 1998, TACE has been performed in patients with cross-sectional imaging diagnostic of HCC, with a bilirubin <2 mg/dL and well-compensated cirrhosis. A bilirubin up to 4 mg/dL was considered in selective cases. A mixture of chemotherapy (mitomycin and cisplatin) and ethiodized oil, followed by embolization with absorbable gelatin sponge was used most commonly for TACE. MRI follow-up was performed 6 weeks after TACE to assess for completeness of the ablation. If a complete response (no remaining tumor enhancement) was observed, interval surveillance was scheduled at 3 months. If there was evidence of residual disease, repeat TACE was performed. For tumors outside of Milan boundaries, the patient received repeated TACE in an attempt to down-stage to "within Milan." Radiofrequency ablation was performed in a smaller number of patients, as TACE is our preferred locoregional therapy. In cases where RFA was used, this was performed percutaneously and the antenna was introduced into the tumor under image guidance. Ablation was performed according to manufacturers' standard recommendations.

Transplantation technique

Standard piggy-back technique with caval preservation without the use of veno–venous bypass has been used since 1995 at our center. Our standard immunosuppression is a 3-drug regimen with tacrolimus, mycophenolic acid, and a short steroid taper. The explant was assessed in pathology and incidental HCC was defined when the diagnosis of HCC was not made on preoperative imaging. Post-transplantation surveillance every 6 months for 5 years with α-fetoprotein and MRI was the routine. Recurrence of HCC was treated depending on the location (see Results).

Statistical analysis

Overall patient survival and disease-specific and recurrence-free survival were traced using Kaplan-Meier curves. Curves were compared using log-rank test. For all comparisons, differences were considered statistically significant whenever p value was <0.05. Categorical variables were compared using Fisher's exact test. Student's *t*-test was used to compare continuous variables. Unless otherwise specified, results are expressed as mean $\pm$ SD or median with range.

RESULTS

There were 1,422 liver transplantations (1,227 adult and 195 pediatric) performed between January 1, 1990 and April 30, 2011. Two hundred and sixty-four patients had HCC (18.5%) and in 32 (12%) of those recipients, the