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Liver transplant offers a survival benefit over margin negative resection in patients with small unifocal hepatocellular carcinoma and preserved liver function

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ABSTRACT

Background. Studies comparing orthotopic liver transplantation to margin negative resection for patients with small unifocal hepatocellular carcinoma have not controlled for degree of cirrhosis.

Methods. The National Cancer Database was used to identify patients with preserved liver function (Model for End-stage Liver Disease score ≤ 12) who underwent orthotopic liver transplantation or margin negative resection for American Joint Committee on Cancer stage I hepatocellular carcinoma lesions < 3 cm between 2010 and 2013. Multivariable and Cox regression adjusting for age, demographics, comorbid disease burden, Model for End-stage Liver Disease score, tumor size, and operation were used to compare overall survival between cohorts.

Results. In the study, 241 (53%) patients underwent orthotopic liver transplantation. In addition, 219 (47%) underwent margin negative resection. On multivariable regression, patients having a Charlson comorbidity score ≥ 2 were more likely to undergo orthotopic liver transplantation, (odds ratio 1.94, $P = .03$). African American patients (odds ratio 0.44, $P = .02$), and patients of advanced age (odds ratio 0.92, $P < .001$) were more likely to undergo margin negative resection. Patients undergoing orthotopic liver transplantation had longer overall survival than those undergoing margin negative resection (median OS not reached versus 67.6 months, $P < .001$). Multivariable Cox regression identified surgical procedure as the only independent determinant of survival with margin negative resection conferring a nearly 3-fold increased risk of death (hazard ratio 2.86, $P < .001$).

Conclusion. Orthotopic liver transplantation offers a survival advantage relative to margin negative resection for patients with small unifocal hepatocellular carcinoma and preserved liver function. (Surgery 2017;160:XXX-XXX.)

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Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy in the United States with $> 30,000$ cases diagnosed annually.¹ Surgical therapy, either orthotopic liver transplantation (OLT) or surgical resection (LR), remains the cornerstone of curative treatment for patients with HCC. Most patients who develop HCC do so in the setting of cirrhosis and compromised liver function. LR in these patients is associated with increased risk of perioperative liver failure and death.² Patients with

advanced cirrhosis who have solitary tumors or multiple tumors and fall within established criteria for transplantation in the context of HCC are candidates for and best treated by OLT. A small subset of patients presenting with HCC, however, will present with solitary, early stage tumors and preserved liver function. For these patients with early stage disease and preserved liver function, OLT offers the potential advantage of treating the tumor and the underlying field defect in the remnant liver, thereby decreasing future risk of hepatocellular cancer. OLT is, however, more expensive than LR, requires long term immunosuppression, and uses a liver allograft that may be used in patients not amenable to LR, such as those with more significant cirrhosis or liver failure in the absence of cancer. These patients would be expected to do well with surgical resection, may gain significant survival benefit from resection and avoid years of immunosuppression and a potential need for

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repeat transplantation by having resection. In these cases, LR is an attractive therapeutic option and the optimal management of the patient subject to debate.³⁻⁶

Prior studies comparing OLT and LR for patients with early stage HCC have shown varying results regarding the merits of each approach and their effect on survival. Many of these studies have been limited by small sample size and heterogeneous patient populations. Most do not control for severity of underlying cirrhosis, or have included patients with multinodular tumors.⁶⁻¹⁰ Meta-analyses attempting to overcome limitations of sample size as well as study design, by including studies with intention-to-treat analyses, have shown a significant survival advantage for patients undergoing OLT or no difference in outcomes between OLT and LR, with findings often dependent on degree of liver dysfunction.^{3,4,11,12} A more recent intention-to-treat retrospective analysis of 217 patients with tumors <5 cm showed increased recurrence in the LR group, but similar long-term survivals for the 2 treatment modalities.^{5,7} For these reasons, optimal treatment for the patients presenting with HCC in the context of preserved liver function has not been defined definitively.

In the present study, we use the National Cancer Database (NCDB) to evaluate the potential benefit of OLT over LR for patients with HCC who would be candidates for either LR or OLT—those presenting with small solitary HCC in the context of preserved liver function. We compare survival profiles for patients undergoing OLT versus LR for solitary HCC with tumors <3 cm and biochemical evidence of preserved liver function (MELD <12).

Methods

Data source

Data was obtained from the NCDB, a joint program of the American College of Surgeons Commission on Cancer and the American Cancer Society. The database contains oncologic outcomes for patients treated in >1,500 accredited cancer centers and captures ~70% of new cancer diagnoses in the United States and Puerto Rico. The study design was reviewed by the NCDB and IRB exemption was obtained.

Study population

We queried the National Cancer Database to identify patients with preserved liver function (defined as a MELD score ≤12) who underwent margin negative LR or OLT for American Joint Committee on Cancer stage I HCC lesions <3 cm between 2010 and 2013. We restricted our query to patients treated after 2010, as that is the first year that components of the MELD score were first included in the database. Patients were excluded if they had metastatic disease, comorbid cancer diagnoses, or missing MELD scores.

Patient specific covariates included age (<45, 45–65, >65 years), race (White, Black, Hispanic, Asian, and other), socioeconomic status (low, middle, high), insurance status (private, Medicaid, Medicare, and uninsured), Charlson comorbidity index, MELD score, and tumor size. MELD score is calculated and reported as a discrete value in the NCDB participant user file from 2010 to present. The formula for determining MELD is:

$$\text{MELD} = 3.78 \times \ln[\text{serum bilirubin (mg/dL)}] + 11.2 \times \ln[\text{INR}] + 9.57 \times \ln[\text{serum creatinine (mg/dL)}] + 6.43$$

Statistical analysis

Descriptive statistics were performed using the χ^2 test for categorical variables and Student *t* test for continuous variables. Survival times were calculated from the time of diagnosis to the date of death

or last contact. Overall survival (OS) and 5-year survival were estimated using Kaplan-Meier analysis and compared using the log-rank test. Multivariable logistic regression was used to determine predictors of OLT versus LR, controlling for patient age, socioeconomic status, insurance status, race, and Charlson comorbidity index. Additionally, multivariable Cox proportional hazards models were used to compare outcomes after OLT and LR while adjusting for age, race, insurance status, comorbidity burden, tumor size, and MELD score. The variables included in the multivariable and Cox analyses were selected by the coauthors as the clinical variables available in the dataset that would, on the basis of the collective authors' prior experience and evidence in the literature, be most likely to have a causal relation to patient survival. Analyses were performed using SAS version 9.3 (SAS institute, Inc, Cary, NC).

Results

Patient demographics

Four-hundred sixty patients with preserved liver function, defined as a MELD score ≤12, underwent operative management for solitary HCC <3 cm. Patient demographics are shown in Table 1. Of the 460 patients identified, 241 (52%) underwent OLT and 219 (48%) underwent LR. Patients undergoing surgical therapy for HCC solitary HCC were more likely to be male (70%) than female. Sex ratios in the OLT (72.2%) and LR (73.1%) cohorts were statistically identical. The average age for the study population was 59.9 ± 6.2 years overall. Patients undergoing OLT were statistically younger (58.0 ± 6.6 years vs 61.9 ± 10.4 years, *P* < .001), were more likely to have a Charlson comorbidity index ≥2 (*P* < .001) and had higher MELD scores (Fig 1) than those undergoing LR.

OLT versus LR

Multivariable logistic regression adjusting for age, demographics, comorbid disease burden, MELD score and tumor size was performed to identify pretreatment clinical factors associated with choice of surgical therapy. Patients with a Charlson comorbidity index score ≥2, higher MELD scores, private insurance or Medicare were more likely to undergo OLT, whereas patients of African American descent and patients of advanced age were more likely to undergo resection (Table 2). There was no difference in tumor size between patients who underwent OLT versus LR (Fig 2). Pathologic staging

Table 1
Patient demographics.

	Resection (n = 219)	Transplantation (n = 241)	<i>P</i> value
Age, mean (STD)	61.9 (10.4)	58.0 (6.6)	<.001
Male, n (%)	160 (73.1)	174 (72.2)	.84
Race			<.001
Caucasian	129 (58.9)	195 (80.9)	
African American	32 (14.6)	24 (9.1)	
Other	58 (26.5)	22 (10.0)	
Socioeconomic status			.003
Low	74 (33.8)	93 (38.6)	
Middle	80 (36.5)	54 (22.4)	
High	65 (29.7)	94 (39.0)	
Insurance			<.001
Private	89 (40.6)	146 (60.6)	
Medicare	88 (40.2)	81 (33.6)	
Medicaid/Uninsured	42 (19.2)	14 (5.8)	
Charlson comorbidity index, n (%)			<.001
0	87 (39.7)	92 (38.2)	
1	85 (38.8)	78 (32.4)	
2+	47 (21.5)	71 (29.5)	
MELD, mean (STD)	8.09 (1.79)	9.86 (1.94)	<.001
Tumor size, cm, mean (STD)	2.19 (0.58)	2.41 (0.61)	.56

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