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# Surgical Treatment of Hepatocellular Carcinoma in North America: Can Hepatic Resection Still Be Justified?



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- BACKGROUND:** The incidence of hepatocellular cancer (HCC) is increasing dramatically worldwide. Optimal management remains undefined, especially for well-compensated cirrhosis and HCC.
- STUDY DESIGN:** This retrospective analysis included 5 US liver cancer centers. Patients with surgically treated HCC between 1990 and 2011 were analyzed; demographics, tumor characteristics, and survival rates were included.
- RESULTS:** There were 1,765 patients who underwent resection (n = 884, 50.1%) or transplantation (n = 881, 49.9%). Overall, 248 (28.1%) resected patients were transplant eligible (1 tumor <5 cm or 2 to 3 tumors all <3 cm, no major vascular invasion); these were compared with 496 transplant patients, matched based on year of transplantation and tumor status. Overall survivals at 5 and 10 years were significantly improved for transplantation patients (74.3% vs 52.8% and 53.7% vs 21.7% respectively,  $p < 0.001$ ), with greater differences in disease-free survival (71.8% vs 30.1% at 5 years and 53.4% vs 11.7% at 10 years,  $p < 0.001$ ). Ninety-seven of the 884 (11%) resected patients were within Milan criteria and had cirrhosis; these were compared with the 496 transplantation patients, with similar results to the overall group. On multivariate analysis, type of surgery was an independent variable affecting all survival outcomes.
- CONCLUSIONS:** The increasing incidence of HCC stresses limited resources. Although transplantation results in better long-term survival, limited donor availability precludes widespread application. Hepatic resection will likely remain a standard therapy in selected patients with HCC. In this large series, only about 10% of patients with cirrhosis were transplant-eligible based on tumor status. Although liver transplantation results are significantly improved compared with resection, transplantation is available only for a minority of patients with HCC. (*J Am Coll Surg* 2015;220:628–637. © 2015 by the American College of Surgeons)
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**Disclosure Information:** Nothing to disclose.

Presented at the Southern Surgical Association 126th Annual Meeting, Palm Beach, FL, November 30–December 3, 2014.

Received December 15, 2014; Accepted December 16, 2014.

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Hepatocellular cancer (HCC) is the fifth most common cause of malignancy worldwide and is one of the leading causes of cancer-related mortality. Liver transplantation (LT) and liver resection (LR) are the mainstays of surgical therapy for HCC, which occurs in the setting of chronic liver disease in the majority of patients (65% to 85%), limiting consideration of hepatic resection because of the risk of postoperative liver failure. Many patients also present with advanced stages of disease that often preclude consideration of LT.<sup>1</sup> For these reasons, only highly selected patients receive curative therapy for HCC; overall curative therapy occurs in 25% to 40% of American patients after presentation.<sup>1</sup>

Liver resection with partial hepatectomy is the first-line approach for all patients with resectable tumors in the

**Abbreviations and Acronyms**

DFS	= disease-free survival
HBV	= hepatitis B virus
HCC	= hepatocellular carcinoma
HCV	= hepatitis C virus
HR	= hazard ratio
LR	= liver resection
LT	= liver transplantation
MELD	= Model for End-Stage Liver Disease
OS	= overall survival

absence of chronic liver disease and is standard therapy in most areas of the world for patients with well-compensated cirrhosis and no evidence of portal hypertension. Liver resection is an attractive therapy because it is immediately available, allows for pathologic assessment of the tumor and background liver, and does not require use of an increasingly scarce donor liver that could be used for the overall transplant pool. A significant limitation of liver resection, regardless of underlying liver disease, is the high rate of intrahepatic recurrences of HCC in the remnant liver (60% to 80% at 10-year follow-up).<sup>1</sup>

Liver transplantation offers a more ideal treatment for HCC because it achieves removal of the tumor and also the potential sites of recurrence in the diseased liver. Interestingly, the liver is the only solid organ for which transplantation is considered appropriate in the setting of malignancy, albeit under highly selected circumstances. Survival rates after LT for HCC have improved significantly over the last 20 years through implementation of the Milan criteria, limiting patient selection to those with earlier stage disease. However, most presenting patients do not fulfill the Milan criteria.<sup>2-9</sup> Vascular invasion involving intrahepatic portal or hepatic veins, or evidence of metastases, preclude consideration of LT. Given the rigorous selection process and the ever-present scarcity of donor organs, LT as the treatment of choice for HCC is not feasible in a significant number of patients who present with HCC. The growing indications for LT further strain the already limited pool of usable organs, so resection as a primary modality for the treatment of HCC remains an attractive therapeutic approach for suitable patients.<sup>10-14</sup>

Outcomes after LR vs LT for the treatment of HCC must be approached with the understanding that baseline patient characteristics in these 2 groups are often different. Patients with normal background liver (ie, no fibrosis or cirrhosis) almost never undergo transplantation; those with decompensated cirrhosis and/or portal hypertension almost never undergo hepatic resection. Controversy exists regarding the treatment approach for

the subset of patients who have early stage malignancy and well-compensated cirrhosis or hepatic fibrosis, who may qualify for either therapy. Randomized controlled trials comparing these modalities have not been conducted and retrospective reviews are confounded by variations in patient and tumor characteristics, standard practice patterns, and waitlist dropout. Intention-to-treat analyses have supported LR as achieving similar overall survival as LT, with the advantage of being readily available and not subject to the limitations of organ shortages and wait times.<sup>13,15</sup> However, recurrence rates after LR far exceed those after LT, with a 5-year recurrence after LR at 69%, compared with 18% after LT.<sup>16</sup> Ten-year survival rates were higher for LT patients, at 49%, compared with 33% for LR.<sup>16</sup> A meta-analysis of 10 studies comparing LT and LR offered to patients with cirrhosis showed a significant 5-year survival advantage in the LT group (odds ratio [OR] 0.581, 95% CI 0.359 to 0.939;  $p = 0.027$ )<sup>17</sup>; however, when only those studies using intention-to-treat analysis were included, there was no survival advantage.

In this report, we examined our experience treating patients with HCC at 5 large US liver centers using both liver resection and transplantation. Only patients who underwent one of these surgical approaches were included in the analysis. We were especially interested in patients with background liver disease who might potentially qualify for either surgical therapy.

**METHODS**

Data were collected from patients with surgically treated HCC between January 1, 1990 and August 31, 2011 at 5 centers in the US in a de-identified fashion, after IRB approval from each center. Background demographic data, including type of liver disease if present, was collected for each patient. Hepatocellular carcinoma tumor nodule size and number were identified based on presentation imaging and also from the resected or explant specimen after liver resection and transplantation, respectively. Pathologic features, including the presence of fibrosis and cirrhosis, as well as the presence of lymphovascular invasion or major portal venous or hepatic venous invasion, were identified. General demographics, tumor characteristics, and survival outcomes were obtained. Patient age, sex, race, diagnosis of cirrhosis, hepatitis status, lab values and calculated clinical scores of liver function, and tumor characteristics were compiled for analysis.

A series of analyses were performed in order to optimize patient characterization and matching. In the first, patients undergoing hepatic resection with tumors meeting

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