Predictors of Microvascular Invasion in Patients with Hepatocellular Carcinoma Who Are Candidates for Orthotopic Liver Transplantation

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Microvascular invasion affects survival after orthotopic liver transplantation (OLT) for hepatocellular carcinoma (HCC). We sought to identify preoperative predictors of microvascular invasion in patients with HCC who were candidates for OLT. A cohort of 245 patients who underwent resection for HCC and fulfilled the criteria for OLT (i.e., single tumors ≤5 cm or no more than three tumors ≤3 cm) were identified from a multi-institutional database. Thirty-three percent of the patients had pathologic evidence of microvascular invasion. Thirty percent of patients with single tumors and 47% with multiple tumors had microvascular invasion (P = 0.04). Only 25% of patients with tumors smaller than ≤2 cm had microvascular invasion, compared to 31% and 50% with tumors greater than 2 to 4 cm or larger than 4 cm, respectively (P = 0.01). Tumor grade was highly correlated with microvascular invasion: 12% of patients with well-differentiated tumors had microvascular invasion, compared to 29% and 50% with moderately or poorly differentiated tumors, respectively (P < 0.001). The independent predictors of microvascular invasion were tumor size greater than 4 cm (odds ratio [OR], 3.0; 95% confidence interval [CI], 1.2 to 7.1), and high tumor grade (OR, 6.3; 95% CI, 2.0 to 19.9). Tumor size and grade are strong predictors of microvascular invasion. A tumor biopsy with pathologic grading at the time of pretransplant ablative therapy could improve selection of patients with HCC for OLT. (J GASTROINTEST SURG 2002;6:224–232.) © 2002 The Society for Surgery of the Alimentary Tract, Inc.

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Recent advances in the diagnosis of hepatocellular carcinoma (HCC) and perioperative management after resection have resulted in 5-year survival rates ranging from 17% to 53%. The presence of cirrhosis in the adjacent liver is often associated with diminished functional reserve, reduced resectability rates, and decreased overall and disease-free survival. In a recent analysis of 159 patients who survived 5 or more years after resection for HCC, the presence of moderate-to-severe fibrosis or cirrhosis was the most powerful predictor of death, overshadowing all other clinicopathologic factors. Recent studies suggest that orthotopic liver transplantation (OLT) is a viable alternative in patients with cirrhosis and HCC, particularly in patients with early-stage malignant disease. In a study by Bismuth et al., overall survival rates after resection and OLT were similar, but disease-free survival rates at 3 years were higher after OLT (46% vs. 27%), particularly in patients with tumors measuring less than 3 cm (83% vs. 18%). In a recent study by Mazzaferro et al., the 4-year overall and dis-
ease-free survival rates after OLT in patients with cirrhosis/HCC and early-stage disease (defined as one tumor ≤ 5 cm or no more than three tumors, none >3 cm) were 85% and 92%, respectively.9

Vascular invasion is a major determinant of outcome after resection or transplantation for HCC.10–14 None of the patients in the report by Mazzafero et al.15 had evidence of microvascular or major vascular invasion. In contrast, a recent study by Otto et al.16 showed that the 3-year survival rate after resection or transplantation for HCC was reduced by more than half in patients with vascular invasion. In another series of 71 patients with HCC treated with OLT, none of the patients who had microvascular invasion were alive at 3 years.16 Although magnetic resonance imaging and ultrasonography can detect tumor invasion of the major branches of the portal or hepatic veins 81% to 95% of the time,17–19 the presence of microvascular invasion cannot be established prior to resection or transplantation. Recent figures from the United Network of Organ Sharing indicate that although as many as 17,000 patients are currently awaiting liver transplants, fewer than 5000 figures from the United Network of Organ Sharing published prior to resection or transplantation. Recent changes due to mass effect.

### Statistical Analysis

Age, serum alpha-fetoprotein (AFP) level, and tumor size were treated as both continuous and dichotomous variables, using their respective medians as the breakpoints for statistical analyses. Because of sample size limitations, patients with poorly differentiated and undifferentiated tumors were combined into a single group. The associations between the continuous and the categorical clinicopathologic variables and microvascular invasion were analyzed using Mann-Whitney U tests and chi-square tests, respectively. Univariate prognostic factors (P ≤ 0.1) were entered into a stepwise logistic regression model to identify the independent predictors of microvascular invasion. Statistical significance was defined as a P value ≤ 0.05. SPSS 10.0 software package (SPSS Inc., Chicago, IL) was used for the statistical analyses.

### RESULTS

#### Patient and Tumor Characteristics

The demographic and clinicopathologic characteristics of the 245 patients in the study cohort are shown in Table 1. The median age was 62 years, and the ma-