Prognostic Factors for Hepatocellular Carcinoma Recurrence: Experience With 83 Liver Transplantation Patients


ABSTRACT

Introduction. Orthotopic liver transplantation (OLT) is a rational therapeutic option for early-stage hepatocellular carcinoma (HCC) providing a potential cure and improving survival.

Methods. This retrospective study of a longitudinal cohort used an electronic database collected prospectively from September 1997 to May 2010. The variables were gender, age (years), and alpha-fetoprotein (AFP) level (ng/mL). In explanted livers we observed: microvascular or macrovascular invasion, number of nodules and their largest size, Edmondson-Steiner histological differentiation, incidental tumor transarterial chemoembolization (TACE), Milan criteria, and previous down-staging.

Results. Five of 83 (6.0%) subjects including 68 (82%) males with a mean time to diagnosis of 9 months experienced tumor relapses. Mean patient age at HCC recurrence was 55.3 years for male and 44.6 years for female subjects. Vascular invasion was detected in 17/83 (20.5%) subjects, namely 2% of macrovascular invasion, and 52.5% with expanded Milan criteria due to an increased number and size of nodules in the explanted livers. An incidental tumor was observed in 29.5% of cases. Preoperative TACE treatment was performed in 13 (15.6%) patients. None of the patients who had a HCC recurrence had undergone TACE. AFP level at the time of recurrence was around 1,900 ng/mL. The predictive factor for mortality was nodule size ($P = .04$; hazard ratio $0.0269$; confidence interval [CI], 95% 0.0094–0.299).

Conclusion. Patients with relapses showed the worst survival and tumor size was a predictive factor for recurrence.

Orthotopic liver transplantation (OLT) is a rational therapeutic option for early-stage hepatocellular carcinoma (HCC) providing a potential cure and improving survival.

Their 75% 5-year survival rate, which is similar to that of cirrhotics without HCC, is achieved using the Milan criteria, namely, a single nodule $<5$ cm in diameter or up to 3 nodules $<3$ cm. Nevertheless, recurrence rates varying from 3.5%–26% remain. Several factors related to OLT have been implicated in tumor recurrence. Tumor size, histological grade of differentiation, both microvascular and macrovascular invasion, and alpha-fetoprotein (AFP) levels are currently the best predictors for recurrence after OLT. In the present study, we have described the outcomes in terms of tumor recurrence among a series of OLT for HCC by analyzing risk factors for recurrence: AFP levels, macrovascular and microvascular invasion, grade of differentiation, number and size of nodules, incidental nodules, and preoperative chemoembolization. Our aim was to verify the survival rate, relapse rate, and prognostic factors among OLT patients with HCC.

PATIENTS AND METHODS

This retrospective study of a longitudinal cohort used an electronic database collected prospectively from September 1997 to May 2010.
The inclusion criteria were as follows: age older than 18 years, OLT due to HCC, and survival of at least three months. All patients obeyed the Milan criteria according to current Brazilian law.

The diagnosis was confirmed using Doppler ultrasonography, abdominal computerized tomography (CT), and magnetic resonance imaging that showed arterial hypervascularization and washout in the portal venous phase associated with an AFP value >400 ng/mL before 2009 and >200 thereafter. The gold standard was liver biopsy. To exclude bone or pulmonary metastasis, we used scintigraphy and thoracic CT. Patients who did not meet the Milan criteria (expanded Milan criteria [EMC]) were treated by transarterial chemoembolization (TACE) or percutaneous alcohol injection. When down-staging was achieved the patient underwent transplantation.

The variables were gender, age (years), and AFP level (ng/mL). In the explanted liver we observed the presence of the following: microvascular or macrovascular invasion, number of nodules and their largest size, Edmondson-Steiner histological differentiation, incidental tumor, TACE before transplantation, Milan criteria, and down-staging. After OLT, patients were assessed at months 3, 6, 12, and 24 using AFP serum levels and hepatic ultrasonography. If tumor recurrence was suspected we performed abdominal CT.

Statistical Analysis

The Kaplan-Meier survival method was used to analyze survival rates with log-rank tests. Cox proportional hazard regression was used to evaluate predictive factors for tumor recurrence. A descriptive statistic to characterize patients with versus without recurrence used a nonparametric test (Kolmogorov-Smirnov). Statistically significant differences were considered when \( P < .05 \).

RESULTS

Among 480 patients who underwent OLT at our department, 83 had a preoperative diagnosis of HCC and 5 (6.0%) experienced a tumor relapse at a mean time to diagnosis of 9 months. These subjects included 68 (82%) males and 15 (18%) females. The mean patient age at HCC recurrence was 55.3 years for male and 44.6 years for female subjects. The patient characteristics are summarized in Table 1.

Vascular invasion was detected in 17/83 (20.5%), namely 2% with macrovascular or microvascular invasion (Fig 1). Among the cases 52.5% were classified as EMC due to the number and size of nodules in the explanted livers. An incidental tumor was observed in 29.5% of cases. Preoperative TACE was performed in 13 (15.6%) patients, none of whom displayed HCC recurrence.

The initial sites of recurrence were as follows: the liver (n = 3), the lung (n = 1) and multiple sites simultaneously (n = 1). AFP level at the time of recurrence was around 1,900 ng/mL. Overall cumulative and recurrence survival are shown in Figure 2. Twenty-eight millimeters was the cutoff size that differentiated the risk of recurrence. The predictive factor for mortality was the size of the nodules \( (P = .04; HR = 0.0269; 95\% \text{ confidence interval [CI], } 0.0094–0.299) \).

In all cases, the treatment of a recurrence was systemic chemotherapy with various schedules, including 1 patient treated with Sorafenib. In all 5 patients tumor recurrence was the cause of death with an average survival time of about 6 months.

DISCUSSION

Tumor recurrence is the cause of death among 3% to 26% of cirrhotic patients with HCC who undergo transplantation. In our study the recurrence rate was 6%, similar to that reported in the literature. The patients with recurrent
tumor showed a tendency to have greater vascular invasion \((P = .059)\) but not to have an incidental tumor \((P = .051)\). An important finding in our cohort was that the diameter of nodule size in the explanted liver was an independent predictor of HCC recurrence. The cutoff size to differentiate the risk of recurrence was 28 mm \((P = .001)\).

We observed a large number of cases with EMC (52.5%) in their explanted livers. These up-staged patients have also been observed by other authors\(^6,8\) who have suggested that there may be an argument against further extending the criteria for transplantation, as the staging accuracy may need to be improved first. In a previous study\(^7\) we reported 42.2% of recipients to be under-staged, showing low accuracy of radiographic criteria, as also observed in the literature.\(^6,8\)

Microvascular invasion is difficult to detect before HCC treatment even if recent better imaging procedures are used during patient evaluation. Although several studies have suggested that the presence of microvascular invasion is an independent factor predictive of poor survival after HCC resection, the significance of microvascular invasion is still unclear.\(^3\) In our study we observed just a tendency for this premise. It is important to define the degree of microvascular or macrovascular invasion, because some authors include wall, muscle vessel, or contiguity with the liver parenchyma, whereas others define microvascular invasion as lesions visible only on microscopic examination.\(^3,12\)

Shah et al\(^2\) related large tumor size and vascular invasion to be correlated with poor survival, but there is a complex interplay among liver function, portal hypertension grade, and host and tumor factors, which has been unclear. Although we observed a tendency to find this association, prognostic factors must be interpreted with caution.

Patients with incidental tumors showed similar survival rates as those with known tumors in previous reports,\(^2\) which is consistent with our findings.

AFP was not a good tumor marker, because the median level before transplantation was lower than the level at diagnosis for candidacy on the waiting list; some authors have searched for new HCC tumor markers.\(^9,12\)

We evaluated the results of our 5 patients with HCC recurrences after OLT by considering traditional and more recently proposed, prognostic factors for HCC recurrence. Other preoperative factors, such as tumor growth rate and biological aggressiveness, need to be assessed because they might predict the prognosis as well.

REFERENCES