



Ten-Year Experience With Liver Transplantation for Hepatocellular Carcinoma in a Federal University Hospital in the Northeast of Brazil

P.E.G. Costa^{a,*}, J.B.M. Vasconcelos^a, G.R. Coelho^a, M.A.P. Barros^a, B.A.F. Neto^a, D.S.R. Pinto^a, J.T.V. Júnior^b, F.G.S. Correia^c, and J.H.P. Garcia^a

^aDepartment of Surgery, Federal University of Ceará, Ceará, Brazil; ^bDepartment of Pathology, Federal University of Ceará, Ceará, Brazil; and ^cDepartment of Community Health, Federal University of Ceará, Ceará, Brazil

ABSTRACT

Hepatocellular carcinoma (HCC) is the most frequent and important primary liver tumor, with annual worldwide incidence of over 1 million cases, accounting for at least 500,000 deaths per year. The majority of cases of HCC occur in the setting of liver cirrhosis. In this retrospective, descriptive, and analytical study, between May 2002 and April 2012, 664 liver transplantations (LT) were conducted at a Federal University Hospital in the Northeast of Brazil, among which 140 LT were performed in patients with HCC. The tumor was more frequent in men with an average age of 56 years and infected with hepatitis C virus, many with a history of alcohol abuse. Alpha-fetoprotein was not useful in the diagnosis, and imaging methods have failed to diagnose the nodules in 19 patients (13.6%). Transarterial chemoembolization was the most-used bridging therapy to inhibit tumor growth for patients with HCC eligible for transplantation. The implementation of the Model for End Stage Liver Disease score in 2006 brought benefits to these patients. The rate of HCC recurrence after LT was 8.57% and occurred more often in the first 2 years after transplantation, with the liver graft being the most common site. Significant risk factors for recurrence were a long time on the LT waiting list, number of liver nodules over 3.5, and the presence of vascular invasion. In conclusion, LT for HCC leads to excellent long-term survival, with relatively few patients dying from tumor recurrence.

HEPATOCELLULAR carcinoma (HCC) is the fifth most common cancer in men and the eighth most common cancer in women worldwide, resulting in at least 500,000 deaths per year [1]. It is the most frequent and important of malignant liver tumors, with an annual worldwide incidence of more than 1 million cases. About 90% to 95% of tumors are associated with cirrhosis [2]. Nowadays, the high prevalence of alcohol and hepatitis C associated with the global epidemics of obesity and diabetes, strongly implicated with the development of nonalcoholic steatohepatitis (NASH), are recognized causes of cirrhosis and increased risk of development of HCC. Few cirrhotic patients with HCC are candidates for liver resection due to portal hypertension and the inadequate functional hepatic reserve with the risk of postoperative liver failure. Therefore liver transplantation (LT) is a highly effective treatment for HCC in patients within the Milan criteria [3]. However, recurrent HCC after LT occurs in 8% to 20% of cases and is the rate-limiting factor for long-term survival [4]. The aim of

this article is to present a 10-year experience with liver transplantation for HCC at the Walter Cantídio University Hospital (HUWC) of the Federal University of Ceará, in the Northeast of Brazil, analyzing survival and tumor recurrence risk factors.

PATIENTS AND METHODS

Between May 2002 and April 2012, 223 patients with HCC were treated at the outpatient liver transplant clinic at the HUWC, among which 140 patients underwent LT. Diagnoses were made according to the criteria established by the Brazilian National Transplant System and following the American Association for the Study of Liver Disease recommendations. In all patients, the

*Address correspondence to Paulo Everton Garcia Costa, Department of Surgery, Federal University of Ceará, Capitão Francisco Pedro Street 1290, Rodolfo Teófilo, CEP: 430370, Fortaleza, Ceará, Brazil. E-mail: pegcosta@uol.com.br

diagnosis of HCC was made using alpha-fetoprotein levels (AFP) and radiological examination: ultrasonography, computed tomography (CT), and/or magnetic resonance imaging (MRI). All patients underwent a chest CT and whole-body bone scintigraphy.

We performed a retrospective study of these 140 patients analyzing sex, age, etiology of cirrhosis, pretransplantation AFP level, Child-Turcotte-Pugh class, Model for End-Stage Liver Disease (MELD) score, transplant waiting list time (WLT), survival and HCC recurrence after transplantation. Analyzed in the liver explants were the number and size of nodules, histological differentiation of the tumor, and the presence of microscopic vascular invasion. Regarding the total of 223 patients treated, the type of treatment, deaths on the transplant waiting list, and number of patients who lost criteria for transplantation (dropout) were analyzed. Records with incomplete data were excluded. Statistical analysis was performed using the Statistical Package for Social Sciences software version 16.0 (SPSS, Inc., Chicago, IL, USA) and STATA version 11.1 (Stata Corporation, College Station, USA). The Shapiro-Wilk test was used to test the normality of each continuous variable, and χ^2 and Fisher exact tests were used to compare categorical variables. Multivariate analyses of risk factors associated with HCC recurrence after LT were performed. Also the Mann-Whitney test was used for independent samples, and Kaplan-Meier curves were used for survival. A *P* value of $<.05$ was considered significant.

RESULTS

In the 10-year experience with liver transplantation at the HUWC, 664 LT were performed and 223 patients were investigated with HCC. In 42 patients LT was contraindicated, either because patients presented with liver nodules outside the Milan criteria (29 cases) or because they had distant metastatic disease (2 cases) or macrovascular invasion (8 cases). Three patients underwent emergency surgery for tumor rupture with abdominal bleeding, and all died of postoperative hepatic failure. Six patients were removed from the LT list (dropout)—5 cases in the pre-MELD era as a result of disease progression by nodules outside the Milan criteria (3 cases), bone metastasis in the skull (1 case), and vascular invasion of the portal vein (1 case). Three records with incomplete data were excluded from the analysis.

Liver resection was proposed as a treatment for HCC in 13 patients, with 69.23% rate recurrence. Salvage LT was performed in these cases. We identified 28 deaths in patients with HCC awaiting LT. A total of 140 patients received LT, 19 in the pre-MELD era, and the remaining 121 LT were performed after implementation of MELD score in Brazil, in June 2006. Just 1 patient received an organ from a living donor (domino liver transplantation). Patients transplanted for HCC were predominantly men (82.1%). The mean age was 56.52 years, with a median of 59 years. Sixty percent of the patients were aged between 40 and 60 years. Hepatitis C virus infection was responsible for 53.57% of patients undergoing LT for HCC, either alone or associated with other causes, such as alcohol. Hepatitis B infection was associated with cirrhosis and HCC in 27 cases (19.2%), 9 cases occurred associated with delta virus.

Alcohol alone was responsible for 24 cases (17.14%). Regarding the diagnostic methods used, ultrasound (US) plus CT were performed in 48.6% of cases, US plus CT plus MRI in 22.9%, and US plus MRI in 10%. Biopsy was performed in just 3.6% of cases. Pretransplantation AFP levels were below 200 ng/mL in 85% of cases. In 19 patients (13.6%) the imaging methods revealed no tumor and HCC was incidentally discovered during detailed pathological examination of the explant livers. Regarding the classification of Child-Turcotte-Pugh, 104 (74.3%) of patients were Child class B or C. The mean MELD score was 16.22 points, with a median of 16 points. Forty patients underwent pretransplantation treatment with transarterial chemoembolization (TACE). Nine cases were successfully downstaged after treatment. Taking into consideration only the number of nodules in pathological findings, the mean was 2.53 nodules, with a median of 2 nodules. Regarding tumor size, the mean was 2.91 cm with a median of 2.55 cm. Ninety-five explanted cirrhotic livers were within the Milan criteria for LT (Table 1).

Regarding the histological differentiation, 67 cases (47.86%) were poorly differentiated. There was microvascular invasion in 20 explanted livers with HCC (14.29%). Patient and tumor characteristics are summarized in Table 2. HCC recurrence occurred in 12 patients (8.57%); furthermore, most cases occurred in the first 2 years after liver transplantation. Recurrent HCC was responsible for deaths in all cases (Table 3). The main recurrent sites were the graft in 8 cases (66.67%), followed by lung (16.67%) and bone (16.66%). In 1 case occurred recurrence in the adrenal gland associated with graft recurrence. There was no association between HCC recurrence and age, sex, cause of cirrhosis, Child class, MELD score, tumor size, and histological differentiation. When time of diagnosis was studied no effects were observed on recurrence rates of HCC. However, the analysis of the transplant WLT showed that a long WLT (above 7.8 months) was an important risk factor for HCC recurrence ($P = .0078$). The number of nodules produced an impact on recurrence rates. In the group of patients with HCC recurrence, a mean number of nodules was 4.5 nodules, with a median of 3.5 nodules. Therefore, when the number of nodes exceeded 3.5 nodules, higher HCC recurrence rates occurred (hazard ratio = 1.00842, 95% confidence interval (CI) 0.8402427 to

Table 1. Relationship Between Size and Number of Tumors in 140 Liver Explants

	Number and Size of Tumors	Frequency	%	Valid Percent	Cumulative Percent
Milan	1 nodule <5 cm	58	41.42	41.42	41.42
IN	≤3 nodules <3 cm	37	26.42	26.42	67.84
	1 nodule >5 cm	7	5.0	5.0	72.84
Milan	>3 nodules <3 cm	14	10.0	10.0	82.84
OUT	>3 nodules >3 cm	10	7.16	7.16	90.0
	3 nodules with 1 >3 cm	14	10.0	10.0	100.0
	Total	140	100.0	100.0	100.0

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