Incidental Hepatocellular Carcinoma: Risk Factors and Long-Term Outcome After Liver Transplantation

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ABSTRACT

Background. Orthotopic liver transplantation (OLT) currently represents the treatment of choice for early hepatocellular carcinoma (HCC). Preoperatively known HCC (pkHCC) is diagnosed via imaging methods before OLT or before HCC is found postoperatively in the liver explant, denoted as incidental HCC (iHCC). The aim of this study was a comprehensive analysis of the post-transplantation survival of patients with iHCC and the identification of risk factors of iHCC occurrence in cirrhotic liver.

Methods. We retrospectively reviewed 33 adult cirrhotic patients with incidentally found HCC, comparing them with 606 tumor-free adult cirrhotic patients with end-stage liver disease (group Ci) who underwent OLT in our center from January 1995 to August 2012. Within the same period, a total of 84 patients underwent transplantation for pkHCC. We compared post-transplantation survivals of iHCC, Ci, and pkHCC patients. In the group of cirrhotic patients (Ci + iHCC), we searched for risk factors of iHCC occurrence.

Results. There was no difference in sex, Model for End-Stage Liver Disease score, and time spent on the waiting list in either group. In the multivariate analysis we identified age >57 years (odds ratio [OR], 3.37; 95% confidence interval [CI], 1.75–8.14; $P < .001$), hepatitis C virus or alcoholic liver disease (OR, 3.89; 95% CI, 1.42–10.7; $P < .001$), and alpha-fetoprotein level >6.4 μg/L (OR, 6.65; 95% CI, 2.82–15.7; $P = .002$) to be independent predictors of iHCC occurrence. Both the 1-, 3-, and 5-year overall survival (OS) and the 1-, 3- and 5-year recurrence-free survival (RFS) differed in iHCC patients compared with the Ci group (iHCC: OS 79%, 72%, and 68%, respectively; RFS 79%, 72%, and 63%, respectively; vs Ci: OS = RFS: 93%, 94%, and 87%, respectively; $P < .001$).

Conclusions. The survival of iHCC patients is worse than in tumor-free cirrhotic patients, but similar to pkHCC patients. The independent risk factors for iHCC occurrence in cirrhotic liver are age, hepatitis C virus, or alcoholic liver disease etiology of liver cirrhosis and alpha-fetoprotein level.

ORTHOTOPIC liver transplantation (OLT) currently represents the treatment of choice in patients with early hepatocellular carcinoma (HCC) [1–4]. Despite the increasing quality of HCC screening methods in patients at risk, distinction of HCC from dysplastic nodules in cirrhotic liver before OLT remains challenging. Therefore, HCC detected incidentally in the liver explant after OLT, denoted

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Table 1. Methods of Local Ablative Therapy Used in Patients With Previously Known Hepatocellular Carcinoma (pkHCC)

Method of Local Ablative Therapy in pkHCC	No of Patients (24/81)
Radiofrequency ablation	2
Percutaneous ethanol injection	3
Transarterial chemoembolisation	19

as incidental HCC (iHCC), is not infrequent [5,6]. However, the data describing the characteristics of iHCC patients and their clinical outcomes are limited. The aim of the present study was a comprehensive analysis of post-transplantation survival of patients with iHCC in our center, comparison of their survival rate with patients with preoperatively known HCC (pkHCC), and identification of risk factors of iHCC occurrence in cirrhotic liver.

PATIENTS AND METHODS

From January 1995 to August 2012, 868 patients underwent OLT in our center. With a single-center waiting list, all of the study period was subjected to the same allocation criteria without the impact of the introduction of the Model for End-Stage Liver Disease (MELD) allocation system adopted in most centers after 2002. A total of 145 patients without underlying liver cirrhosis (acute liver failure, polycystic liver disease, other than HCC liver tumors, metabolic liver disease without cirrhosis) and children <18 years old were excluded from further evaluation. We retrospectively reviewed 639 adult cirrhotic patients with end-stage liver disease (ESLD) who had undergone OLT for liver cirrhosis with no preoperative evidence of tumor. All of the patients had an abdominal contrast-enhanced computerized tomographic (CT) scan at the time of enrollment for OLT and then were regularly screened for HCC by means of abdominal ultrasound during the waiting period. Of 639 adult patients with ESLD, 33 patients were found to have iHCC, and the remaining 606 cirrhotic patients were tumor free (group Ci). Incidental HCC was defined as HCC found postoperatively based on histopathologic examination of the liver explant. Within the same period, a total of 84 adult patients with pkHCC underwent transplantation, of whom 83 cirrhotic patients had ESLD and 1 HCC was diagnosed in noncirrhotic liver. Twenty-four patients with pkHCC with the tumor node >3 cm and the expected waiting period >3 months underwent local ablative therapy after enlistment (Table 1).

We compared post-transplantation survival of iHCC, Ci, and pkHCC patients. In the group of cirrhotic patients (Ci + iHCC), we searched for risk factors of iHCC occurrence.

Statistical Analysis

Data are presented as mean and standard deviation, median and range, or frequencies as appropriate. The *t* test or Mann-Whitney test was used for comparison of the means and chi-square test for comparison of frequencies. Significant univariate risk factors were entered into the logistic regression analysis. Cut points for continuous variables were obtained from receiver operating characteristic analysis. Survival analysis was performed with the use of the Kaplan-Meier method. Group survival curves were compared with the use of a log-rank test. A P value of <.05 was considered to be statistically significant throughout the study. Statistical analysis was performed with the use of JMP 10.0.0.

RESULTS

Demographic and clinical data of the patients are presented in Table 2. There was no difference in sex, MELD score, and time spent on the waiting list in both groups. The mean age was 57 ± 7 years in iHCC patients compared with 49 ± 11 years in the Ci group ($P < .001$). The mean Child-Pugh score was 10 ± 2 in iHCC patients vs 9 ± 2 in the Ci group ($P = .012$), and the median alpha-fetoprotein (AFP) level was 9.3 vs 4.0 μg/L, respectively ($P < .001$). Incidental HCC was predominantly found in patients transplanted for

Table 2. Patient Characteristics

Variable	Ci ($n = 606$)	iHCC ($n = 33$)	P Value
Men/Women	367/239 (60.6%/39.4%)	24/9 (72.7%/27.3%)	.164
Mean age at OLT (y)	49 ± 11	57 ± 7	<.001
Median AFP (μg/L, range)	4 (0.5–474)	9.3 (1.8–293)	<.001
Child-Pugh A	38 (6.3%)	0	.077
Child-Pugh B	291 (48.0%)	12 (36.4%)	
Child-Pugh C	277 (45.7%)	21 (63.6%)	
Mean Child-Pugh score at the time of enlistment on the WL	9 ± 2	10 ± 2	.012
Mean MELD score at the time of enlistment on the WL	16 ± 5	16 ± 4	.839
Median time on the WL (d, range)	84 (0–1331)	75 (5–413)	.819
Etiology of underlying disease			<.001
ALD	176 (29.1%)	17 (51.5%)*	
HCV	99 (16.3%)	11 (33.4%)*	
HBV	38 (6.3%)	3 (9.1%)	
Cholestatic	169 (27.9%)	0*	
Metabolic	27 (4.5%)	1 (3.0%)	
AIH	34 (5.6%)	0	
Cryptogenic	45 (7.4%)	1 (3.0%)	
Other (Budd-Chiari syndrome, Caroli disease, congenital dysplasia)	18 (3.0%)	0	

Abbreviations: Ci, liver cirrhosis without tumor; iHCC, incidental hepatocellular carcinoma; OLT, orthotopic liver transplantation; AFP, alpha-fetoprotein; WL, waiting list; MELD, Model for End-Stage Liver Disease; ALD, alcohol liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus; AIH, autoimmune hepatitis.
*$P < .05$.