Original Articles

Chirurgia (2013) 108: 446-450
No. 4, July - August

Outcome of Liver Transplantation for Hepatocellular Carcinoma – A Single Center Experience

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Rezumat

Rezultatele transplantului hepatic pentru carcinomul hepatocelular – experiența unui centru

Premize: Transplantul hepatic (LT) este o metodă terapeutică viabilă pentru pacienții cu ciroză hepatică și carcinom hepatocelular (HCC). Scopul studiului nostru a fost de a evalua particularitățile de stadializare clinico-patologică a pacienților transplantați hepatic pentru HCC în Centrul nostru precum și datele de supraviețuire fără recidivă și supraviețuire globală post LT la acești pacienți.
Material și metodă: În intervalul ianuarie 2006 – decembrie 2011 au for transplantați hepatic 38 pacienți cu HCC în centrul nostru. Au fost înregistrate standardizat datele demografice, clinice, de imagistică și anatomie patologică. Pentru a identifica predictori semnificativi ai recurenței tumorale sau ai decesului post transplant hepatic s-a realizat o analiză de supraviețuire utillizând modelul Cox.
Rezultate: În lotul nostru de studiu 18 pacienți (47.7%) au îndeplinit criteriile Milano. Intervalul mediu de supraveghere post LT a fost de 22 luni iar rata de recurență tumorală în acest interval 13.2%. Rata de supraviețuire fără recurență la 1 și respectiv 3 ani a fost de 85% și respectiv 74.3%. Rata de supraviețuire globală la 1 an și respectiv 3 ani a fost de 83.5% și respectiv 63.6%. Nu s-a identificat nici un predictor semnificativ al recurenței tumorale post LT luând în considerare 13 variabile standardizate. Drept predictori independenți ai decesului post LT în lotul nostru de studiu au fost identificate următoarele variabile: prezența diabetului zaharat (p=0.001), prezența a mai mult de 3 noduli tumorali (p=0.03) și recurența tumorii post LT (p=0.03).
Concluzii: Pe durata studiului nostru, rata de recurență a HCC post LT a fost de 13.2%. Diabetul zaharat, prezența a mai mult de 3 noduli tumorali și recurența tumorii post LT au fost identificați drept predictori independenți ai decesului post LT pentru HCC.

Cuvinte cheie: transplant hepatic, carcinom hepatocelular, recurența tumorală, supraviețuire, factori predictivi

Abstract

Background &Aims: Liver transplantation (LT) is a promising treatment for patients with liver cirrhosis associated with hepatocellular carcinoma (HCC). The aim of our study was to evaluate our experience regarding the clinical and pathological staging of HCC in patients who underwent LT, as well as recurrence free and overall survival.
Methods: From January 2006 to December 2011, 38 patients with diagnosis of HCC, underwent LT in our Center. Demographic, clinical, imaging and pathologic information were recorded. A Cox proportional hazards survival analysis was performed in order to identify significant predictors of tumor recurrence and patient's death after LT.
Results: Eighteen patients (47.4%) in our study group were

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within Milan criteria. The mean follow-up was 22 months and the recurrence rate of HCC after LT was 13.2%. The 1, 3-year recurrence free survival rates were 85%, 74.3% respectively. The 1 and 3-year overall survival rates were 83.5% and 63.6% respectively. No significant predictor for HCC recurrence was identified in our study group by survival analysis, taking into account 13 different variables. As independent predictors of patient's death after LT for HCC however, the presence of diabetes mellitus (p=0.001), presence of more than 3 HCC nodules (p=0.03) and tumor recurrence after LT (p=0.03) were identified by multivariate Cox proportional hazards survival analysis.

Conclusion: In our cohort HCC recurrence rate after LT was 13.2%. Diabetes mellitus, presence of more than 3 HCC nodules and HCC recurrence were significant predictors of poor overall survival after LT.

Key words: liver transplantation, hepatocellular carcinoma, tumor recurrence, survival, predictive factors

Introduction

Hepatocellular carcinoma (HCC) is one of the commonest cancers worldwide and its incidence is increasing. In Europe there are important epidemiological differences between countries and geographic areas. Romania has a high rate of incidence and a high rate of liver cancer-related death in a Top 20 rank of European countries. In Romania there are approximately 2000 new liver cancer cases/year, HCC being the 12th most common cancer and the 7th cause of cancer mortality (1,2).

In non-cirrhotic patients diagnosed with HCC liver resection is taken into account with good results (3). Liver transplantation (LT) is now considered the best treatment option for patients with HCC and liver cirrhosis (4). Mazzafero et. al introduced in 1996 the so-called Milan criteria, demonstrating that patients fulfilling these criteria have a 5 - year survival rate comparable to patients undergoing LT for non-malignant indications (5-8). It is currently accepted that, as we go further beyond Milan criteria with the indications for LT, there is a higher chance of tumor recurrence and patient's death (the so-called "Metro ticket principle") (9,10). However, a substantial proportion of patients not fulfilling the Milan or University of California at San Francisco (UCSF) criteria has been found to survive longer than expected after LT (11,12). Therefore, it seems reasonable to attempt further reduction of unnecessary dropouts arising from the strict application of narrow HCC selection criteria.

In Romania, the Liver Transplantation Programme, with only one Center performing LT nationwide, is characterized by a long waiting time and a high mortality while on the waiting list (13), so graft allocation policies and graft-recipient matching are critical in order to optimize the procedure's results. Given the organ shortage and the increasing number of HCC patients on our waiting list, the adopted strategy of our Center is to use marginal grafts (with graft steatosis, macroscopic appearance of the liver, older age, high vasopressor requirements, long ischemia times, with a risk of transmitting an infection or malignancy to the recipient, hypernatremia, prolonged ICU stay) (14) in HCC recipients.

The Romanian liver transplantation program from Fundeni Clinical Institute has started in the year 2000. All types of current surgical techniques including living related liver transplantation have been performed here, and the results are comparable with those from other international centers (15-17). We report here our experience with regard to LT performed for HCC during a 6 years period.

Materials and Methods

During the period January 2006 – December 2011 242 LT were performed in our center. Only patients with histologically proven HCC were included in the analysis. The patients with potential live liver donors were considered and evaluated individually, taking into account the age, the severity of the underlying liver disease, AFP value and HCC characteristics at time of presentation. The Milan criteria (single tumor $\leq$ 5 cm or 2-3 tumors $<$ 3 cm) were not strictly applied especially in the case of live donor liver transplantation (LDLT) as previously described (18,19). Bridging treatment (RFA, TACE) was performed in selected cases, taking into account the long waiting time of our waiting list.

Following LT, careful pathologic study of all liver explants was performed and analysis of tumor characteristics was made according to pathologic findings. Number of tumors, maximal tumor diameter, intrahepatic lobar distribution of tumors were recorded. After LT, patients were followed-up by abdomen and chest CT scans and AFP value every 6 months during the first two years and yearly thereafter. Tumor recurrence and patient death were recorded for survival analysis following LT. Univariate and multivariate Cox regression analyses were performed. A p value $<$ 0.05 was considered statistically significant.

Results

During the study period 38 patients underwent LT for HCC. Patient's characteristics at the moment of LT are presented in *Table 1*. The vast majority of patients had a viral infection as etiology of the underlying liver disease, HCV and HBV+HDV co-infections being the most frequently encountered. Transplanted patients had an advanced BCLC stage in 29% of cases. Overall patients were transplanted outside Milan Criteria in 52.6% of cases. Six patients had radiofrequency ablation prior to LT and 8 patients underwent TACE as bridging therapy. LDLT for HCC was performed in 10 patients.

Mean follow-up after LT was 22 months. In our study cohort, HCC recurrence was encountered in 5 patients

Table 1. *Patient characteristics*

Patient characteristic	Value ± SD or percentage of patients
Age (years)	52.3 ± 7.7
Male gender (%)	78.9%
Etiology of liver disease	
HCV	38.2%
HBV	20.6%
HBV+HDV	38.2%
Ethanol	2.9%
MELD score at LT	13.3 ± 4.6
MELD > 18 points	16%
AFP value (ng/ml)	278 ± 676.5
AFP > 100	38.5%
AFP > 300	23.1%
BCLC Classification	
Early stage	15.8%
Intermediate stage	55.3%
Advanced stage	29%
Number of nodules	
1	44.4%
2	23.5%
3	11.8%
multiple	20.6%
Diameter of the largest nodule (cm)	4.8 ± 2.7
Edmondson-Steiner Grading	
good	32.4%
moderate	52.9%
poor	14.7%
Patients within Milan criteria (%)	47.4%
Patients with bridging therapies (%)	
RFA	15.7%
TACE	21%
Living donor liver transplantation (%)	26.3%

(13.2%), after a mean time period of 14.5 months. All 5 patients died during the follow-up. Kaplan Meier survival curves for disease free and overall survival after LT for HCC are presented in *Fig. 1*. One year and 3-year disease free survival rates were 85% and 74.3% respectively. One year and 3-year overall survival rates were 83.5% and 63.6% respectively.

As predictive factors for tumor recurrence or patient's death after LT the following variables were included in the univariate Cox survival analysis: BMI >25kg/m^2, recipient's age >60 years, HCV etiology of liver disease, presence of diabetes mellitus, Child-Pugh class C, MELD >18 at LT, AFP > 300 ng/ml, BCLC stage C/D, transplantation outside Milan criteria, more than 3 HCC nodules, maximum tumor diameter >5 cm, poorly differentiated tumor histology, LDLT. No significant predictor for HCC recurrence was identified in our study group by the survival analysis. As predictors of patient's death after LT for HCC, the presence of diabetes mellitus (p=0.004), presence of more than 3 HCC nodules (p=0.02) and tumor recurrence after LT (p=0.04) were statistically significant. The multivariate Cox proportional hazards survival analysis indicated all three factors as independent predictors of patient's death after LT (*Table 2*).

Discussion

We report here our single center experience with regard to the outcome of LT for HCC. Disease free survival and overall survival are comparable to other published series (18,20-24). No significant predictors for HCC recurrence were identified by survival analysis in our study group, possibly due to the low

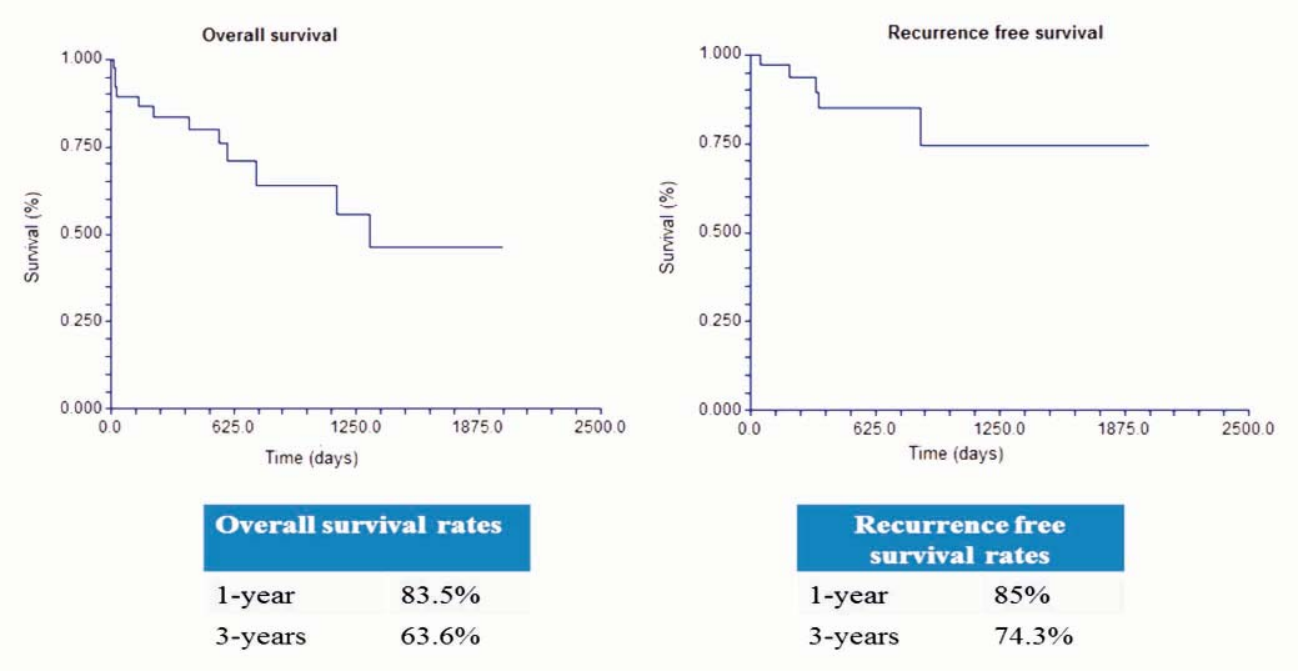

Figure 1. *Overall and recurrence free survival following LT for HCC*

Table 2. *Independent predictors of patients' death after LT for HCC (multivariate Cox proportional hazards regression)*

Variable	Regression coefficient (B)	Exp (B)	p-value
Presence of diabetes mellitus	3.5	33.4	0.001
Recurrence of HCC after LT	1.8	6.1	0.03
More than 3 HCC nodules at LT	1.5	4.6	0.03

number of patients in our series. Multivariate survival analysis indicated, however, three independent predictors of patient's death after LT for HCC: presence of diabetes mellitus, tumor recurrence and the presence of more than 3 nodules at the moment of LT. Many published series have investigated predictors of outcome of LT for HCC (25-27) and some of them have been addressed also in our study. Milan criteria are generally accepted as optimal for selection of HCC candidates for LT. Expanded criteria including UCSF, Kyoto, Asian, "up-to-seven" criteria have been proposed in order to recruit more candidates for LT, with good results in experienced referral centers (5,9,10,28,29). However 10-20% of patients experience HCC recurrence even if these criteria are met (27,30-32). In our study group, although the majority of patients (52.6%) were transplanted outside Milan criteria, this was not a significant predictor of tumor recurrence or patient's death. In a large meta-analysis, both Milan criteria and UCSF criteria, although significant in the univariate analysis, have failed to reach statistical significance in the multivariate analysis as predictors of outcome following LT for HCC (18). Also, a more recent paper (33), including a total of 23 studies, showed that there is no significant difference in patient survival rate and tumor recurrence free rate of patients with expanded Milan criteria compared to those patients that followed the Milan criteria.

However, the presence of more than 3 tumor nodules was a significant predictor of poor survival post-LT in our study, similar to other published series (20). Chan et al. (20) identified 11 predictors of recurrence free survival by univariate analyses, but only tumor number and presence of microvascular invasion were independent predictive factors by multivariate analysis. It has been suggested that the difficulty to estimate the correct number of nodules < 2 cm in cirrhotic livers can reduce the predictive value of this parameter [14] and could explain its infrequent use in multivariate analyses (34,35).

Several centers have reported strategies for increasing the donor pool in order to meet the growing demand for organs. In particular, the use of extended criteria donors (ECDs) has been increasing, and this has been associated with adequate outcomes (36,37). After the year 2009, in our Center, 11.2% were marginal grafts compared to 2% before 2009 (personal unpublished data). An appropriate combination of recipient disease (eg. HCC non-HCV Child A/B cirrhosis) and donor characteristics, even ECDs, can be associated with reasonable survival rates as demonstrated by our cohort. In contrast, use of ECDs in patients with HCC and diabetes mellitus may be associated with a poor graft function and decreased patient survival.

In a recent paper analysing a large retrospective cohort of 342 consecutive patients who underwent LT for HCC the relationship between obesity, diabetes mellitus and HCC recurrence was examined (38). BMI $> 30 kg/m^2$ was an independent predictor of poor overall survival by multivariate Cox survival analysis and patients with diabetes had worse outcome in the univariate analysis. In a multicenter study (39) realized on data obtained from The National Institute of Diabetes and Digestive and Kidney Diseases LT Database on 798 transplant recipients was shown that both pretransplant and posttransplant diabetes (whether new onset or sustained diabetes) and HCC at LT, were predictors of overall mortality beyond 1 year after LT. Similarly, in our patient cohort the presence of diabetes mellitus was an independent predictor of poor survival following LT for HCC.

In summary, the analysis of our patient cohort emphasizes the importance of tumor burden and diabetes mellitus as predictors of outcome following LT for HCC. Accurate preoperative staging and good long term control of diabetes mellitus and its metabolic complications could improve the outcomes of LT for HCC. High-risk donor livers can be safely used in expanded HCC criteria recipients if appropriate individual donor-recipient matching is adopted.

Acknowledgement

This paper has been supported by the research grant PD 23/2011.

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