Liver transplantation for hepatocellular carcinoma: is zero recurrence theoretically possible?

Sabine Irtan, Louise Barbier, Claire Francoz, Federica Dondéro, François Durand and Jacques Belghiti

Clichy, France

BACKGROUND: Hepatocellular carcinoma (HCC) recurrence remains a key issue after liver transplantation. This study aimed to determine a subgroup of HCC patients within the Milan criteria who could achieve a theoretical goal of zero recurrence rates after liver transplantation.

METHODS: Between 1999 and 2009, 179 patients who received liver transplantation for HCC within the Milan criteria were retrospectively included. Analysis of the factors associated with HCC recurrence was performed to determine the subgroup of patients at the lowest risk of recurrence.

RESULTS: Seventy-two percent of the patients received a bridging therapy, including 54 liver resections. Eleven (6.1%) patients recurred within a delay of 19±22 months and ultimately died. Factors associated with recurrence were serum alpha-fetoprotein level >400 ng/mL, satellite nodules, poor differentiation, microvascular invasion and cholangiocarcinoma component. Recurrence rates decreased from 6.1% to 3.1% in patients without any of these factors.

CONCLUSIONS: Among HCC patients within the Milan criteria, selecting patients with factors based on histology would allow tending towards zero recurrence, and prior histological assessment by liver biopsy or resection may be essential to rule out poorly differentiated tumors, microvascular invasion, and cholangiocarcinoma component.

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KEY WORDS: hepatocellular carcinoma; liver transplantation; neoplasm recurrence; survival rate

Introduction

Liver transplantation (LT) remains the best treatment of early hepatocellular carcinoma (HCC) developed on chronic liver disease. However, results are hampered by the long-lasting imbalance between an increasing number of candidates and graft shortage.[1] The unsatisfactory initial results of LT for clinically advanced HCC, together with the observation that small HCCs incidentally detected during surgery have an extremely low risk of post-LT recurrence, led to propose strict selection criteria.[2, 3] In this setting, the Milan criteria (single tumor ≤5 cm or 2-3 tumors ≤3 cm, in the absence of macroscopic vascular invasion) were adopted as guidelines for LT with the aim to achieve a 5-year overall survival rate of 70% and a recurrence rate of below 15%.[3] Increasing experience showed that some HCC patients beyond the Milan criteria, without vascular invasion or poorly differentiated HCC, demonstrated acceptable rates of survival and recurrence.[4] Several studies[5, 6] showed that high or rapidly increasing alpha-fetoprotein (AFP) levels were associated with increased recurrence. A study from a Toronto team showed that patients beyond the Milan criteria with AFP level >400 ng/mL and well differentiated HCC could achieve excellent results after LT.[7] On the other hand, even restricting LT for patients within the Milan criteria fails in completely ruling out post-LT for HCC recurrence[8] since some small HCCs have aggressive features such as poorly differentiated grade or vascular invasion.[9] In a context of graft shortage, a policy to select HCC candidates with post-LT outcomes similar to non-HCC recipients, while eliminating recurrence risk factors, should theoretically be considered. The

Author Affiliations: Department of Hepato-Pancreato-Biliary Surgery (Irtan S, Barbier L, Dondéro F and Belghiti J) and Department of Hepatology (Francoz C and Durand F), Beaujon Hospital, Assistance Publique-Hôpitaux de Paris, University Denis Diderot-Paris VII, Clichy, France

Corresponding Author: Louise Barbier, MD, Department of Hepato-Pancreato-Biliary Surgery, Beaujon Hospital, 100 Boulevard du Général Leclerc, 92118 Clichy Cedex, France (Tel: +33-1-4087-5895; Fax: +33-1-4087-1724; Email: louise.barbier@bjn.aphp.fr)

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aim of this study was therefore to determine a subgroup of patients within the Milan criteria, which could theoretically achieve a zero recurrence rate after LT.

Methods

Patient's selection and study population

All patients who underwent LT at Beaujon Hospital for HCC within the Milan criteria From 1999 to 2009 and survived at least 3 months after LT were included in the study. Data of the patients were retrospectively collected from their clinical files. The endpoint was HCC recurrence after LT and all factors were associated with recurrence.

Diagnostic modalities

HCC diagnosis was based on two imaging studies including triple-phase computed tomography scan and/or magnetic resonance imaging showing both early hyperenhancement and delayed hypo-enhancement, in accordance with the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines of Management of Hepatocellular Carcinoma.[10] Patients with lesions within the Milan criteria had a solitary liver nodule not exceeding 5 cm in diameter, or 2 or 3 tumors not exceeding 3 cm in diameter, without detectable vascular invasion.[3] Patients underwent regular ultrasound scan every 3-month to check that they remained within the Milan criteria.

Pathological variables

Tumor size, number, differentiation grade, vascular invasion, and satellite nodules were analyzed systematically. Vascular invasion was identified either as macroscopic, when vessel invasion was visible on gross examination, or as microscopic, when it was visible only under microscopy. Satellite nodules were defined as tumors ≤2 cm in size and located at ≤2 cm from the main tumor. Cholangiocarcinoma differentiation (CC component) was reported when present. Combined HCC-CC was diagnosed according to histological findings of both tumor types.

Immunosuppression

A triple immunosuppressive regimen consisting of mycophenolate mofetil, tacrolimus and steroids has been routinely used since 1999. In the present study, patients were free of steroids at 4-month post-LT, and no patients were subjected to systematic mammalian target of rapamycin inhibitors.

Post-LT follow-up

Follow-up included liver function tests, serum AFP and ultrasound examination every 3 months. Elevation of AFP and/or presence of nodule at ultrasound led to perform triple-phase computed tomography or magnetic resonance imaging. HCC recurrence was defined as appearance of a new lesion with radiological features of HCC. Additional imaging techniques (bone scan, magnetic resonance imaging) were used if necessary.

Statistical analysis

Qualitative variables were expressed as number (percentage), and quantitative data as mean±standard deviation (SD). Overall survival was defined as time from surgery to death (excluding 90-day postoperative mortality). Disease-free survival was defined as time from surgery to the first recorded evidence of recurrence. Cumulative overall survival and disease-free survival rates were determined using the Kaplan-Meier method, and bivariate analysis of survival was performed using the log-rank test. Significance was considered at the P value of 0.05. All analyses were performed with the GraphPad Prism® 5.0c for Mac OS X (GraphPad Software, Inc., USA).

Results

Among the 851 patients who underwent LT in our unit between 1999 and 2009, 258 (30.3%) had HCC on chronic liver disease and 218 (84.5%) had lesions within the Milan criteria before LT. Of these patients, 179 survived more than 3 months and comprised the study population.

Morphological evaluation before LT revealed that 96 (53.6%) patients had a single nodule with a mean diameter of 23.2±9.3 mm (range 30-50) and 72 had 2 or 3 nodules with a mean of 1.5±0.7 nodules each patient. Demographic data, etiology of underlying liver disease and MELD score are shown in Table 1. In this series, 129 (72.1%) patients received bridging therapy including transarterial chemoembolization (45 patients), percutaneous ethanol injection (14), radiofrequency ablation (55), and liver resection (54). Thirty-nine patients received two or more of these treatments in combination before LT. The mean duration on the waiting list was 5.7±5.3 months with no significant difference between the groups with and without bridging therapy (6.1±5.2 vs 4.7±5.5 months, respectively).

LT was performed using full grafts in 139 (77.7%) patients and partial grafts in 40 (22.3%), including grafts from living donors (23 patients) and from split procedures (17). Pathological examination of the explanted liver showed that 132 (73.7%) patients remained within the Milan criteria. Among the 47 patients beyond the Milan criteria histologically, 15 had a tumor size >50 mm and 23 had 4 nodules or more, and 9 patients had 2 or 3 nodules, with one nodule >30 mm. Ten patients (5.6%)