

LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA IN PATIENTS BEYOND THE MILAN BUT WITHIN THE UCSF CRITERIA

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Abstract

Aim: Liver transplantation (LT) is the best therapy for early hepatocellular carcinoma (HCC) in cirrhosis. Whereas the Milan criteria are routinely applied, the University of California San Francisco (UCSF) criteria are occasionally considered in large-volume transplant centers. Poor information is available about the real "gain" in patients' outcome when extending the listing criteria from Milan to UCSF.

Patients and Methods: Out of 100 patients transplanted for HCC at our center, 4 patients exceeding the Milan but meeting the UCSF criteria were identified. Data of these patients were analysed for the purposes of this study.

Results: Three of them are currently alive after a median follow up of 57 months. One patient died 20 months post-transplant as a result of complications from hepatitis. Of the three who are alive, one underwent surgery for HCC recurrence 81 months post transplant. The remaining two have no evidence of tumor 56 and 57 months post transplant, respectively.

Conclusion: Our results, as well as the reviewed literature, showed that only a small percentage of transplanted HCC patients can be classified as "beyond Milan-within UCSF". These patients seem to have acceptable overall, as well as recurrence free survivals. Large-volume patients' series, intention- to-treat analysis based on the radiological findings and multi-center prospective studies are required, in order to further explore the outcome of patients "beyond Milan-within UCSF" criteria and in order to better define the risk/benefit ratio of a potential expansion of the current listing criteria.

Key words: Liver transplantation; hepatocellular carcinoma; Milan criteria; UCSF criteria; tumor recurrence.

Abbreviations: AFP = alpha fetoprotein; HCC = hepatocellular carcinoma; LT = liver transplantation; UCSF = University of California San Francisco; UICC = Union International Contre le Cancer

INTRODUCTION

Liver transplantation (LT) is considered to be the treatment of choice for early hepatocellular carcinoma (HCC) in patients with end-stage liver failure. Over

the past years, the Milan criteria introduced by Mazzafero et al. [10] in 1996 became "the gold standard" in the evaluation and candidacy of patients with HCC for LT. Together with the worldwide adoption of these criteria, the 5-year survival rates for such patients increased to 60-80% [1, 3, 7]. However, the Milan criteria have been expanded in some major LT centers, especially when performing live donor LT for HCC, and the outcomes have remained somewhat comparable, especially regarding patient survival [5, 8-9, 14-15]. Although some studies have addressed comparison of survivals according to the Milan and the University of California San Francisco (UCSF) criteria [4, 15], only limited information is available about the real benefit for patients when expanding the listing criteria from the Milan to the UCSF guidelines.

The purpose of this study was to retrospectively evaluate the results after LT for HCC patients beyond the Milan but within the UCSF criteria based on pathological findings.

PATIENTS AND METHODS

Data corresponding to patients transplanted for HCC were reviewed. All potential candidates were evaluated for LT by means of abdominal ultrasonography, thoraco-abdominal computed tomography and/or magnetic resonance imaging, angiography, and bone scintigraphy. Liver biopsies were not performed on a routine fashion to confirm the diagnosis of HCC. Serial levels of alpha fetoprotein (AFP) were obtained prior to and after LT. Both deceased donor and live donor LT recipients were considered.

All explanted livers were examined micro and macroscopically (1 cm thick slices) by a single pathologist. Tumor classification was made according to the 6th Edition of the Tumor-Node-Metastasis System of classification of the Union International Contre le Cancer (UICC) [11]. Nodules with a preoperative diameter less than 2 cm and no confirmatory biopsy that showed complete necrosis after bridging treatments were not considered as tumors as stipulated by the Barcelona criteria [2]. Of special interest was the classification of the HCC according to both the Milan criteria (single tumor ≤ 5 cm, 2-3 tumors none of them > 3 cm, no vascular invasion) and the UCSF criteria (single tumor < 6.5 cm, 2-3 tumors none of them

>4.5cm or total diameter \leq 8cm, no vascular invasion).

No patient was lost to follow-up. Follow-up studies included CT scans of the abdomen and chest, and measurement of AFP levels every 4 months during the first year after transplantation, every 6 months during the second year, and yearly thereafter. No patients received adjuvant chemotherapy after LT.

RESULTS

Out of 100 patients transplanted for HCC at our center during the last 7 years, 4 patients exceeding the Milan but meeting the UCSF criteria were identified. All four recipients underwent first-time LT, receiving a graft either from a deceased (n = 2) or a live donor (n = 2). Recipient characteristics were age of 59 years, waiting time to LT of 45 days, MELD score of 8, and AFP serum levels of 144 ng/ml (median values, Table 1). Two patients were Child-Turcotte-Pugh class A, one class B, and one class C. Two patients had a diagnosis of cirrhosis secondary to hepatitis B infection, one secondary to hepatitis C infection, and one due to autoimmune hepatitis. One patient underwent transarterial chemoembolization as tumor bridging treatment prior to LT. Three patients had no tumor specific treatment prior to LT.

Pathological evaluation of the explanted liver showed multifocal tumors without vascular invasion in all patients. Hepatocellular carcinomas were moderately differentiated in 3 patients and poorly differentiated in one patient. In all cases, HCC characteristics were beyond the Milan criteria, classified as 2-3 tumor lesions > 3cm, but within the UCSF criteria, classified as 2-3 tumor lesions with a total diameter \leq 8cm (Table 1). In all instances HCCs were UICC stage II.

All patients experienced uneventfully postoperative courses. Three of them are alive after a median follow up of 57 months. One patient died 20 months post-transplant due to liver failure from hepatitis B re-infection. One patient was re-evaluated for LT 4.8 years post transplant because of recurrent hepatitis C cirrhosis. Two years after the new listing and 6.7 years post transplant, this patient developed HCC recurrence in the mediastinal lymph nodes. He was treated surgically and removed from the "Eurotransplant" waiting list. Currently, he remains in stable clinical condition, 5 months postoperatively and 86 months post transplant. The remaining 2 patients enjoy an excellent quality of life without evidence of HCC recurrence, 56 and 57 months post transplant, respectively.

DISCUSSION

Although the UCSF criteria proposed by Yao et al. in 2001 [15] has led to frequent and prolonged discussions, only few published studies report on the results after LT according to both the Milan and UCSF criteria. Hwang et al. [4] reviewing the Korean multi-center experience in LT for HCC reported a 3-year-survival for patients who met and exceeded the Milan criteria of 89.9% and 66.4% after deceased donor LT (p=0.181) and 91.4% and 62.6% after live donor LT (p<0.001), respectively. When the UCSF criteria were applied, the 3-year-survival rates within and beyond

Table 1. Patients' characteristics. All patients were in UICC stage II, having HCCs without vascular invasion.

| Patients | Age (years) | Diagnosis | Technique | AFP (ng/ml) | Bridging | MELD | Tumor characteristics | Total tumor diameter | Grading | Recurrence | Follow-up (months) |
|----------|-------------|-----------|-----------|-------------|----------|------|----------------------------|----------------------|----------|----------------------------------|--------------------|
| 1. | 63 | HBV | DDLT | 3000 | TACE | 5 | 2 lesions, 3.5cm+2.5cm | 6cm | Poor | No | 20† |
| 2. | 64 | HCV | DDLT | 174 | No | 8 | 3 lesions, 4.5cm+1cm+1.5cm | 7cm | Moderate | Mediastinal LN 81 months post LT | 86 |
| 3. | 55 | HBV | LDLT | 114 | No | 8 | 2 lesions, 4cm+2.5cm | 6.5cm | Moderate | No | 57 |
| 4. | 44 | AUCI | LDLT | 87 | No | 24 | 2 lesions, 4cm+1.5cm | 5.5cm | Moderate | No | 56 |

HBV: Hepatitis B viral cirrhosis; HCV: Hepatitis C viral cirrhosis; AUCI: cirrhosis due to autoimmune hepatitis; DDLT: Deceased donor LT; LDLT: Live donor LT; TACE: transarterial chemoembolization; MELD: Model for End Stage Liver Disease; LN: Lymph nodes

the UCSF criteria were 88.1% and 66.8% after deceased donor LT ($p=0.199$) and 90.6% and 58.5% after live donor LT ($p<0.001$), respectively [4]. In the series of Yao et al. [15] 2- and 5-year survival rates were 81% and 72% respectively, for the patients who met the Milan criteria, versus 71% and 57%, respectively for patients exceeding them ($p = 0.12$). According to the UCSF criteria, 2- and 5-year survival rates were 82% and 75% respectively for patients within the criteria, and 50% after 2 years for patients beyond these criteria (5-year survival was not achieved at the time of the study).

Leung et al. [6] presenting a multicenter study in LT outcome for early-stage HCC reported 10 out of a total of 144 patients evaluated (7%) who had tumors that exceeded Milan criteria but met the UCSF criteria postoperatively. This group of 10 patients had a 2-year survival rate of 77.1%. Two patients died, one at 3 months and the other at 22 months after deceased donor LT. Of the remaining 8 patients, median follow-up time was 32 months (range 6.6-73.5 months). In the series of Yao et al. [15] 14 patients "exceeding the Milan but meeting the UCSF criteria" were identified. Two patients died, one from posttransplant lymphoproliferative disease 5 months after LT, and the other from rapid recurrence of HCC 2 months after LT associated with extrahepatic metastases. Unfortunately, no further information about the specific survival of these patients is provided [15].

In the present study we have performed our analysis according to the pathological findings of the explanted liver, due to the well-known inaccuracy of the radiological HCC evaluation, especially for tumors $<2\text{cm}$ [12], and the corresponding discrepancies between radiological and pathological HCC staging [5, 6, 12]. The high rates of reported "incidental HCCs" in a recent systematic review of the literature correspond probably to high rates of "undetected HCCs" during the waiting time to LT, [13], a situation that contributes to the further deviation from the radiological Milan criteria. Furthermore, the purpose of our study was to evaluate the oncological findings and the real outcome of HCC patients according to one or the other criteria.

Our results, in accordance to the results of Leung et al., showed that only a small percentage of HCC patients undergoing LT have tumor findings "beyond Milan but within UCSF criteria" (4% and 7%, respectively). Furthermore, these patients have an acceptable long survival (median of 57 months in our series, 32 months in the report of Leung et al.), and probably not necessarily a higher recurrence rate (only one patient in our series, 81 months post transplant, with no corresponding information available from Leung et al.). These findings could add some encouraging information in the discussion about the possible expansion of the Milan to the UCSF criteria. However, large-volume patients' series, intention- to-treat analysis based on the radiological findings and multi-center prospective studies are required, in order to further explore the outcome of patients "beyond Milan but within UCSF" and in order to better define the risk/benefit ratio of a potential expansion of the current listing criteria.

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