ORIGINAL ARTICLE

# Expanded Criteria for Liver Transplantation in Patients with Cirrhosis and Hepatocellular Carcinoma

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Orthotopic liver transplantation (OLT) selection for patients with hepatocellular carcinoma (HCC) is a matter of debate. The Milan criteria (MC) have been largely adopted by the international community. The main aim of this study was to evaluate the survival rates and recurrence probabilities of a new proposal for criteria (up to 3 tumors, each no larger than 5 cm, and a cumulative tumor burden ≤ 10 cm). Patients with cirrhosis and HCC included on the waiting list (WL) from 1991 to 2006 were retrospectively analyzed. Outcomes in patients who had tumors within and beyond the MC were compared. The survival analysis was done (1) with the intention-to-treat principle and (2) among transplanted patients. A total of 281 patients were included in WL. Twenty-four cases did not undergo OLT (a dropout rate of 8.5%); all but 1 case had tumors within the MC. Of the 257 transplanted patients, 26 had tumors beyond the MC in the pre-OLT evaluation. Based on the intention-to-treat analysis, the 5-year survival was 56% versus 66% in patients who had tumors within and beyond the MC, respectively ($P$ = 0.487). Among transplanted patients, the 5-year survival was 62% versus 69%, respectively ($P$ = 0.734). Through multivariate analysis, microvascular invasion was an independent prognostic factor of poor survival ($P$ = 0.004). The recurrence probabilities at 1 and 5 years were 7% versus 12% and 14% versus 28% in patients with tumors within and beyond the MC, respectively ($P$ = 0.063). The multivariate analysis demonstrated that both poorly differentiated tumors ($P$ < 0.001) and microvascular invasion ($P$ < 0.001) increased the risk of recurrence. The expansion to up to 3 nodules, each up to 5 cm, and a cumulative tumor burden ≤ 10 cm did not result in a reduction of survival in comparison with patients who had tumors within the MC. ***Liver Transpl 14:1449-1460, 2008.*** © **2008 AASLD.**

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Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, causing more than 1 million deaths annually.[1] Up to 90% of HCCs are associated with underlying cirrhosis, and the main risk factors are chronic infections by hepatitis B virus (HBV) and hepatitis C virus (HCV), chronic alcohol abuse, and hereditary hemochromatosis.[2] Historically, the diagnosis of HCC was almost always made in advanced stages, and the treatment options did not demonstrate satisfactory results. Currently, however, many patients are diagnosed at an early stage with preserved liver function. In addition, there are optional treatments that can potentially have an impact on survival.[3] Basically, there are 2 alternatives with a

**Abbreviations:** AFP, alpha-fetoprotein; BMI, body mass index; CHILD, Child-Pugh-Turcotte score; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ITT, intention-to-treat analysis; MC, Milan criteria; N/A, not available; OLT, orthotopic liver transplantation; PEI, percutaneous ultrasound-guided ethanol injection; RAFE, radiofrequency ablation; RR, relative risk; TACE, transarterial chemoembolization; UCSF, University of California, San Francisco; WL, waiting list.

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curative intention: liver resection and orthotopic liver transplantation (OLT).

OLT is the optimal treatment of HCC because it results in the widest possible resection margins for the cancer, removes the underlying cirrhotic liver, and restores the liver function. The international transplantation community has largely adopted an approach to OLT for HCC based on the Milan criteria (MC), by which, according to an empirical rule for selection of patients (a solitary liver nodule not exceeding 5 cm or at most 3 nodules, with none larger than 3 cm), a survival rate above 70% in 5 years is reached, and the risk of recurrence is relatively low (about 10%).[4] However, the application of this selection criteria might lead to the exclusion of patients who otherwise would benefit from this procedure.[5] Because of these limitations, several recent studies have evaluated whether more liberal criteria for tumor staging could be adopted without significant impairment of patient survival or tumor recurrence.[6-19] Presently, however, there is no consensus yet on recommending the expanded criteria as the standard of care.[20,21]

In view of these uncertainties, we have considered OLT for patients with cirrhosis with up to 3 tumors, with none larger than 5 cm, and a cumulative tumor burden $\leq$ 10 cm without evidence of macrovascular invasion, extrahepatic spread, or nodal involvement. The main aim of this study was to evaluate whether the outcome (patient survival and tumor recurrence) is impaired when our expanded selection criteria are adopted. More specifically, we aimed at (1) comparing the survival rate in patients who had tumors within and beyond the MC on the basis of the intention-to-treat principle, (2) comparing the survival rate and the recurrence probabilities in transplanted patients who had tumors within and beyond the MC, and (3) analyzing potential risk factors associated with these endpoints.

## PATIENTS AND METHODS

Medical records of all transplanted patients during the period between 1991 and 2006 at the Hospital Universitario La Fe (Valencia, Spain) were retrospectively analyzed. During this period, 1337 OLTs were performed. Three hundred thirty-six patients (25%) had HCC. After the exclusion of 79 patients [incidental tumors (n = 44), noncirrhotic livers (n = 2), retransplantation (n = 24), previous resection (n = 4), and pre-OLT evaluation demonstrating more than 3 tumors or a single tumor larger than 5 cm (n = 5)], 257 patients were analyzed. Among these, 26 (10%) had HCC beyond the MC on the basis of radiology. During the same period, 24 patients with similar characteristics included on the waiting list (WL) did not undergo OLT because of tumor progression or death (a dropout rate of 8.5%); all but 1 case had tumors within the MC. Preoperative patient and tumor characteristics, perioperative outcomes, pathologic data, tumor recurrence, and survival rates were prospectively collected from a research database. The survival rate was analyzed on the basis of the intention-to-treat principle. In addition, among transplanted patients, we compared the outcomes of (1) those with tumors within the MC versus those with tumors beyond the MC on the basis of radiology and (2) those with tumors within our expanded selection criteria and those with tumors beyond our expanded selection criteria (up to 3 tumors, with none larger than 5 cm, and a cumulative tumor burden $\leq$ 10 cm) on the basis of pathology.

The algorithm for the management of patients with HCC was as follows. Patients with HCC were first considered for resection. If this procedure was not judged to be appropriate (liver function impairment, central location of the tumor, and significant portal hypertension assessed by the presence of varices, splenomegaly, a platelet count less than 100,000/mm$^3$, or a history of ascites), patients were considered for OLT. Patients with prior liver resection were excluded from analysis in order to avoid confusion related to "salvage OLT" because this procedure was always performed with a curative intention.

All candidates for OLT underwent abdominal Doppler ultrasonography and serum alpha-fetoprotein (AFP) testing. Nodules suspicious for HCC were investigated with abdominal magnetic resonance imaging, computed tomography scanning of the abdomen, brain, and chest, bone gammography, fine-needle puncture aspiration, and/or biopsy when necessary. Arteriography with lipiodol and histopathologic confirmation were routinely performed before the Barcelona 2000 conference.[22] Since then, biopsy has been performed only in cases in which diagnostic uncertainty persists after a thorough radiologic assessment. Doppler ultrasonography was performed every 3 months after tumor diagnosis in order to identify the cases that had to be excluded from the WL.

During the WL period, patients were treated with alternative approaches. In general, percutaneous ultrasound-guided ethanol injection (PEI) was considered for patients with a single tumor up to 3 cm, and transarterial chemoembolization (TACE) was used for cases with more than 1 nodule or a single tumor larger than 3 cm. In the last 6 years, radiofrequency ablation (RAFE) has been performed in a few cases. In patients with advanced liver disease, no treatment was undertaken.

The presence of microscopic vascular invasion and tumor differentiation were determined on the basis of the resected specimens. Tumor differentiation was assessed with Edmonson-Steiner grading.[23] Liver dysfunction was classified according to the Child-Pugh-Turcotte score.[24]

During the post-OLT period, the following procedures were routinely performed to rule out tumor recurrence: serum AFP plus abdominal ultrasound every 3 months, chest radiography every 6 to 12 months, and computed tomography scans of the chest and abdomen annually. Patients were followed up until August 1, 2007 or up to their last visit; survivors were followed up for at least 8 months.

Immunosuppressive therapy consisted of cyclosporine or tacrolimus and prednisone. In patients with renal

dysfunction, mycophenolate mofetil, basiliximab, or both were generally used.

### Predictive Factors of Tumor Recurrence and Patient Survival

The following factors were analyzed as predictors of tumor recurrence: (1) demographics [age at transplantation, sex, time and treatment on the WL (yes/no), etiology of the liver disease (HCV/non-HCV), and body mass index], (2) pre-OLT tumor-related variables [MC (within/beyond), serum AFP, and lobar involvement (unilobar/bilobar)], and (3) histopathologic data [microvascular invasion (yes/no), differentiation grade (poor/moderate or good), and lobar involvement (unilobar/bilobar)]. The same variables were applied to evaluate the association with patient survival plus the variable "tumor recurrence" (yes/no).

### Statistical Analysis

Categorical variables were compared with the chi-square test or Fischer's exact test when indicated. Continuous variables were expressed as means ± standard deviation and compared through the Student *t* test. When a normal distribution could not be assumed, continuous variables were summarized as medians and ranges and compared with the Mann-Whitney test. A receiver operating characteristic curve was used to identify the most sensitive and specific cutoff points for continuous variables. Probability curves of survival and recurrence were calculated according to the Kaplan-Meier method and compared with the log-rank test. Variables with $P < 0.1$ were selected for multivariate Cox or logistic regression. A value of $P < 0.05$ was considered significant. The calculations were done with the SPSS for Windows 13.0 package.

## RESULTS

### Patients' Baseline Features

Baseline features are summarized in Table 1. Of the 257 transplanted patients, 207 were men, with a median age of 60 years (range, 27-69). The etiology of cirrhosis was HCV in 188 cases (associated with alcohol abuse in 30), HBV in 17 cases, alcohol in 45 cases, and other causes in 7 cases. The median body mass index was 26 kg/m$^2$ (range, 17-36). According to the Child-Pugh-Turcotte classification, 118 patients corresponded to group A, 93 corresponded to group B, and 46 corresponded to group C. Two hundred thirty-one patients had tumors within the MC and 26 had tumors beyond the MC on the basis of radiology. In the group beyond the MC, 23 patients had 2 nodules, and 3 cases had 3 nodules. The median tumor burden was 6 cm (range, 4.5-10) in the expanded group (Table 2).

During the WL period, PEI, TACE, and RAFE were used in 27, 172, and 7 patients, respectively. Fifty-one patients did not receive any type of treatment. Of the

**TABLE 1. Characteristics of the 257 Patients Undergoing Liver Transplantation**

| Variable | Value |
|---|---|
| Baseline characteristics | |
| Age (years) | 60 |
| Range | 27–69 |
| Male (%) | 207 (80.5) |
| Days on WL | 54 |
| Range | 1–641 |
| Treatment while on WL (%) | |
| No | 51 (19.8) |
| TACE | 172 (66.9) |
| PEI | 27 (10.6) |
| RAFE | 7 (2.7) |
| Cirrhosis etiology (%) | |
| HCV | 158 (61.4) |
| HCV + alcohol | 30 (11.6) |
| Alcohol | 45 (17.6) |
| HBV | 17 (6.7) |
| Others | 7 (2.7) |
| CHILD (%) | |
| A | 118 (45.9) |
| B | 93 (36.2) |
| C | 46 (17.9) |
| BMI (kg/m$^2$) | 26 |
| Range | 17–36 |
| Follow–up (months) | 38 |
| Range | 0–180 |
| AFP (ng/mL) | 19 |
| Range | 1.2–24,444 |
| Radiologic evaluation (%) | |
| Unilobar | 212 (82.5) |
| Bilobar | 45 (17.5) |
| Tumor findings (%) | |
| 1 up to 5 cm | 173 (67.4) |
| 2 to 3 up to 3 cm | 58 (22.5) |
| Expanding the Milan criteria | 26 (10.1) |
| Pathologic evaluation (%) | |
| Unilobar | 206 (80.1) |
| Bilobar | 51 (19.9) |
| Underestimation of the established criteria: up to 3 tumors up to 5 cm and tumor burden ≤ 10 cm (%) | |
| Yes | 46 (17.8) |
| No | 211 (82.2) |
| Microvascular invasion (%) | |
| Yes | 25 (9.7) |
| No | 208 (80.9) |
| No data | 24 (9.4) |
| Differentiation degree (%) | |
| Poor | 8 (3.1) |
| Moderate | 62 (24.3) |
| Good | 111 (43.2) |
| Total necrosis | 30 (11.6) |
| No data | 46 (17.8) |

**Abbreviations:** AFP, alpha-fetoprotein; BMI, body mass index; CHILD, Child-Turcotte-Pugh score; HBV, hepatitis B virus; HCV, hepatitis C virus; PEI, percutaneous ethanol injection; RAFE, radiofrequency ablation; TACE, transarterial chemoembolization; WL, waiting list.

**TABLE 2. Characteristics of the Tumors Among Patients Included in the Group Beyond the Milan Criteria**

| Case | Number of Nodules | Size of Nodules (cm) | Tumor Burden (cm) | According to UCSF Criteria | Case | Number of Nodules | Size of Nodules (cm) | Tumor Burden (cm) | According to UCSF Criteria |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 1.5 and 4 | 5.5 | Within | 14 | 2 | 3 and 4 | 7 | Within |
| 2 | 2 | 3 and 5 | 8 | Beyond | 15 | 2 | 2 and 4 | 6 | Within |
| 3 | 2 | 4 and 5 | 9 | Beyond | 16 | 2 | 2 and 5 | 7 | Beyond |
| 4 | 2 | 1 and 3.5 | 4.5 | Within | 17 | 2 | 3 and 5 | 8 | Beyond |
| 5 | 2 | 1 and 5 | 6 | Beyond | 18 | 2 | 2 and 5 | 7 | Beyond |
| 6 | 2 | 2 and 4.5 | 6.5 | Within | 19 | 2 | 2 and 5 | 7 | Beyond |
| 7 | 2 | 2 and 4 | 6 | Within | 20 | 2 | 1.5 and 3.5 | 5 | Within |
| 8 | 2 | 1 and 4.5 | 5.5 | Within | 21 | 2 | 1.5 and 5 | 6.5 | Beyond |
| 9 | 3 | 1, 1.5, and 5 | 7.5 | Beyond | 22 | 3 | 1.5, 2, and 4 | 7.5 | Within |
| 10 | 2 | 1 and 4 | 5 | Within | 23 | 2 | 1.5 and 4 | 5.5 | Within |
| 11 | 2 | 2 and 4 | 6 | Within | 24 | 2 | 1 and 4 | 5 | Within |
| 12 | 2 | 2 and 4 | 6 | Within | 25 | 2 | 1.5 and 4 | 5.5 | Within |
| 13 | 2 | 2 and 4 | 6 | Within | 26 | 3 | 1, 4, and 5 | 10 | Beyond |

**Abbreviations:** UCSF, University of California, San Francisco.

**TABLE 3. Cause and Time of Death for the 257 Patients Undergoing Liver Transplantation**

| Cause of Death | First Month | 1 to 3 Months | 3 to 12 Months | >12 Months |
|---|---|---|---|---|
| Sepsis | 11 | 7 | 4 | |
| HCV infection | | | 4 | 25 |
| HCC recurrence | | | 10 | 19 |
| Chronic rejection | | | 3 | |
| Cardiovascular diseases | 1 | 1 | | 1 |
| De novo tumor | | | | 4 |
| Others | 5 | 1 | | 4 |

**Abbreviations:** HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

181 tumors analyzed in order to assess the degree of differentiation, 8, 62, and 111 were poorly, moderately, and well differentiated, respectively. Microvascular invasion was found in 25 cases (10.7%). The pre-OLT radiologic evaluation underestimated the established criteria in 46 cases (17.8%). Total tumor necrosis was described in 30 cases; all but 6 had been treated with TACE during the WL period.

## Patient Survival

The median follow-up for the whole study group was 38 months (range, 0-180). Among survivors, the median follow-up was 58 months (range, 8-180). One hundred patients died during the follow-up period (39%), with a mortality rate of 10% within the first 3 months. HCV and tumor recurrence were the most common causes of death (29 cases in each group; Table 3).

Patients' survival at 1, 3, and 5 years after OLT was 83%, 69%, and 63%, respectively. When we considered those excluded from the WL (intention-to-treat analysis), survival rates were 75%, 63%, and 57%, respectively. This difference was not statistically significant ($P = 0.121$). The univariate analysis showed that HCV cirrhosis, AFP levels higher than 20 ng/mL, microvascular invasion, poorly differentiated tumors, bilobar involvement based on pathology, and tumor recurrence were significantly associated with poor survival. In the multivariate analysis, only microvascular invasion independently reduced survival rates [$P = 0.004$, hazard ratio (HR) = 3.02, 95% confidence interval (CI) = 1.44-6.34; Table 4].

When we considered only variables that could be assessed in the pre-OLT period, HCV cirrhosis, serum AFP higher than 20 ng/mL, and poorly differentiated tumors were associated with reduced survival in the univariate analysis. HCV cirrhosis ($P = 0.035$, HR = 2.00, 95% CI = 1.05-3.83) and poorly differentiated tumors ($P < 0.001$, HR = 6.43, 95% CI = 2.64-15.66) remained statistically significant in the multivariate analysis (Table 5).

## Tumor Recurrence

Recurrence occurred in 33 cases (13%) at a median follow-up of 11 months (range, 3-100). Liver and bone were the most frequent sites (11 cases each), followed by lung (n = 6), peritoneum (n = 2), nodes (n = 1), skin (n = 1), and adrenal glands (n = 1). Recurrence

**TABLE 4. Analysis of Factors Associated with Patient Survival and Tumor Recurrence After Orthotopic Liver Transplantation for Hepatocellular Carcinoma**

| | *P* | |
|---|---|---|
| Univariate Analysis (n = 257) | Survival | Recurrence |
| Age | 0.834 | 0.554 |
| Sex | 0.107 | 0.711 |
| Time on WL | 0.123 | 0.454 |
| Treatment while on WL: yes/no | 0.896 | 0.150 |
| Cirrhosis etiology: HCV/non-HCV | 0.020 | 0.518 |
| BMI | 0.118 | 0.173 |
| AFP | 0.041 | 0.917 |
| Tumor criteria: within Milan/beyond Milan | 0.734 | 0.074 |
| Radiologic evaluation: unilobar/bilobar | 0.695 | 0.157 |
| Pathologic evaluation: unilobar/bilobar | 0.094 | <0.001 |
| Microvascular invasion: yes/no | <0.001 | <0.001 |
| Differentiation degree: poor/moderate or good | <0.001 | <0.001 |
| Recurrence: yes/no | <0.001 | N/A |
| | *P* | |
| Multivariate Analysis (n = 257) | Survival | Recurrence |
| Cirrhosis etiology: HCV/non-HCV | 0.061 | N/A |
| AFP | 0.335 | N/A |
| Tumor criteria: within Milan/beyond Milan | N/A | 0.080 |
| Pathologic evaluation: unilobar/bilobar | 0.499 | 0.931 |
| Microvascular invasion: yes/no | 0.004 | <0.001 |
| Differentiation degree: poor/moderate or good | 0.056 | <0.001 |
| Recurrence: yes/no | 0.184 | N/A |

**Abbreviations:** AFP, alpha-fetoprotein; BMI, body mass index; HCV, hepatitis C virus; N/A, not available; WL, waiting list.

**TABLE 5. Analysis of Factors Associated with Patient Survival and Tumor Recurrence Using Only Variables That Can Be Assessed Before Orthotopic Liver Transplantation**

| | *P* | |
|---|---|---|
| Univariate Analysis (n = 257) | Survival | Recurrence |
| Age | 0.834 | 0.554 |
| Sex | 0.107 | 0.711 |
| Time on WL | 0.123 | 0.454 |
| Treatment while on WL: yes/no | 0.896 | 0.150 |
| Cirrhosis etiology: HCV/non-HCV | 0.020 | 0.518 |
| BMI | 0.118 | 0.173 |
| AFP | 0.041 | 0.917 |
| Tumor criteria: within Milan/beyond Milan | 0.734 | 0.074 |
| Lobe: unilobar/bilobar | 0.695 | 0.157 |
| Differentiation degree: poor/moderate or good | <0.001 | <0.001 |
| | *P* | |
| Multivariate Analysis (n = 257) | Survival | Recurrence |
| Cirrhosis etiology: HCV/non-HCV | 0.035 | N/A |
| AFP | 0.476 | N/A |
| Tumor criteria: within Milan/beyond Milan | N/A | 0.896 |
| Differentiation degree: poor/moderate or good | <0.001 | <0.001 |

**Abbreviations:** AFP, alpha-fetoprotein; BMI, body mass index; HCV, hepatitis C virus; N/A, not available; WL, waiting list.

occurred in 18 patients during the first year (54%). After recurrence was diagnosed, the median survival was 6 months (range, 1-47). Recurrence probabilities at 1, 3, and 5 years were 7%, 14%, and 16%, respectively. Univariate analysis showed tumors beyond the MC, bilobar involvement on the basis of pathology, microvascular invasion, and poorly differentiated tumors as significant predictors of tumor recurrence. In

**TABLE 6. Characteristics of the 257 Patients Who Had Tumors Within and Beyond the Milan Criteria on the basis of Radiology**

| Characteristic | Within the Milan Criteria (n = 231) | Beyond the Milan Criteria (n = 26) | *P* |
|---|---|---|---|
| Pre-OLT Variables | | | |
| Age (range) | 59 (27–69) | 59 (47–67) | 0.680 |
| Male (%) | 183 (79.2) | 24 (92.3) | 0.125 |
| Days in WL | 57 | 46.5 | 0.561 |
| Range | 1–641 | 5–339 | |
| Treatment while on WL (%) | | | |
| No | 50 (21.6) | 1 (3.8) | 0.035 |
| Yes | 181 (78.4) | 25 (96.2) | |
| Cirrhosis etiology (%) | | | |
| HCV | 167 (72.3) | 21 (80.8) | 0.485 |
| Non-HCV | 64 (27.7) | 5 (19.2) | |
| CHILD (%) | | | |
| A | 104 (45.2) | 14 (53.8) | 0.793 |
| B | 84 (36.5) | 8 (30.8) | |
| C | 42 (18.3) | 4 (15.4) | |
| BMI ($kg/m^2$) | 26.6 ± 3.6 | 26.1 ± 3.3 | 0.502 |
| AFP (ng/mL) | 18.4 | 51.4 | 0.102 |
| Range | 1.2–24,444 | 1.7–6550 | |
| Lobe (%) | | | |
| Unilobar | 197 (85.3) | 15 (57.7) | 0.002 |
| Bilobar | 34 (14.7) | 11 (42.3) | |
| Pathologic features | | | |
| Underestimated criteria | | | |
| No | 191 (82.7) | 16 (61.5) | 0.014 |
| Yes | 40 (17.3) | 10 (38.5) | |
| Microvascular invasion (%) | | | |
| No | 188 (81.3) | 20 (76.9) | 0.302 |
| Yes | 21 (9.2) | 4 (15.4) | |
| | 22 (9.5) | 2 (7.7) | |
| No data | | | |
| Differentiation degree (%) | | | |
| Poor | 6 (2.6) | 2 (7.7) | 0.183 |
| Moderate/good | 157 (67.9) | 16 (61.5) | |
| No data | 68 (29.5) | 8 (30.8) | |
| Lobe (%) | | | |
| Unilobar | 195 (84.4) | 11 (42.3) | <0.001 |
| Bilobar | 36 (15.6) | 15 (57.7) | |
| Recurrence (%) | | | |
| No | 205 (88.7) | 19 (73.1) | 0.056 |
| Yes | 26 (11.3) | 7 (26.9) | |

**Abbreviations:** AFP, alpha-fetoprotein; BMI, body mass index; CHILD, Child-Turcotte-Pugh score; HCV, hepatitis C virus; OLT, orthotopic liver transplantation; WL, waiting list.

the multivariate analysis, only microvascular invasion ($P < 0.001$, HR = 19.57, 95% CI = 5.91-64.83) and poorly differentiated tumors ($P < 0.001$, HR = 26.16, 95% CI = 5.45-125.45) independently increased the risk of recurrence (Table 4).

When we considered only variables that could be assessed in the pre-OLT period, tumors beyond the MC and poor differentiation were associated with increased risk of recurrence in the univariate analysis. Only poorly differentiated tumors ($P < 0.001$, HR = 12.32, 95% CI = 6.61-22.43) remained statistically significant in the multivariate analysis (Table 5).

## Comparison Between Patients Who Had Tumors Within and Beyond the MC on the Basis of Radiology

The baseline characteristics between the groups within and beyond the MC are shown in Table 6. The overall survival at 1, 3, and 5 years was 82% versus 92%, 68% versus 79%, and 62% versus 69% in patients with tumors within and beyond the MC, respectively ($P = 0.734$; Fig. 1). When we considered those excluded during the WL (intention-to-treat analysis), survival rates at 1, 3, and 5 years were 74% versus 89%, 62% versus

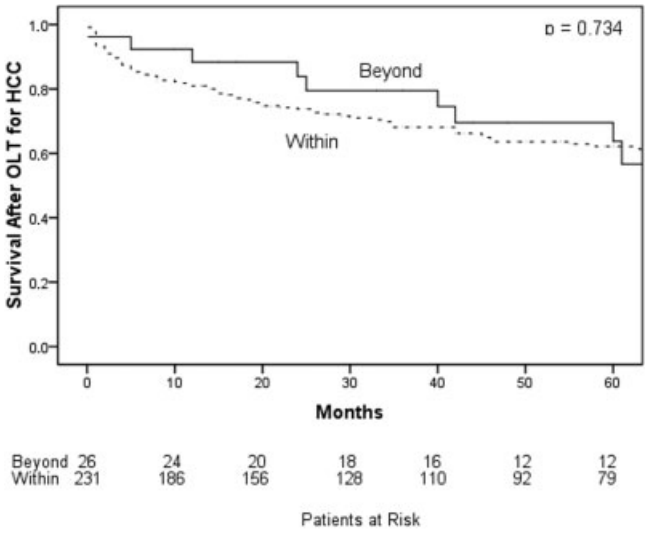


**Figure 1. Survival between patients who had tumors within and beyond the Milan criteria on the basis of radiology. Abbreviations: HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation.**

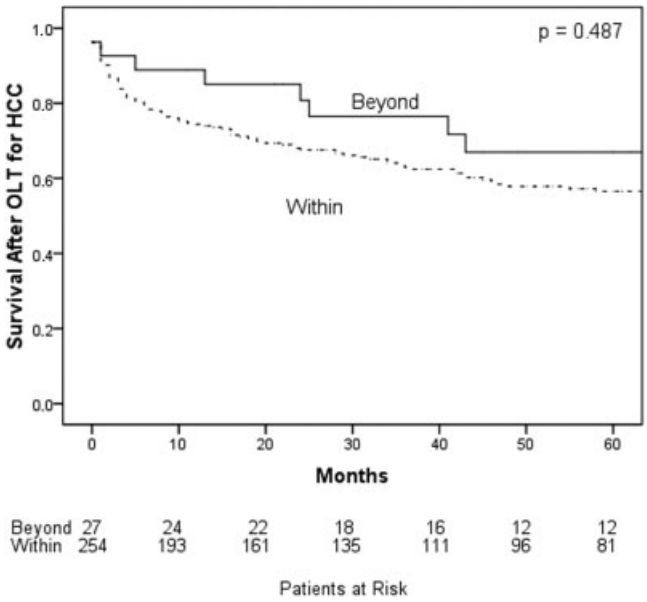


**Figure 2. Survival between patients who had tumors within and beyond the Milan criteria on the basis of the intention-to-treat principle. Abbreviations: HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation.**

76%, and 56 versus 66%, respectively ($P = 0.487$; Fig. 2). The recurrence probabilities at 1, 3, and 5 years were 7% versus 12%, 13% versus 21%, and 14% versus 28% in patients who had tumors within and beyond the MC, respectively ($P = 0.063$).

## Comparison Between Patients Who Had Tumors Within and Beyond the Established Criteria on the Basis of Pathology

In order to evaluate the possible negative impact of radiologic tumor underestimation, we carried out a comparison of cases in which the tumor extension had been underestimated and cases correctly evaluated according to the established criteria (up to 3 tumors, with none larger than 5 cm, and a cumulative tumor burden ≤ 10 cm) identified in the explant analysis. The survival at 1, 3, and 5 years was 85% versus 74%, 72% versus 55%, and 67% versus 40% in patients who had tumors within the criteria versus those whose tumor extension had been underestimated, respectively ($P = 0.001$; Fig. 3). Regarding recurrence probabilities, we also noted differences between the curves, with rates at 1, 3, and 5 years of 5% versus 19%, 9% versus 43%, and 11% versus 43%, respectively ($P < 0.001$). We evaluated whether there were any variables that could be assessed in the pre-OLT period associated with radiologic underestimation. Tumors beyond the MC ($P = 0.007$), bilobar involvement ($P < 0.001$), and poorly differentiated tumors ($P < 0.001$) were associated with tumor underestimation in the univariate analysis (Table 7). Only bilobar involvement [$P = 0.027$, relative risk (RR) = 2.23, 95% CI = 0.018-0.296] and poorly differentiated tumors ($P < 0.001$, RR = 3.98, 95% CI = 0.26-0.78) remained associated in the logistic regression analysis.

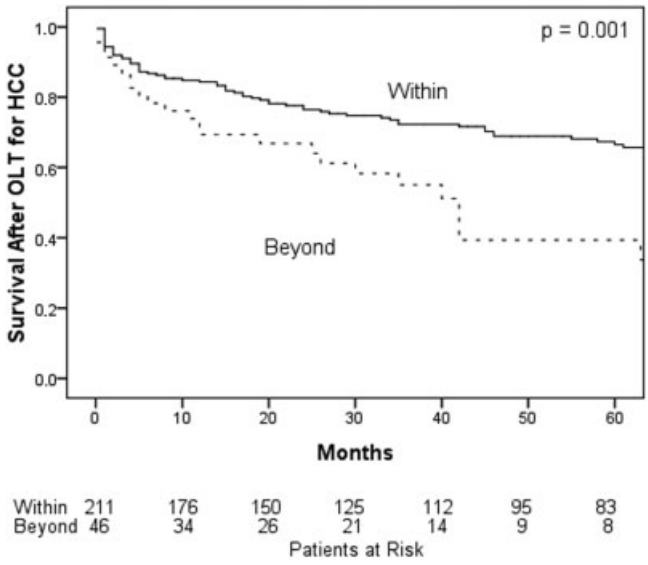


**Figure 3. Survival between patients who had tumors within and beyond the established criteria (up to 3 tumors up to 5 cm and tumor burden ≤ 10 cm) on the basis of pathology. Abbreviations: HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation.**

## Pre-OLT Features Associated with Microvascular Invasion

Because microvascular invasion was the only independent predictor of poor survival, we determined whether there were any other variables that could be assessed in the pre-OLT period associated with microvascular invasion. Higher levels of AFP ($P = 0.037$), bilobar involvement ($P = 0.099$), and poorly differentiated tumors ($P = 0.001$) appeared to be significantly asso-

**TABLE 7. Pre–Orthotopic Liver Transplantation Variables: Association Between Cases in Which the Tumor Extension Had Been Underestimated and Cases Correctly Evaluated According to the Established Criteria**

| Characteristic | Not Underestimated (n = 211) | Underestimated (n = 46) | *P* |
|---|---|---|---|
| Age (range) | 59 (27–69) | 61 (41–67) | 0.921 |
| Male (%) | 167 (79.1) | 40 (86.9) | 0.157 |
| Days in WL | 51 | 68 | 0.527 |
| Range | 1–641 | 5–308 | |
| Treatment while on WL (%) | | | |
| No | 40 (18.9) | 11 (23.9) | 0.282 |
| Yes | 171 (80.1) | 35 (76.1) | |
| Cirrhosis etiology (%) | | | |
| HCV | 156 (73.9) | 32 (69.5) | 0.331 |
| Non-HCV | 55 (26.1) | 14 (30.5) | |
| CHILD (%) | | | |
| A | 96 (45.5) | 22 (47.8) | 0.865 |
| B | 76 (36) | 17 (36.9) | |
| C | 39 (18.5) | 7 (15.3) | |
| BMI ($kg/m^2$) | 26.6 ± 3.5 | 26.1 ± 3.7 | 0.527 |
| AFP (ng/mL) | 17.3 | 17.3 | 0.613 |
| Range | 1.2–972 | 1.4–24,444 | |
| Tumor criteria | | | |
| Within Milan | 195 (92.4) | 36 (78.2) | 0.007 |
| Beyond Milan | 16 (7.6) | 10 (21.8) | |
| Lobe (%) | | | |
| Unilobar | 185 (87.6) | 27 (58.7) | <0.001* |
| Bilobar | 26 (12.4) | 19 (41.3) | |
| Differentiation degree (%)† | | | |
| Poor | 2 (1.4) | 6 (18.8) | <0.001* |
| Moderate or good | 147 (98.6) | 26 (81.2) | |

**Abbreviations:** AFP, alpha-fetoprotein; BMI, body mass index; CHILD, Child-Turcotte-Pugh score; HCV, hepatitis C virus; WL, waiting list.
*Significantly associated in the logistic regression analysis.
†Data are not available in 76 cases.

ciated with microvascular invasion in the univariate analysis. Only poorly differentiated tumors persisted to be associated in the logistic regression analysis ($P < 0.001$, RR = 25.53, 95% CI = 4.55-143.04; Table 8).

## DISCUSSION

Early results after OLT in unselected patients with cirrhosis and HCC were poor, with high recurrence rates and short survival.[25-28] In the 1990s, OLT for malignancy focused on early cancer detection in an attempt to increase the recurrence-free survival rates. In that sense, a study from Milan in 1996 found that restrictive selection (a single tumor up to 5 cm or up to 3 tumors up to 3 cm) predicted similar outcomes in comparison with OLT performed in patients without HCC.[4] The MC were subsequently used by the United Network for Organ Sharing to assign the listing priority of patients presenting HCC. On the other hand, some studies have recently suggested that the MC might be too restrictive, with relatively good results achieved when different proposals are used (Table 9). In 2001, Yao et al.[7] from the University of California, San Francisco (UCSF), reported a 5-year survival of 75% in patients with a single tumor as large as 6.5 cm or a maximum of 3 tumors up to 4.5 cm and a cumulative tumor burden ≤ 8 cm. With mostly retrospective data, some groups have independently tested these criteria.[9,13,16] These results have, however, been challenged because of the use of explant pathology, rather than preoperative imaging, as a determinant for the definition of the tumor stage.

Given the controversy surrounding the expansion of the MC, we decided to evaluate the results of OLT in a large number of patients with HCC at a single institution (281 cases). More specifically, we wanted to analyze both the MC and the established criteria at our center (up to 3 tumors, with none larger than 5 cm, and a cumulative tumor burden ≤ 10 cm). In short, our results can be summarized as follows: (1) the expansion of the MC does not result in impaired survival; (2) microvascular invasion is associated with poorly differentiated tumors leading to increased risk of tumor recurrence and an impairment of survival; (3) when we consider only variables that can be assessed in the pre-OLT period, HCV cirrhosis and poorly differentiated tumors are associated with decreased survival; and (4) pathologic analysis showing more than 3 tumors, any nodule larger than 5 cm, or a cumulative tumor burden > 10 cm predicts poor survival.

**TABLE 8. Pre–Orthotopic Liver Transplantation Variables: Association with Microvascular Invasion**

| Characteristic | Without Microvascular Invasion (n = 208) | With Microvascular Invasion (n = 25) | *P* |
|---|---|---|---|
| Age (range) | 57.3 (27–69) | 59.3 (41–66) | 0.196 |
| Male (%) | 168 (80.7) | 19 (76) | 0.368 |
| Days in WL | 57 | 55 | 0.935 |
| Range | 1–641 | 5–281 | |
| Treatment while on WL (%) | | | |
| No | 39 (18.7) | 7 (28) | 0.199 |
| Yes | 169 (81.3) | 18 (72) | |
| Cirrhosis etiology (%) | | | |
| HCV | 154 (74) | 20 (80) | 0.354 |
| Non-HCV | 54 (26) | 5 (20) | |
| CHILD (%) | | | |
| A | 94 (45.1) | 13 (52) | 0.425 |
| B | 75 (36.2) | 9 (36) | |
| C | 39 (18.7) | 3 (12) | |
| BMI (kg/m$^2$) | 26.7 ± 3.6 | 25.7 ± 3.6 | 0.240 |
| AFP (ng/mL) | 17.2 | 39.4 | 0.037 |
| Range | 1.4–6550 | 1.2–4020 | |
| Tumor criteria | | | |
| Within Milan | 188 (90.3) | 21 (84) | 0.246 |
| Beyond Milan | 20 (9.7) | 4 (16) | |
| Lobe (%) | | | |
| Unilobar | 176 (84.6) | 18 (72) | 0.099 |
| Bilobar | 32 (15.4) | 7 (28) | |
| Differentiation degree (%)† | | | |
| Poor | 3 (1.8) | 5 (23.8) | 0.001* |
| Moderate or good | 157 (98.2) | 16 (76.2) | |

**Abbreviations:** AFP, alpha-fetoprotein; BMI, body mass index; CHILD, Child-Turcotte-Pugh score; HCV, hepatitis C virus; WL, waiting list.
*Significantly associated in the logistic regression analysis.
†Data are not available in 76 cases.

**TABLE 9. Results from Series Reporting Expanded Criteria for Orthotopic Liver Transplantation in Patients with Cirrhosis and Hepatocellular Carcinoma**

| Authors, Year | Criteria | Patients | | 5-Year Survival | |
|---|---|---|---|---|---|
| | | All | Expanded | Milan | Expanded |
| Herrero et al.,[6] 2001 | Radiology | 49 | 12 | N/A | N/A |
| Yao et al.,[7] 2001 | Pathology | 70 | 24 | 75 | N/A |
| Roayaie et al.,[8] 2002 | Radiology | 80 | 80 | N/A | 25 (ITT) |
| Khakhar et al.,[14] 2003 | Radiology | 39 | 17 | 70 | 24 |
| Marsh et al.,[9] 2003 | Pathology | 393 | 145 | 67 | N/A |
| Leung et al.,[18] 2004 | Radiology | 88 | 14 | 51 | N/A |
| Ravaioli et al.,[15] 2004 | Radiology | 63 | 8 | 78 | 38 |
| Decaens et al.,[16] 2006 | Radiology | 479 | 44 | 60 | 45 (ITT) |
| | Pathology | 467 | 39 | 70 | 63 |
| Onaca et al.,[12] 2007 | Pathology | 1206 | 407 | 62 | 43 |
| Parfitt et al.,[17] 2007 | Pathology | 75 | 25 | 83 | 44 (in 3 years) |
| Duffy et al.,[13] 2007 | Radiology | 364 | 185 | 79 | 64 |
| | Pathology | 467 | 208 | 86 | 81 |
| Yao et al.,[19] 2007 | Radiology | 168 | 38 | 90* | 93* |

**Abbreviations:** ITT, intention-to-treat analysis; N/A, not available.
*Recurrence-free probabilities.

In the present report of 281 cases, OLT proved to be an effective treatment for HCC in cirrhotic livers, with a 5-year survival rate of 57% based on the intention-to-treat principle. The 5-year survival rate was 63% among transplanted patients. Moreover, we determined that patients beyond the MC had a survival rate similar to that of those within these criteria, even including patients excluded from WL. There are essential aspects that should be considered when treatments related to HCC are evaluated: (1) treatments that achieve survival rates higher than 50% in 5 years are considered effective therapies, given the fact that studies have demonstrated the 3-year survival of early HCC to be about 50%[29,30]; (2) the deleterious impact of the progressive increase in the WL time has to be considered when the efficacy of OLT as a treatment for HCC is evaluated because of the risk of tumor progression and death during this period;[31,32] and (3) it is well known that preoperative imaging techniques underestimate HCC staging in about 20% of cases, and thus the extrapolation of the histopathologic data to the preoperative scenario might be misleading.[33] In that sense, the analysis of the overall survival is better evaluated when it is based on the intention-to-treat principle. We have found only 2 studies that evaluated the expansion of the MC on the basis of these considerations.[8,16] Both demonstrated low 5-year survival rates (25% and 45%, respectively). Given these results and the fact that the studies which have explored the possibility of expanding the MC are considered less robust from an epidemiologic point of view, there have been concerns regarding the expansion of these criteria.[34] In our study, after comparing the overall survival in patients effectively transplanted with that of patients excluded from the WL, we found no differences in the survival rates. This is probably related to the low dropout rate due to the short WL time (median, 54 days; range, 1-641 days).

As mentioned previously, the UCSF proposal is the approach mostly tested; however, it has been challenged because of the use of explant pathology. Duffy et al.[13] and Yao et al.[19] recently published their excellent results analyzing the survival rates and recurrence probabilities on the basis of the pre-OLT radiologic assessment. However, we consider the extensive alidation based on radiology and analysis according to the intention-to-treat principle to be fundamental information. Furthermore, because of the enormous clinical and economic implications of such expansion worldwide, further prospective studies are necessary.

The present study includes cases with a cumulative tumor burden of 10 cm (Table 2). Interestingly, the cumulative tumor burden of the MC is 9 cm, whereas the one used in the UCSF criteria is 8 cm. In addition, 10 patients had tumors beyond the UCSF criteria. No differences in survival ($P = 0.468$) or in recurrence ($P = 0.448$) were found between cases within and beyond the UCSF criteria (data not shown). Although these results suggest that this expansion does not result in an impaired outcome, we understand that they need validation, given the relatively small number of patients.

Microvascular invasion was the only factor that predicted poor survival in the multivariate analysis. Unfortunately, this variable cannot be assessed in the pre-OLT period. Therefore, we evaluated which of these characteristics could be associated with microvascular invasion; only poor differentiation degree was independently associated with this event. This is in accordance with previous studies that have demonstrated low rates of vascular involvement in cases in which the pre-OLT biopsy demonstrated moderately or well differentiated tumors.[10,35] Indeed, several studies have shown that the differentiation degree and microvascular invasion represent direct indicators of the biologic progression of HCC, being associated with tumor recurrence and poor long-term survival.[4,6,8,10,13,35,36] In 1 study that evaluated the results of OLT in 48 patients in which the pre-OLT pathologic examination showed only moderately or well differentiated tumors, the 5-year survival rate reached 75%, regardless of the number or size of the lesions.[10] Unfortunately, there are data suggesting that this strategy might not be adequate because the tumor degree based on the pre-OLT assessment is potentially misleading, without a direct correlation with final histopathologic features.[37] In our study, of the 8 cases that presented this feature, 7 died during the follow-up period, and 6 developed tumor recurrence (data not shown). The small number of cases presenting such characteristics might explain the absence of a significant difference as a predictor of poor survival in the multivariate analysis.

Recurrence of HCC occurred in 33 cases (13%); the rate was similar to rates found in other studies.[4,7,13,17-19] This event occurred in 11.3% and 26.9% of patients within and beyond the MC ($P = 0.056$). Microvascular invasion and a poor differentiation degree were the only independent predictive factors of tumor recurrence, as previously demonstrated.[35,38] This difference was not statistically significant, however. This might be due to the relatively small number of patients included in the group beyond the MC criteria (26 cases).

The development of noninvasive alternatives to identify tumors with aggressive biology is a fertile area for research. Shirabe et al.[39] measured des-gamma-carboxy-prothrombin in the serum of patients with HCC and found that elevated levels have 75% sensitivity and 85% specificity for detection of microvascular invasion. Despite being a useful approach, it requires further studies for validation. According to the principle that the main challenge is to identify patients with tumors with favorable biology based on preoperative features, we have also analyzed prognostic factors considering only the variables that can be assessed in the pre-OLT period. The only variables that independently predicted low survival were HCV cirrhosis and a poor differentiation degree. The negative impact of HCV on post-OLT outcome has already been demonstrated in our experience,[36] and as mentioned previously, the identification of the differentiation degree in the pre-OLT period might be a useful tool, despite its limitations.

Another aspect that has to be taken into consider-

ation is that, according to our study and other previously published studies, the histopathologic analysis of the explant, identifying tumors exceeding the pre-OLT evaluation in a substantial proportion of cases, leads to significantly poorer survival.[4,12,13,16,19] In that sense, the use of radiologic tests (triphasic computed tomography, magnetic nuclear resonance, or contrast ultrasound) on the day of OLT might be an option to solve that problem. On the other hand, when variables that could be assessed in the pre-OLT period were analyzed, bilobar involvement and a poor differentiation degree proved to be 2 independent factors associated with radiologic underestimation. Once confirmed, these factors might be useful in identifying patients who, despite fulfilling the established criteria, belong to the group of patients considered not suitable for OLT because of the high risk of underestimation.

Controversy exists as to whether antitumor treatments might be effective if used in patients waiting for OLT. In the present study, although pre-OLT antitumor alternatives were used in 80% of patients, they did not appear to be associated with the survival rate or tumor recurrence. This approach was more frequently performed in patients included in the expanded group ($P = 0.035$). However, the design of the present study was not adequate to draw firm conclusions about the efficacy of these therapies. Further prospective analyses are necessary to assess the value of pre-OLT locoregional treatments.

In conclusion, although the expansion of the criteria for OLT in patients with cirrhosis and HCC must be done cautiously, we have demonstrated that expansion to up to 3 nodules, with none larger than 5 cm, and a cumulative tumor burden $\leq$ 10 cm (based on radiology) does not result in a reduction of survival. This expansion, however, might be associated with greater HCC recurrence. Prospective studies are hence required to confirm our findings.

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