Outcome of Patients with Hepatocellular Carcinoma Listed for Liver Transplantation Within the Eurotransplant Allocation System

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Although hepatocellular carcinoma (HCC) has become a recognized indication for liver transplantation, the rules governing priority and access to the waiting list are not well defined. Patient- and tumor-related variables were evaluated in 226 patients listed primarily for HCC in Belgium, a region where the allocation system is patient-driven, priority being given to sicker patients, based on the Child-Turcotte-Pugh (CTP) score. Intention-to-treat and posttransplantation survival rates at 4 years were 56.5 and 66%, respectively, and overall HCC recurrence rate was 10%. The most significant predictors of failure to receive a transplant in due time were baseline CTP score equal to or above 9 (relative risk [RR] 4.1; confidence interval [CI]: 1.7-9.9) and α fetoprotein above 100 ng/mL (RR 3.0; CI: 1.2-7.1). Independent predictors of posttransplantation mortality were age equal to or above 50 years (RR 2.5; CI: 1.0-3.7) and United Network for Organ Sharing pathological tumor nodule metastasis above the Milan criteria (RR 2.1; CI: 1.0-5.9). Predictors of recurrence (10%) were α fetoprotein above 100 ng/mL (RR 3.2; CI: 1.1-10) and vascular involvement of the tumor on the explant (RR 3.6; CI: 1.1-11.3). Assessing the value of the pretransplantation staging by imaging compared to explant pathology revealed 34% accuracy, absence of carcinoma in 8.3%, overstaging in 36.2%, and understaging in 10.4%. Allocation rules for HCC should consider not only tumor characteristics but also the degree of liver impairment. Patients older than 50 years with a stage above the Milan criteria at transplantation have a poorer prognosis after transplantation. Liver Transpl 14:526-533, 2008. © 2008 AASLD.

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tion (either as a downstaging procedure or to control the evolution of the tumor while on the waiting list), may also constitute an important confounding variable. Studies are often small and single-center, and above all, liver allocation policies for HCC vary greatly from one allocation organization to another. The shortage of organs, combined with the increased incidence of HCC in the United States and Europe, largely due to the medical consequences of the hepatitis C epidemic, make it more crucial than ever to optimize the criteria of both selection and priority for transplantation. Various strategies have been adopted by the transplant community, ranging from no priority for HCC (such as in the current Eurotransplant system), to a center-oriented system by which the local team chooses the recipient who could benefit most from the donor organ (a procedure used in most other European centers) or to the new allocation policy based on the Model for End-Stage Liver Disease (MELD) adopted in the United States since February 2002. The latter system, based on the estimated risk of tumor progression within the Milan criteria, has been shown to reduce the dropout rate and increase the transplantation rate, while maintaining an excellent post-LTX outcome. However, all these different sets of selection and priority criteria introduce biases that influence the outcome of patients with HCC.

We therefore set out to identify, in a large multicenter study, the predictive factors of the various outcomes for HCC patients on the waiting list, with the aim of offering the possibility of LT only to those who were most likely to be cured as possible. The fact that the Eurotransplant allocation system used is patient-driven, but outside the MELD system, gave us the unique opportunity to estimate their natural history while on the waiting list.

**PATIENTS AND METHODS**

Between October 1, 1999 and October 1, 2004, 272 HCC patients belonging to the 6 Belgian transplant centers, grouped into the Belgian Liver Intestine Committee of the Belgian Transplant Society, were consecutively listed for cadaveric LT within the framework of Eurotransplant, a foundation responsible for the allocation of donor organs in Austria, Belgium, Germany, Luxembourg, the Netherlands, and Slovenia. During the same period, 955 patients with chronic liver disease without malignancy were listed, so that our HCC population constituted 29% of the total Belgian series of patients listed. The charts of these patients were retrospectively reviewed. During the study period, no listing priority based on HCC characteristics alone was possible. According to the Eurotransplant allocation rules, as from July 2000, only cirrhotic patients with a Child-Turcotte-Pugh (CTP) score ≥10 and complications were given priority and, from September 2003 the cutoff point for this score was raised to ≥11.

Only patients with a diagnosis of HCC at listing were included in the present series. Their diagnosis was based on parameters similar to those proposed by the European Association for the Study of Liver diseases: either histological proof, or the presence of a nodule with a diameter exceeding 2 cm, identified by ultrasonography and confirmed to be hypervascular, either at computed tomography (CT) or magnetic resonance imaging or by 1 imaging study combined with an α fetoprotein (αFP) level above 400 ng/mL. HCC was considered as the primary diagnosis (n = 226) when the cancer was the reason for transplantation, and the secondary diagnosis (n = 46) when decompensated cirrhosis was the indication, HCC being detected incidentally during the prelisting workup.

Our study focused on the first group, because it is the most prevalent (226/272, 83%), for more homogeneous results interpretation and to study the natural history of the malignancy without the direct bias of the degree of liver impairment. Patients with HCC were selected for transplantation according to the Milan criteria as requested by Eurotransplant and this was accepted by the 6 transplant centers represented by the Belgian Liver Intestine Committee, a national organization, recognized by Eurotransplant. Patients with extrahepatic spread, assessed by bone scan and chest CT and/or vascular invasion were excluded. During the waiting period for LTX, imaging was repeated every 3 to 6 months. Delisting for tumor progression was decided upon detection of either major vascular involvement or extrahepatic spread.

Adjuvant therapy before listing or while waiting was given to 123 of the 226 patients (54%), and consisted of transarterial chemoembolization in 93 (76%), percutaneous alcoholization in 16 (13%), liver resection in 9 (7%), and radiofrequency ablation in 5 (4%).

Because of the absence of clear guidelines, the magnitude of incorrect assessment of HCC staging by the current imaging methods, and the availability of potentially useful treatments, which either downstage the tumor or limit its progression, these were decided upon a case-by-case basis during the weekly multidisciplinary medicosurgical conference in each center. In particular, they were implemented in patients outside the Milan criteria and/or in those who had tumor progression. This category of patients was also listed for a marginal graft.

After listing for HCC, various distinct clinical outcomes were considered. Before LTX, these comprised the total number of failures (that is, death before delisting and/or delisting because of tumor progression) and, after LTX, overall mortality and HCC recurrence, while the patients still alive were evaluated at the last follow-up (April 1, 2005).

Thirteen categorical or continuous variables concerning the prognostic value of all these outcomes were analyzed. The clinical and demographic variables considered were age at listing and at transplantation, gender, transplant center, waiting time, blood group, year of listing, year of LTX, CTP score, and MELD score. Tumor-related variables were αFP at baseline, use of prerereferal or postreferral adjuvant therapy or no therapy, the number of nodules, the size of the largest nodule, the presence or absence of vascular invasion, and tumor-node-metastasis (TNM) staging according to
Tumor staging was based on preoperative imaging using the UNOS clinical tumor-node-metastasis (cTNM) staging and was evaluated at the time of listing and, after LTX, from explant pathology using the UNOS pathological tumor-node-metastasis (pTNM) staging and American Joint Committee on Cancer (AJCC)/International Union Against Cancer (Union Internationale contre le Cancer, UICC) criteria. Explanted liver was examined by experienced local pathologists using 1-cm-thick sections. One of the 179 explanted liver specimens could not be staged. The number of nodules, maximal tumor size, and evidence of macrovascular involvement allowed the evaluation of UNOS cTNM and pTNM, and the differences between them.

The UNOS cTNM and pTNM staging used for our study comprised the following: no HCC: absence of HCC on the pathological specimen; T0: evidence of tumoral necrosis within the explant, the disappearance of hypervascularity on follow-up imaging after adjuvant therapy, or tumor resection before transplantation; T1: single nodule <2.0 cm; T2: single nodule 2-5 cm or 2 or 3 nodules ≤3 cm (that is, Milan criteria); T3: single nodule >5 cm or 2 or 3 nodules, at least one >3.0 cm; T3A: single nodule ≤6.5 cm or ≤3 nodules with the largest lesion ≤4.5 cm and total tumor diameter ≤8 cm (that is, UCSF criteria); T3B: T3 other than T3A; T4A: 4 or more nodules of any size; and T4B: T2, T3, or T4A plus macroscopic intrahepatic portal or hepatic vein involvement. The definition of the AJCC/UICC pTNM was the following: T0, no evidence of tumor; T1, solitary tumor without vascular invasion; T2, solitary tumor with vascular invasion or multiple tumors, none more than 5 cm; T3, multiple tumors more than 5 cm or tumor involving a major branch of the portal or hepatic vein(s); and T4, tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum. Tumor grading according to the Edmonson criteria was available in 154 of the 178 pathological reports.

The liver transplant procedure involved only cadaveric donors.

Immunosuppressive therapy after LTX consisted of a double or triple drug regimen of tacrolimus combined with steroids and/or mycophenolate mofetil in the case of renal failure. Tacrolimus was switched to cyclosporine in the case of unstable diabetes or neurologic side effects. Steroids were tapered gradually and discontinued within 3 months.

All patients were followed regularly at the outpatient clinic. The frequency of visits varied according to the patient’s condition and type of complications.

Screening for HCC recurrence after LTX was done by ultrasound and aFP measurement every 6 months, abdominal CT every year, with bone scan, magnetic resonance imaging, or chest CT if necessary. No adjuvant chemotherapy was administered.

**Statistical Analysis**

Univariate and multivariate analyses of the potential prognostic variables were performed for the various outcomes, that is, risk of death and dropout on the waiting list before LTX, death, and recurrence of HCC after LTX.

In each analysis, failures due to events other than the event of interest were treated as censored observations. In the univariate analysis, categorical variables were compared using the chi-square or Fisher’s exact tests, as appropriate. Continuous variables were compared using the nonparametric Mann-Whitney test or the Student t test (if they were Gaussian), or logarithmically transformed for the skewed variables. They were categorized in two groups, the cutoff value being selected in a pragmatic way in order to obtain the highest possible statistical significant difference between the survival curves. To assess the risk factors for the different outcomes, Cox hazard regression models were constructed and the relative risks estimated, together with their 95% confidence intervals.

Only variables which emerged with a P value <0.1 after univariate analysis were included in the Cox model. They were selected stepwise for statistical significance. The proportional assumption of the Cox model was graphically verified by the linear relationship between the log, (ln) of cumulative events and the ln of time. Graphic displays of the results were obtained using the actuarial method and the survival curves for a given prognostic factor were adjusted using stratification in order to account for the influence of the other factors, thus avoiding confounding biases. Calculations were carried out using the StatView program.

**RESULTS**

**Baseline Demographic Data Including Patient and Tumor Characteristics**

The general characteristics of the 226 patients with primary HCC are given in Table 1.

Most patients were men (79%), and 42% had hepatitis C virus as the underlying liver disease. Median CTP and MELD scores at listing were 6.7 and 9.3, respectively. The number of patients listed yearly was fairly constant, taking into account the fact that in 1999 and 2004, the inclusion periods considered were 3 and 9 months, respectively.

At listing, 149 patients (66%) were candidates for LTX according to the Milan criteria (that is, T1 or T2), 29 (13%) were within the UCSF criteria and 48 (21%) did not fulfill the UCSF or Milan criteria and were listed for a marginal graft for which no other recipient was available for that organ.

**Survival According to Intention-to-Treat and Post-LTX**

The 6-month and 1-, 2-, 3-, and 4-year survival rates for the 226 patients listed with primary HCC, according to intention-to-treat analysis (time zero point being the
inclusion of the subject on the waiting list) were 84, 74, 63, 58, and 56%, respectively. For those actually receiving transplantation, the corresponding survival rates were 84, 79, 72, 69, and 66%, respectively (Fig. 1). The 10% difference between the 2 curves reflected failure of the listing due to dropout, or death before dropout.

Probability of Pre- and Post-LTX Outcomes and Prognostic Factors

The actuarial probabilities of the most pertinent pre-LTX events in the 226 patients listed with primary HCC, that is, failures to get a transplant and chance of receiving a graft, show a 24% and 78% rate at 18 months, respectively (Fig. 2). The results of stepwise Cox regression analysis of the impact of the 13 baseline variables on these outcomes are given in Table 2, with their cutoff values, regression coefficient, standard error, statistical significance, relative risk, and 95% confidence intervals.

Of the 226 patients listed, 30 were delisted (19 for tumor progression, 2 for severe liver failure, 1 for social reasons, 5 for noncompliance, and 3 for responding well to adjuvant therapy). Ten patients died before being delisted (3 of sepsis, 2 of liver failure, 2 of cardiovascular events, 1 of tumor progression, 1 of cytomegalovirus hepatitis, and 1 of unknown reason). Twenty-nine (12.8%) patients, including the 19 delisted for tumor progression and the 10 who died before delisting, were thus considered as pre-LTX failures.

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Based on the multivariate analysis, CTP score (relative risk [RR] 4.1), aFP > 100 ng/mL at baseline (RR 3.0), and preoperative adjuvant therapy (RR 2.5) were independent risk factors for a failure to get a transplant in time (Table 2). One hundred forty-five of the 226 (64%) patients were transplanted after a median waiting period of 4 months (range, 0-27.2). The waiting time (mean ± standard error of the mean) increased steadily with the year of listing: 1999, 2.6 ±

**TABLE 1. Baseline Characteristics of the 226 Patients with Primary HCC Listed for Transplantation**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>58 (17-72)</td>
</tr>
<tr>
<td>Gender: male/female (%)</td>
<td>173 (77)/57 (23)</td>
</tr>
<tr>
<td>ABO blood group n: O/A/B/AB</td>
<td>78/111/28/9</td>
</tr>
<tr>
<td>Transplant center: KUL/GUH/UHA/UCL/ULB/ULg</td>
<td>92/32/9/46/24/23</td>
</tr>
<tr>
<td>Etiology of underlying liver disease n (%): HCV/alcohol/other</td>
<td>96 (42)/65 (29)/65 (29)</td>
</tr>
<tr>
<td>UNOS TNM staging at listing n (%): T1/T2/T3A/T3B/T4A</td>
<td>20 (9)/129 (57)/29 (13)/11 (5)/37 (16)</td>
</tr>
<tr>
<td>Adjuvant therapy n = 123 (54%) n (%): TACE/alcoholization/resection/RF</td>
<td>93 (76)/16 (13)/9 (7)/5 (4)</td>
</tr>
<tr>
<td>Median Child-Turcotte-Pugh score (range)</td>
<td>6.7 (5-13)</td>
</tr>
<tr>
<td>Median MELD score (range)</td>
<td>9.3 (6-30)</td>
</tr>
</tbody>
</table>

**Abbreviations:** GUH, Ghent University Hospital; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; KUL, Katholieke Universiteit Leuven; MELD, Model for End-Stage Liver Disease; RF, radiofrequency ablation; TACE, transarterial chemoembolisation; TNM, tumour node metastasis; UCL, Université Catholique de Louvain; ULB, Université Libre de Bruxelles; ULg, Université de Liège; UZA, Universiy Hospital Antwerpen.
Probabilities of Post-LTX Outcomes and Prognostic Factors

The actuarial post-LTX risks of overall mortality and probability to remain free of HCC recurrence for the 145 patients actually transplanted are illustrated in Fig. 3, showing a rate of death and recurrence of 34% and 17% at 4 years. Patient survival after LTX is thus 66% at 4 years. HCC recurred in 14 patients (10%), after a mean period 11.3 ± 3.8 months (range, 2-46). Two independent risk factors predicted HCC recurrence: αFP (>100 ng/mL) and presence of vascular invasion on the heptectomy specimen, with RRs of 3.2 and 3.6, respectively (Table 2).

Correlation Between Clinical and Pathological TNM

The findings by pre-LTX imaging at the time of listing were different from the pathological findings in a significant number of patients, based on the 144 heptectomy specimens (data not shown). The mean and median periods between UNOS cTNM at listing and UNOS pTNM were 5.4 and 4.4 months, respectively. No tumor, T0 stage, same staging, understaging (more lesions in the explanted liver, that is, UNOS pTNM, than those observed by preoperative imaging, that is, UNOS cTNM), and overstaging (more lesions on UNOS cTNM than UNOS pTNM) were observed in 8.3% (12/144), 11.1% (16/144), 34% (49/144), 10.4% (15/144), and 36.2% (52/144), respectively.

DISCUSSION

In this large multicenter series of HCC patients from a European region where only patients with decompensated cirrhosis receive priority for LTX, we have identified a subset of patients at high risk of not receiving transplantation either because of death before delisting or dropout because of tumor progression. Their identification is based on tumor characteristics and the degree of liver impairment caused by the underlying liver disease.

The importance of an intention-to-treat analysis to evaluate the benefit of LTX as a treatment of HCC was first suggested by Llovet et al. and was subsequently emphasized by other groups. On the basis of our intention-to-treat analysis, we obtained a 10% difference in comparison with the 66% 4-year actuarial survival, which reflected the natural history of our HCC patients on the waiting list, for whom there was no novo neoplasms in 5, and unknown reasons in 3. Only UNOS pTNM above T2 (RR 2.1) and age above 50 years (RR 2.5) were significant predictors of post-LTX death.

When the AJCC/UICC TNM was included in the Cox multivariate regression analysis, it did not add significant independent discriminative power (P = 0.48).
priority bias. For the patients actually receiving transplantation, our 6-month, 1-, 2-, 3-, and 4-year long-term survival rates were 84, 79, 72, 69, and 66%, respectively, together with a low (10%) actuarial incidence of recurrent HCC, results which are comparable to those recently reported.\(^2^1\) Our results confirm that αFP is an important predictor of poor pre-LTX clinical outcome\(^2^2,2^3\) and suggests that this simple, objective biological parameter could be used to refine the transplant allocation policy for HCC patients listed for LTX. Apart from αFP, we showed that the degree of liver impairment, a determining element for the organ allocation decisions, still represents a significant risk factor for failure to get a transplant in due time. This is a striking observation that has already been noted by an Italian\(^2^4\) and a Chinese\(^2^5\) group, outside the MELD priority policy, reporting that the dropout rate before transplanta\n
In conclusion, both tumor characteristics and the degree of liver impairment, with a CTP equal or higher than 9, should be taken into consideration when offering priority on the waiting list for patients with cirrhosis with HCC.

Older patients with an HCC above the Milan criteria based on explant pathology have a poorer prognosis after transplantation. However, this category of patients is difficult to identify at listing because of the poor correlation between preoperative imaging and explant pathological stage. Our data may help in making policy decisions regarding liver allocation for patients with HCC, in particular in the European regions, where there is currently no priority for HCC patients on the waiting list.

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