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The survival benefit of liver transplantation in hepatocellular carcinoma patients

Umberto Cillo[a], Alessandro Vitale[b,*], Michael L. Volk[c], Anna Chiara Frigo[d], Francesco Grigoletto[d], Alberto Brolese[a], Giacomo Zanus[a], Francesco D'Amico[a], Fabio Farinati[e], Patrizia Burra[e], Francesco Russo[e], Paolo Angeli[f], Davide F. D'Amico[a]

[a] Unità di Chirurgia Epatobiliare e Trapianto Epatico, Azienda Ospedaliera - Università di Padova, Via Giustiniani 2, 35128 Padova, Italy
[b] Unità di Chirurgia Oncologica, Istituto Oncologico Veneto, IRCCS, Via Gattamelata 64, 35128 Padova, Italy
[c] Division of Gastroenterology, University of Michigan Health System, Ann Arbor, MI 48109, USA
[d] Unità di Biostatistica ed Epidemiologia, Università di Padova, Via Gattamelata 64, 35128 Padova, Italy
[e] Divisione di Gastroenterologia, Azienda Ospedaliera - Università di Padova, Via Giustiniani 2, 35128 Padova, Italy
[f] Clinica Medica V, Divisione di Gastroenterologia, Azienda Ospedaliera - Università di Padova, Via Giustiniani 2, 35128 Padova, Italy

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ABSTRACT

Background: There are no studies evaluating the survival benefit of liver transplantation over alternative therapies for patients with hepatocellular carcinoma.
Methods: The short- to mid-term survival benefit (study group = 135 aggressively treated patients with hepatocellular carcinoma, 52% beyond Milan criteria at pathology) was calculated by comparing the mortality rates of liver transplantation vs alternative therapies patients.

A Markov prediction model was then created to estimate the long-term survival benefit of liver transplantation (gain in life expectancy) over alternative therapies. The long-term survival rates in the liver transplantation group were calculated using the Metroticket website calculator (http://89.96.76.14/metroticket/calculator/).
Results: The short- to mid-term analysis indicated that liver transplantation afforded no significant survival benefit in the group of patients with hepatoma as a whole (hazard ratio = 1.229, 95% confidence interval 0.544–2.773, $p = .6200$). The benefit was concentrated in patients with a poor initial response to alternative therapies (hazard ratio = 3.137, 95% confidence interval 1.428–6.891, $p = .0044$).

In the long-term analysis, the gain in life expectancy of liver transplantation vs alternative therapies was 6.115 years (base-case analysis) and the main determinants of gain in life expectancy were the 5-year survival prospects after alternative therapies and the patient's age.
Conclusions: The survival benefit of liver transplantation for patients with hepatocellular carcinoma is strongly related to the patient's age and the effectiveness of available alternative therapies.

1. Introduction

The crucial issue of which endpoint to use in patient selection for liver transplantation (LT) is still being debated. Patients with non-malignant (NM) cirrhosis are selected according to a pre-LT focused endpoint, i.e. the mortality risk on the waiting list, which is estimated from the model for end-stage liver disease (MELD) score [1,2]. In recent years, an innovative endpoint covering the overall LT process has been proposed for NM patients, and comparisons of the mortality risk between transplant recipients and listed transplant candidates have been used to assess transplant survival benefit [3]. In a recent paper, Merion showed that LT affords a significant short-term (1 year) survival benefit for patients with NM cirrhosis, and this benefit is particularly evident among patients with more advanced liver disease (MELD > 18). LT for patients at lower risk of pre-LT death (MELD < 18) may be pointless or even dangerous, especially when a marginal donor is used [4].

Conversely, patients with hepatocellular carcinoma (HCC) are currently selected according to a post-LT focused endpoint, i.e. the risk of recurrence after LT, which is predicted from the UNOS tumour stage [5,6]. This selection policy gives rise to a high rate of patients being excluded before or while they are listed in order to optimize post-LT outcome. No formal consideration of the benefit of LT vis-à-vis alternative therapies (AT) is involved for patients with HCC.

This heterogeneous LT selection policy for patients with and without HCC intrinsically creates an ethical paradox, in that donated organs are allocated to the "sickest first" patient among candidates with NM hepatic disease, whereas to the "earliest first"

* Corresponding author. Tel.: +39 0498211695; fax: +39 0498211694.
E-mail address: alessandro.vitale@unipd.it (A. Vitale).

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Table 1
Patient and tumour characteristics at the 3-month visit.

Variable	Study group (n = 135)
Age (years)	55.2 (38.4–68.0)
Sex (male)	111 (82%)
Etiology	
Hepatitis C	91 (67%)
Hepatitis B	20 (15%)
Alcohol	21 (16%)
Other	3 (2%)
Blood groups 0-A	123 (91%)
Clinically relevant portal hypertension (CRPH)	81 (60%)
Child Pugh score	7 (5–12)
Child C class	17 (13%)
MELD score	12 (6–26)
MELD > 18	8 (6%)
UNOS STATUS 2	50 (37%)
Biochemistry	
AST (U/L)	66.5 (10–251)
ALT (U/L)	63.0 (9–302)
Bilirubin (mg/dl)	1.5 (0.4–4.1)
INR	1.3 (0.9–2.7)
Creatinine (mg/dl)	0.9 (0.5–2.1)
AFP levels (ng/ml)	23.4 (2.0–7500.0)
Number of tumour nodules	2 (1–5)
Size of largest nodule (cm)	3.0 (1.0–8.0)
UNOS-TNM T3-T4a	56 (41%)
Alternative treatment strategy	
Resection ± other therapies	17 (12%)
Laparoscopic ablation ± resection	15 (10%)
PEI ± RF ± TACE	80 (54%)
TACE	23 (16%)
Poor response to bridging therapy	51 (38%)

Abbreviations: MELD, model for end-stage liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; TACE, transarterial chemo-embolization; PEI, percutaneous ethanol injection; RF, radiofrequency; LT, liver transplantation.

among HCC candidates, irrespective of their survival prospects with therapies other than transplantation.

The aim of this study was to apply the innovative concept of survival benefit to the complex field of LT for HCC patients. Data from a longitudinal study conducted at our Institution on LT for HCC patients [7] were used to calculate the short- and mid-term survival benefit according to the statistical method used in Merion's paper [5].

A Markov model was then generated to obtain a potential estimate of the long-term LT survival benefit.

2. Patients and methods

2.1. Evaluating short- and mid-term survival benefit

This study used data from a retrospective database on LT for HCC patients developed at our Institution between January 2000 and June 2008 (177 consecutive patients). To obtain a realistic picture of patient and tumour characteristics after therapy for HCC while on the waiting list, we considered the patients' clinical assessment 3 months after they had been listed or their HCC had been diagnosed (if this happened when they were already on the waiting list). Thirty HCC patients had a waiting list period lower than 3 months: 20 had an urgent liver transplantation for severe liver dysfunction (n = 20), 2 died for liver failure, and 8 were listed between April 2008 and June 2008. These patients were ruled out of the present analysis, and so were patients given no HCC treatment during this 3-month period (n = 12). The characteristics of the study group (n = 135) at the time of their work-up are given in Table 1.

Response to AT was calculated at the patients' 3-monthly clinical assessment according to the RECIST (Response Evaluation Criteria in Solid Tumours) [8] and EASL recommendations [9], i.e. local response to treatment was measured from the radiologist's estimate of the reduction in viable tumour volume (based on unenhanced areas on imaging); we also considered AFP levels. As in the recent Millonig et al. study [10], response to therapy was thus classified in two main categories: (i) "good response" (complete or partial response = a reduction of 50% or more in the viable tumour volume of all measurable lesions, AFP ≤ pre-therapy level); or (ii) "poor response" (stable and progressive disease = a reduction of less than 50% in the viable tumour volume of one or more measurable lesions, or the appearance of new lesions, or AFP > pre-therapy level). Response to AT was evaluated from radiologists of the same radiological unit.

2.1.1. Transplant, prioritization and allocation criteria

As reported previously [7,11], exclusion criteria for LT were macroscopic vascular invasion, metastases and poorly differentiated grade at pre-LT biopsy. These criteria were used both as listing and as dropout criteria. According to Italian policy, donated organs are assigned to a given liver transplant unit based on geographical criteria, and each liver unit selects a suitable recipient from its own WL. Only patients listed for emergency re-LT or with a preoperative diagnosis of acute liver failure take national priority as status 1 patients. At our liver unit, priority depended on [1] ABO group; [2] clinical characteristics of recipients classified according to the severity of their cirrhosis (Child Pugh and MELD scores) and any presence of HCC. Among HCC patients with the same blood group, the main discriminator was response to AT and patients with untreatable, stable or progressive disease took priority irrespective of nodule size and number, unless complete re-staging revealed exclusion criteria. All HCC patients were listed hierarchically by response to therapy. Patients with the same blood group and the same response to therapy were listed by UNOS-TNM stage [12] as a second criterion, and by time on the list with HCC as a third criterion.

When an organ became available, we considered patients with HCC and compensated cirrhosis (MELD < 20) separately from those with NM cirrhosis. We selected the first HCC patient (based on response to therapy) and the first NM patient (based on Child Pugh and MELD scores) with a suitable blood group and matched for size. The decision whether to transplant the organ into the patient with or without HCC was left to the surgeon, in the light of the two candidates' relative disease severity, the situation of the WL at the time (the proportion of patients with MELD > 20 or progressive HCC), and the characteristics of the donor. Generally speaking (but this was not an absolute rule), we tried to avoid using suboptimal donors in patients with MELD scores > 20. The median DRI, in fact, was 1.6 (0.9–2.2) for NM patients and 1.8 (1.1–3.0) for HCC patients (p = 0.04). From June 2006 onwards, we formally split our WL into two lists: one containing NM patients stratified according to their MELD scores, and the other with HCC patients and other MELD exceptions with MELD scores < 20 [13].

2.1.2. Statistical analysis

Patient and tumour characteristics at the 3-month visit are expressed as medians (ranges) for continuous data, and as frequencies (percentages) for categorical data.

Survival was calculated from the 3-monthly check-up until death or latest follow-up, irrespective of dropouts or LTs. Follow-up data were collected up until June 30, 2008 when our initial data analysis was performed. Length of follow-up is expressed as median (range). We performed a Cox's survival analysis to evaluate the prognostic role of LT and other recorded variables; in the Cox's regression model, LT was used as a time-dependent covari-