Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

The impact of waiting list alpha-fetoprotein changes on the outcome of liver transplant for hepatocellular carcinoma

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Background & Aims: Liver transplantation is a recognized treatment for selected patients with hepatocellular carcinoma (HCC), but transplant criteria still need to be refined, especially in the case of more advanced or downstaged tumors.

Methods: The present study investigated alpha-fetoprotein (AFP) as a predictor of outcome in 6817 patients listed with a diagnosis of HCC in the Scientific Registry of Transplant Recipients.

Results: Local pre-transplant HCC treatment was used in 41% of patients on the waiting list. Patients with AFP levels >400 ng/ml at the time of listing who were downstaged to AFP ⩽400 ng/ml had better intent-to-treat survival than patients failing to reduce AFP to ⩽400 (81% *vs.* 48% at 3 years, $p \leqslant 0.001$) and comparable survival to patients with stable AFP ⩽400 ng/ml (74%, $p = 0.14$). Patients with AFP levels decreased ⩽400 ng/ml and patients with levels persistently ⩽400 ng/ml also had similar drop-out rates from the list (10% in both groups) and post-transplant survival rates (89% *vs.* 78% at 3 years, $p = 0.11$). Such an AFP downstaging was associated with good survivals whatever the level of the original AFP (even if originally >1000 ng/ml). Only the last pre-transplant AFP independently predicted survival ($p \leqslant 0.001$), unlike AFP at listing or AFP changes.

Conclusions: Overall, downstaging HCC patients with high AFP is feasible and leads to similar intent-to-treat and post-transplant survivals to those of patients with AFP persistently low. Only last AFP appears relevant for patient selection before transplantation and should be used in combination with morphological variables.

Keywords: Liver transplantation; Hepatocellular cancer; Registry; Tumor volume; Alpha-fetoprotein.

Received 23 September 2010; received in revised form 20 November 2010; accepted 22 December 2010; available online 18 February 2011

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Abbreviations: AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; HR, hazard ratio; HRSA, Health Resources and Services Administration; MELD, Model for End-Stage Liver Disease; OPTN, Organ Procurement and Transplantation Network; SRTR, Scientific Registry of Transplant Recipients; TTV, Total Tumor Volume; UNOS, United Network for Organ Sharing; US, United States of America.

Introduction

Liver transplantation is a well recognized treatment for selected patients with hepatocellular carcinoma (HCC) [1]. Since 1996, Milan criteria have been commonly used, allowing transplantation for patients with a single HCC ⩽5 cm in diameter or up to three HCCs, each ⩽3 cm [1]. More recently, several centers have transplanted patients with more advanced HCCs either by expanding selection criteria or by offering downstaging protocols [2–5]. Despite proposals from several groups, broadly accepted guidelines are still lacking regarding selection of these patients [6].

Several studies have shown that downstaging allows acceptable post-transplant outcomes in selected patients [2,3,7–11]. However, studies on downstaging used heterogeneous criteria, were based on relatively few patients and/or analyzed only simple morphological parameters (size and number), while increasing evidence suggests that biological variables such as AFP, whether used as absolute value or as a marker of disease progression, may be at least as important [4–6,12–15].

The present study investigated the relevance and relative impact of AFP absolute values and of AFP changes on the waiting list, with regard to drop-out and survival rates, and whether AFP-downstaging could be a meaningful pre-transplant criterion.

Materials and methods

This study was based on the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States of America (US), submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere [16]. The Health Resources and Services Administration (HRSA), US Department of Health and Human Services, provides oversight for the activities of the OPTN and SRTR contractors.

All listed patients with a diagnosis of HCC from January 2003 to May 2009 were included in the study. Patients with all other types of liver cancers (including fibrolamellar carcinoma and unspecified liver cancers) were excluded. Listed patients underwent liver transplant or dropped-out from the waiting list, due to delisting or death.

HCC characteristics were first assessed, according to AFP and Total Tumor Volume (TTV) both at the times of listing and transplantation. These variables are known to be the only ones predicting survival after liver transplantation for HCC in the SRTR registry [4,17]. TTV was calculated by adding the volume of each HCC ($(4/3)\pi r^3$) based on the maximum radiological radius of each tumor. When only one AFP or TTV measurement was available, it was considered representing

the value at the time of listing and was not used again at transplant. In case of multiple time points, AFP and TTV velocities were computed (possible in 1845 patients for AFP and 1883 patients for TTV). AFP velocity was defined as the change per increment of time and was expressed as ng/ml/month. Similarly, TTV velocity was expressed as cm^3/month. Velocity variables were negative (showing an improvement) or positive (showing a worsening). For some analyses, previously published cut-offs of 400 ng/ml for AFP and 115 cm^3 for TTV were used [4,17–21].

Following UNOS listing criteria, the studied population was very homogeneous regarding tumor size, with most patients within Milan criteria and only 0.5% with HCCs larger than 115 cm^3 [1,4]. As a consequence, statistical power was not appropriate for further TTV analysis and only AFP was taken into account.

Patients undergoing transplantation were compared to those who dropped-out from the waiting list. Drop-out was defined as death on the waiting list or delisting because of patient or tumor characteristics. Of note, delisting on the basis of HCC progression was not specifically reported and could not be analyzed independently.

Survival rates were assessed from the time of listing (intent-to-treat) and from transplant (post-transplant). Of note, the intent-to-treat analysis included all listed patients, which have subsequently either dropped-out, have been transplanted or are still active on the list. The occurrence and the date of death were obtained from data reported to the SRTR by the transplant centers and were completed by data from the US Social Security Administration and from the OPTN. Survival analyses were performed according to the Kaplan Meier method and group comparison with the log-rank test. A multivariate Cox analysis model was used to assess covariate adjusted survival rates. Covariates included: date of listing, age at listing, Model for End-Stage Liver Disease (MELD) score at listing, primary underlying liver disease, TTV, donor risk index (as defined in [22]), and the use of sirolimus and anti-CD25 antibodies. Of note, the last two covariates have been associated with improved outcomes after transplantation for HCC in a previous report based on the same database [23].

Binomial variables were compared using Chi-square test. Results were provided as mean ± standard deviation. Standard alpha level of 0.05 indicated statistical significance. Analyses were conducted using SPSS 15.0 (SPSS, Chicago, IL).

Results

During the study period, 6817 patients were listed for liver transplantation with a diagnosis of HCC. Mean age was 56 ± 8 years, most patients were males and infected with hepatitis C virus (Table 1). The average raw MELD score was 12 ± 6.

Most patients had a limited tumor burden with a mean TTV of 22 ± 104 cm^3. Only 35 (0.5%) had a TTV >115 cm^3 at listing, which is a known cut-off associated with increased risk of recurrence and death after transplantation [4,17]. AFP showed a wide distribution, with a mean of 354 ± 2334 ng/ml. At listing, 559 patients (8.2%) had AFP levels over 400 ng/ml.

The use or the absence of local HCC treatment on the waiting list was reported in 5481 patients (Table 1). Among them, 59% did not undergo any treatment while on the waiting list. The treatments most often used were transarterial chemo-embolisation (TACE) and radio-frequency ablation (RFA, Table 1).

AFP and TTV had independent behaviors in the study population, as very few patients showed an increase of both variables at listing or transplant (patients with both high AFP and TTV were likely considered as having very aggressive HCC and did not reach the waiting list, Fig. 1A and B). Overall, mean AFP, and TTV remained stable on the waiting list (last AFP 386 ± 3151, last TTV 19 ± 123), with mean velocities close to zero (AFP velocity: 37 ± 1027 and TTV velocity: −0.37 ± 6.6, respectively). At transplant, 607 patients had AFP >400 ng/ml and 44 TTV >115 cm^3.

Overall intent-to-treat survival from listing was 67% and 58% at three and five years, respectively. Post-transplant survival was 74% and 63% at three and five years, respectively. Drop-out was associated with higher absolute AFP both at the time of listing and last measurement and AFP velocity (Table 2). TTV and TTV velocity were similar in transplanted and dropped-out patients (Table 2).

Table 1. Demographics of HCC patients on the waiting list.

Number of patients	6817
Mean age at listing (year ± SD)	56 ± 8
Gender (female/male)	1430/5387
Cause of liver disease (%)	
HCV (± alcohol, ± HBV)	3968 (58)
HBV	615 (9)
Alcohol	540 (8)
NASH	185 (3)
Primary biliary cirrhosis	58 (1)
Hemochromatosis	52 (0.5)
Primary sclerosing cholangitis	21 (0.5)
Alpha1-antitrypsin deficiency	18 (0.5)
Other	1360 (19.5)
MELD at listing (± SD)	12 ± 6
Donor Risk Index (± SD)	1.94 ± 0.42
Mean Total Tumor Volume at listing (cm^3)	22 ± 104
Total Tumor Volume >115 cm^3 at listing (%)	35 (0.5)
Mean serum alpha-fetoprotein level at listing (ng/ml)	354 ± 2334
Serum alpha-fetoprotein level >400 ng/ml at listing (%)	559 (8.2)
Pre-transplant treatment (%)	
TACE	1403 (25.5)
RFA	557 (10)
Chemotherapy	75 (1)
Surgery	35 (1)
Cryo-ablation	7 (0.5)
Multiple	172 (3)
No treatment	3232 (59)
Mean waiting time between listing and transplant (month ± SD)	3 ± 5

HCV: hepatitis C virus infection; HBV: hepatitis B virus infection; TACE: transarterial chemo-embolisation; RFA: radio-frequency ablation.
Donor risk index was defined according to Ref. [22].

Further analyses were only conducted with AFP, due to the limited number of patients with high TTV. In an effort to assess the impact of AFP changes, patients were grouped according to AFP at listing and at transplantation, and to whether they were within or beyond the cut-off level of 400 ng/ml. This cut-off was chosen from previous studies [4,18,20,24]. Four groups were created and intent-to-treat survival was first assessed (Fig. 2A). Among patients with stable AFP levels, those ⩽400 ng/ml had significantly better survival rates than those continuously >400 ng/ml (74% *vs.* 48% at 3 years, $p \leqslant 0.001$). Interestingly, patients with increasing AFP levels on the waiting list (⩽400 ng/ml at listing and >400 ng/ml at last value) had similar survival rates as those with persistently high AFP levels (38% at 3 years, $p = 0.25$). Conversely, successfully downstaged patients (>400 ng/ml at listing and ⩽400 ng/ml at last measurement pre-transplant) had similar survival rates as the best group, with persistently low AFP levels (81% at 3 years, $p = 0.14$). These intent-to-treat survival differences were in part related to different rates of drop-out from