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Identification of Liver Transplant Candidates with Hepatocellular Carcinoma and Very Low Dropout Risk: Implications for the Current Organ Allocation Policy

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Abstract

It has been shown that patients with hepatocellular carcinoma (HCC) meeting UNOS T2 (Milan) criteria are advantaged compared to patients without HCC under the current organ allocation system for liver transplant (LT). We hypothesize that within T2 HCC, there is a subgroup with a low risk of waitlist dropout, and should not receive the same listing priority. This study evaluated 398 consecutive patients with T2 HCC listed for LT with MELD exception from 2005 to 2010 at our center. Competing risk (CR) regression was used to determine predictors of dropout. Probabilities of dropout due to tumor progression or death without LT by CR analysis were 9.4% at 6 months and 19.6% at 12 months. The median time from listing to LT was 8.8 months, and from listing to dropout or death without LT was 7.2 months. Significant predictors of dropout or death without LT by multivariate CR regression included 1 tumor 3–5 cm (vs. ≤3 cm), 2 or 3 tumors, lack of a complete response to first loco-regional therapy (LRT), and high alpha-fetoprotein (AFP) after the first LRT. A subgroup (19.9%) meeting the following criteria: 1 tumor 2 to 3 cm, complete response after first LRT, and AFP ≤20 ng/mL after first LRT, had 1- and 2-year probabilities of dropout of 1.3% and 1.6%, respectively, compared to 21.6% and 26.5% for all other patients (p=0.004). In conclusion, a combination of tumor characteristics and complete response to the first LRT define a subgroup of patients with a very low risk of waitlist dropout who does not require the same listing priority. Our results may have important implications for the organ allocation policy for HCC.

INTRODUCTION

The development and validation of the Model for End Stage Liver Disease (MELD) score in predicting mortality in patients with end-stage liver disease (1) has resulted in the implementation of this continuous scoring system by the United Network for Organ Sharing (UNOS) for the prioritization of patients for liver transplantation (LT) since 2002 (2,3). Patients with hepatocellular carcinoma (HCC), on the other hand, may have well preserved liver function and low calculated MELD score, but are at risk for tumor progression and dropout from the LT waiting list, especially if the waitlist time exceeds 6 months (4).

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Consequently, attempts were made to give patients with HCC extra priority based on the expected risk of dropout from the waiting list due to tumor progression, and to allow for equitable dropout rates between HCC and non-HCC patients (5). This priority system for HCC has so far only applied to those meeting Milan criteria (6). In the UNOS staging classification, the Milan criteria are further divided into T1 (1 lesion < 2 cm) and T2 stage (1 lesion 2–5 cm, 2–3 lesions each ≤3cm). It became evident that HCC patients were initially given excessive priority due to over-estimations of their risks of dropout from the waiting list. After several modifications of the HCC-MELD algorithm, most recently in January 2005, patients with stage T2 have since been given a lower MELD exception score starting at 22 points, which is equivalent to a 15% risk of mortality at 3 months. They are eligible for continued upgrades at every 3-month intervals (equivalent to a 10% increase in mortality), as long as the tumors remain within T2 criteria. Additionally, patients with T1 HCC are no longer eligible for priority listing since 2004 in large part due to a high rate of HCC misdiagnosis in these patients (7).

Even with each of these changes in organ allocation policy giving reduced priority to patients with T2 HCC, data have continued to emerge suggesting that patients with HCC remain significantly advantaged when compared to patients without HCC on the LT waiting list (8–12). This is a challenging problem and the solution remains unclear (10). A confounding factor is the regional variations in this discrepancy (9). Using a different organ allocation scheme to give priority to HCC patients at high risk of dropout (9, 13) may end up selecting those with more aggressive tumor biology for LT (10, 14). Another important consideration is the increased use of loco-regional therapy (LRT) for HCC as a bridge to LT, which may influence the risk of dropout from the waiting list. A previous report from our center showed waitlist dropout rates of 11% at 6 months and 57% at 12 months, while only 41% of patients received LRT (4). In contrast, a number of subsequent studies applying trans-arterial chemoembolization (TACE) or radiofrequency ablation (RFA) to all HCC patients have shown waitlist dropout rates of 0% to 5.8% over a mean waitlist time of 5.9 to 12.7 months (15–17), but the sample size was small. On the other hand, large studies using national databases to identify predictors of dropout from the waiting list were not able to assess the effects of LRT (9, 13, 18).

Our center is within Region 5 with among the longest average waitlist time for HCC and non-HCC patients. This has allowed us to evaluate the pattern and risks of dropout based on tumor characteristics (4, 19). We hypothesize that response to LRT is an important determinant of the risk of waitlist dropout, and may help identify a subset of patients with a very low rate of waitlist dropout and not warranting equal listing priority as other patients with T2 HCC. We therefore evaluated clinical and radiographic factors including response to LRT as possible predictors of dropout in a large cohort of patients with T2 HCC listed for LT at our center with MELD exception since the latest change in organ allocation policy for HCC in 2005.

PATIENTS AND METHODS

Study Design and Patient Population

This was a retrospective cohort study of patients aged 18 years and older with T2 HCC listed for LT with MELD exception from March 2005 to January 2011 at our center. This start date was chosen to encompass the most recent HCC policy change, in which the initial MELD exception was down-graded to 22 points for T2 HCC. Among the 512 patients initially evaluated, 114 patients were excluded from the study. These 114 patients included 72 patients who underwent tumor down-staging to meet T2 criteria under a down-staging protocol as previously described (20); 18 patients who were transplanted at another institution; 10 patients who were lost to follow-up within one month of transplant listing, 7

patients who were found on liver explant to have cholangiocarcinoma and not HCC, and 7 patients who received a live-donor LT. The final cohort consisted of the remaining 398 patients.

The variables collected included demographic data (age, sex, gender), tumor size and number at time of listing, laboratory data at time of listing (alpha-fetoprotein (AFP) and MELD score), and liver-related factors (etiology of liver disease and Child-Pugh-Turcotte score (CPT) (21)). Since September 2004, the decisions regarding management of patients with HCC awaiting LT have been made in a weekly multi-disciplinary Liver Tumor Board attended by transplant hepatologists, transplant surgeons, oncologists, interventional radiologists, and radiologists with an expertise in diagnostic abdominal imaging. The diagnosis of HCC was based on radiographic features that were characteristic of HCC, including arterial phase enhancement and portal venous phase washout for lesions measuring at least 1 cm. Nodules not showing these characteristics were considered indeterminate for HCC and were followed by CT or MRI every 3 months to observe for interval growth and repeat review in Tumor Board. Percutaneous biopsy was performed for the purpose of diagnosis of HCC only in selected cases with atypical radiographic features. Nodules < 1 cm were not counted as HCC.

We applied LRT, with repetitive interventions if needed, to induce complete necrosis of all tumor nodules if possible prior to LT. The decision regarding the HCC treatment modalities was made based on review of imaging studies in our weekly multi-disciplinary Tumor Board. The choice of LRT was based on the degree of tumor hypervascularity, tumor location, response to prior LRT, and the hepatic and functional reserve of the patient. Per our protocol, patients underwent contrast-enhanced computed tomography or magnetic resonance imaging at one month after each LRT and at a minimum of once every three months after listing for LT. Tumor response to first LRT, regardless of whether before or after LT listing, was assessed by collecting pre- and post-LRT AFP within one month of treatment date as well as radiographic response based on modified RECIST criteria (22,23).

Among patients who underwent LT, explant pathology was reviewed to determine histologic grade based on the modified Edmondson criteria (grade 1: well-differentiated; grade 2: moderately differentiated; and grade 3: poorly differentiated) (24), tumor stage, and presence of vascular invasion. Explant tumor staging in this study was based on size and number of only the viable tumors.

Outcomes

The primary outcome was dropout from the transplant waiting list for any of the following reasons: death without LT, HCC tumor progression beyond T2 criteria, or being too sick or medically unsuitable to undergo LT. Time to dropout or LT was measured from the date of initial HCC listing to waitlist removal or LT, respectively. Among patients who were removed from the waiting list if they were no longer interested in undergoing LT or were non-compliant with our center's transplant policies, follow-up was censored at the time of delisting. Date of death was obtained from our transplant database and confirmed using the Social Security Death Index.

Statistical Analysis

Patient characteristics were summarized using median and ranges for continuous variables and proportions for categorical variables. Patients on the transplant waiting list are at risk for several competing outcomes including LT, dropout from the waiting list for any reason, and death without LT, thus the cumulative incidence of dropout was estimated while accounting for competing risks (CR). Univariate and multivariate analysis of predictors of waitlist

dropout were determined by CR regression using the Fine and Gray method (25). Predictors of dropout with a univariate p value less than 0.1 were evaluated in the multivariate analysis with the final model selected by backward elimination (p for removal greater than 0.05). The model identified a subpopulation of patients with low risk for waitlist dropout. Cumulative incidence for the low dropout risk group versus all other patients was estimated from the baseline function of the multivariate CR model. Clinical characteristics were compared between the two groups using Pearson's chi-square and Wilcoxon tests, as appropriate. Statistical analyses were performed using Stata/IC 11.1 (Statacorp, College Station, TX).

RESULTS

Patient Characteristics

Baseline demographic and clinical characteristics of the 398 patients comprising the study population are summarized in Table 1. The median age was 57 and 76.9% were men. Caucasians (42.7%) and Asians (31.4%) made up the majority of the study population. Hepatitis C virus was the most common etiology of liver disease (60.6%), followed by hepatitis B (24.4%). At the time of listing with MELD exception points based on HCC, the median actual MELD score was 11. The median CPT score was 7, and 46.7% of patients were classified as Child's class A (CPT 5–6), 41.5% were Child's class B (CPT 7–9), and 11.8% were Child's class C (CPT ≥ 10). The median AFP level was 13 ng/mL at the time of LT listing. More than half (57.8%) of the patients had an AFP less than 20 ng/ml, and 6.5% had an AFP greater than 1000 ng/mL. By subcategorizing patients within T2 criteria, 36.9% had a single HCC lesion 2 to 3 cm, 35.2% had a single HCC lesion greater than 3 cm but less than 5 cm, and 27.9% had multiple lesions. Percutaneous biopsy was performed to confirm the diagnosis of HCC prior to LRT in 33 patients (8.3%).

Radiographic and AFP response to Loco-regional Therapy

The vast majority of patients (96.5%) underwent at least one LRT after the diagnosis of HCC was made. TACE was the most commonly used modality for a patient's first LRT (71.7%). A complete response on imaging one month after this initial treatment was seen in 60.2% of patients by modified RECIST criteria, whereas a partial response (23.6%) or stable disease (13.5%) was seen in a majority of the remaining patients. Only 10 patients (2.7%) had progressive disease. Median AFP decreased from 18.0 ng/ml before the first LRT to 9.5 ng/ml after the first LRT. About two-thirds of patients (66.1%) had an AFP under 20 ng/ml after receiving their first LRT (Table 2).

Outcomes while on the Waiting List

Of the 398 patients in the cohort, 271 (68.1%) underwent LT with a median waiting time of 8.8 months (IQR 5.9–12.8). Sixty-six patients (16.6%) had dropped out due to tumor progression and 26 patients (6.5%) died while on the waiting list. The median time from listing to dropout due to tumor progression or death without liver transplant was 7.2 months (IQR 3.5–10.6). Cumulative probabilities of dropout due to tumor progression or death by competing risks analysis were 9.4% (95% CI 6.8–12.5) within 6 months and 19.6% (95% CI 15.8–23.7) within 12 months. Twenty-seven patients were censored at the time of waitlist removal. Reasons for waitlist removal included significant cardiopulmonary disease precluding LT (n=6), non-compliance (n=4), or patient decision not to undergo LT (n=17). At the end of study follow-up, 8 patients (2.0%) remained active on the transplant waiting list.

Factors Associated with Dropout

In univariate analysis, the following covariates were predictive of dropout due to tumor progression or death by CR analysis: multiple HCC tumors or a solitary tumor 3.1–5cm (versus solitary tumor 2–3cm), lack of a complete response to first LRT, and calculated MELD score (Table 3). The 1-year cumulative incidence of dropout was 6.2% (95% CI 3.0–10.9) for patients with a single tumor 2–3cm versus 16.6% (95% CI 9.4–25.7) for those with two tumors, 30.5% (95% CI 22.9–38.4) for a single tumor 3.1–5cm, and 46.4% (95% CI 28.2–62.8) for those with three tumors ($p<0.001$) (Figure 1a). Stratified by response to first LRT based on modified RECIST criteria, the 1-year cumulative incidence of dropout was 9.3% (95% CI 5.9–13.6) for those with a complete response versus 19.2% (95% CI 11.1–29.0) for partial response, 39.5% (95% CI 27.2–51.1) for stable disease, and 85.0% (95% CI 31.8–97.7) for progressive disease ($p<0.001$) (Figure 1b). AFP level at listing and after first LRT both as a continuous variable and also at all cutoffs measured including >1000, >500, >300, >100, and >20 ng/ml were also predictive of dropout on univariate analysis (Table 3). The 1-year cumulative incidence of dropout based on AFP after first LRT was 12.7% (95% CI 8.6–17.6) for those with an AFP<20, 20.7% (95% CI 11.7–31.4) with an AFP 21–100, 24.4% (95% CI 9.9–42.3) with an AFP 101–500, and 59.5% (95% CI 35.3–77.2) with an AFP>500 ($p<0.001$) (Figure 1c). Age, gender, etiology of liver disease, Child's class cirrhosis, and the type of first LRT were not significant predictors of dropout due to tumor progression or death (Table 3).

In CR multivariate analysis (Table 4A), the presence of three tumors (subhazard ratio (SHR) 8.68, 95% CI 3.25–23.19), two tumors (SHR 5.03, 95% CI 2.10–12.04), or a solitary 3.1–5cm tumor (SHR 5.10, 95% CI 2.28–11.41) were predictive of dropout due to tumor progression or death as was lack of a complete response to first LRT (SHR 3.08, 95% CI 1.78–5.35). AFP >20 ng/mL after first LRT (SHR 1.87, 95% CI 1.13–3.10, $p=0.02$) and all other AFP cutoffs in univariate analysis were also significant predictors of dropout in multivariate analysis. MELD score was a predictor of dropout in univariate but not in multivariate analysis.

Subgroup with a Very Low Risk of Dropout

The 3 variables significantly associated with a lower risk of waitlist dropout due to tumor progression or death included a single 2–3cm lesion on presentation, complete response to first LRT, and low AFP level after the first LRT. In order to identify a group of HCC patients with the lowest risk of waitlist dropout, we used the lowest AFP cutoff of 20 ng/ml significantly associated with dropout. Complete data with respect to each of these three variables was available in 317 of 398 (79.6%) patients. Of these 317 patients, a subgroup of 63 patients (19.9%) met the following criteria: 1 tumor 2–3 cm, complete response to first LRT, and AFP =20 ng/ml after first LRT. This subgroup had estimated 1- and 2-year probabilities of dropout or death without LT of 1.3% and 1.6%, respectively, compared to 21.6% and 26.5% for all other patients ($p=0.004$) (Figure 2).

We also performed sensitivity analysis, taking into consideration the high prevalence of hepatitis B in our cohort that is likely to be different from many other transplant centers across the country. Excluding patients with hepatitis B and using the same criteria for a low risk for dropout, the 1- and 2-year probabilities of dropout were 2.2% and 2.5%, respectively, in the low-risk group compared to 22.5% and 27.0% for all other patients ($p=0.02$). Additionally, each component of the low risk group (1 lesion 2 to 3 cm, complete response to first LRT and AFP<=20) remained significantly associated with reduced waitlist dropout in multivariate analysis after excluding all hepatitis B patients (Table 4B).

Clinical characteristics, number of LRT received, and histopathologic characteristics were compared between the subgroup with a low risk of dropout versus all other patients (Table 5). While listing MELD was similar, the low risk group had a lower percentage of Child's C patients (1.6% vs. 9.8%, p=0.03). Patients at low risk of waitlist dropout were significantly more likely to receive a single LRT (82.5% vs 44.9%, p<0.001). LT was performed in 57 of 63 patients (90.4%) in the low risk group and 167 of 254 (65.7%) in the high risk group. Patients in the low risk group were more likely to have complete tumor necrosis on explant (60.7% vs 34.0%, p<0.001) and less likely to have explant tumor burden outside of T2 criteria (3.5% vs. 21.6%, p=0.04). The incidence of macro- or micro-vascular invasion in the explant did not differ significantly between the two groups.

DISCUSSION

The demand for liver allografts far exceeds supply in the United States, in part due to the rising incidence of HCC and the growing numbers of patients with HCC who may benefit from LT (26). Since the MELD allocation scheme for HCC was implemented in 2002, the proportion of patients receiving priority listing with HCC-MELD exception has increased from 10.5% in 2002 to 15.5% in 2008 (11). A pressing problem facing the transplant community is the growing body of evidence that patients with HCC are given an unfair advantage in organ allocation over non-HCC patients listed for LT based on their calculated MELD score (9–12). Using UNOS data from 2005 to 2008, Washburn et al. (9) analyzed the rates of waitlist dropout by CR statistics and found significantly higher rates of waitlist dropout in non-HCC patients compared to HCC patients. This observation was reproducible across all regions, although the disparities were relatively small in 2 of the 11 regions. Goldberg et al. (12) analyzed the UNOS database from 2005 to 2009 and similarly demonstrated that the odds of waitlist removal due to death or clinical deterioration were significantly lower for HCC patients versus non-HCC patients. Furthermore, the observed differences between the two groups in waitlist removal increased steeply as the analysis progressed from the lower MELD strata to the higher strata. At a MELD of 22 for LT candidates with HCC, 4.6% were removed from the waiting list within 90 days, whereas the corresponding waitlist removal rate was 11% for non-HCC candidates with MELD scores of 21–23. The waitlist removal rate within 90 days was only 3% of HCC patients with 28 MELD exception points, compared to 23.6% of non-HCC patients with MELD scores of 27 to 29.

While it is generally recognized that changes are needed to address the disparity in the rate of waitlist dropout for HCC and non-HCC patients, there is no easy solution for this problem (10). Reducing the initial priority score for patients with HCC at the national level does not account for the significant regional variations in the waitlist time as well as waitlist removal rates (27). This strategy of lowering the MELD score uniformly across all regions may in fact place HCC patients at a disadvantage in certain regions (10). A different approach has been advocated to give higher listing priority to those at greater risk of dropout from the waiting list (9, 13, 28). Freeman et al. (13) proposed the HCC-MELD equation, which is a continuous score based on the calculated MELD score at listing, AFP, and maximal tumor size; and the higher the score, the greater the risk of waitlist dropout. This score has been proposed in a scheme that gives the highest organ allocation priority to those with the greatest risk of waitlist dropout as predicted by the HCC-MELD equation (8). Toso et al. (28) analyzed waitlist dropout in the Scientific Registry of Transplant Recipients, and proposed a common waiting list that included both HCC and non-HCC patients who were assigned a continuous deMELD score based on age, calculated MELD score, tumor size and number, AFP, and etiology of liver disease. However, proposals to give priority to patients with higher AFP and larger tumors have also raised concerns of selecting for tumors with worse biology, leading to inferior post-transplant outcomes (10). High AFP has been shown

in a plethora of studies to be predictive of worse prognosis after LT, especially with levels exceeding 400 or 1000 ng/mL (29). There is also good correlation between larger tumor diameter and a greater likelihood of micro-vascular invasion (30). In fact, a recent study by Cucchetti et al. (14) applying the HCC-MELD equation (13) has shown that the higher the probability of waitlist dropout as predicted by the HCC-MELD equation, the lower the survival after LT.

In the present study, we test the hypothesis that there is a subgroup of patients with a very low dropout risk and do not require the same listing priority. Using CR regression, we found that the subgroup meeting all 3 criteria – complete response after the first LRT, AFP ≤ 20 ng/mL after the first LRT, and single lesion 2–3 cm, had a very low probability of waitlist dropout of only 1.3% at 1 year and 1.6% at 2 years, compared to 21.6% and 26.5% rates of dropout at 1 and 2 years, respectively, for all other patients. This group with a very low dropout risk accounts for 20% of our cohort. Reducing listing priority in this group would decrease the burden of HCC patients receiving MELD-exception who truly needs timely LT, and allow non-HCC patients to have greater access to LT. This may potentially reduce the inequities in dropout rates for non-HCC and HCC patients.

Contrary to several other published reports (7, 9, 18), calculated MELD score at the time of listing was predictive of waitlist dropout only in univariate but not in multivariate analysis in our study. Washburn et al. (9) found a 9% increase in waitlist dropout per each additional MELD point at listing. The difference may be explained by the high proportion of well compensated cirrhosis in our cohort, in which the median MELD score was only 11, and only 22.6% of patients had a MELD score of 15 or higher. Only 3.5% of our cohort did not receive LRT and among them, only 28.6% was due to very advanced decompensated liver disease. Patients who are really too sick to receive any LRT likely have calculated MELD scores exceeding the HCC-MELD exception, and receive organ allocation based on their true MELD score. It should also be pointed out that the benefit of LRT in reducing the rate of waitlist dropout has not been confirmed due to the lack of randomized controlled trials, but such a study is not likely to be feasible (31). LRT is recommended, however, when the waitlist time is expected to be at least 6 months (32). Our observation that complete response to LRT correlates with a lower probability of waitlist dropout is consistent with the findings in a previous study by Cucchetti et al (33). Their study included 315 patients in whom 30% had HCC outside of Milan criteria before LT and 93% had received LRT. The median waitlist time was 10 months and the 1-year probability of dropout was 19.9%. They found complete response to LRT (45.7% of patients) to be the only significant predictor of a low risk of dropout in multivariate CR analysis.

It may be argued that using response to the first LRT as a means of determining listing priority is not applicable to regions with short waitlist time, where the benefits of LRT have not been established. Kadry et al. (27) reported regional variations in the use of LRT before LT for HCC. Regions with a median waiting time of > 6 months performed more LRT and had significantly higher waitlist dropout rates. Nevertheless, the differences in the rates of LRT were not as dramatic as one would expect given the disparities in waitlist time. Among 8 of 11 regions in which over 80% of patients received LT within 6 months, the proportion of patients receiving LRT before LT ranged from 36% to 53%, compared to a range of 50% to 54% in the other 3 regions with longer waitlist time. The need to observe tumor response after the first LRT in our current proposal also incorporates the “ablate and wait” principle (34), which aims to avoid transplanting tumors with poor biology that progresses rapidly despite LRT and also do poorly after LT. Our cohort has a high prevalence of hepatitis B and a very low prevalence of fatty liver disease, and therefore may not fit the usual demographics of most other transplant centers across the country. We did perform sensitivity analysis by excluding hepatitis B patients, and found similar results, with a

significantly lower risk of dropout in patients meeting the criteria – complete response after the first LRT, AFP < 20 ng/mL after the first LRT, and single lesion 2–3 cm, when compared to those not meeting these criteria. There

Our study has several limitations, most notably the retrospective study design and the lack of complete information on radiographic and biochemical (AFP) response to first LRT in 20% of patients, in part because we only included data obtained within 1 month before and after the first LRT. are also several strengths of our study. Our center is situated in Region 5 with the nation's longest waitlist time and the highest 6- and 12-month dropout rates, providing a rather unique position to accurately assess factors predictive of waitlist dropout. The use of LRT in almost all of the patients in our cohort also allows us to evaluate the impact of response to LRT on the risk of waitlist dropout, whereas this information was not readily available in previous analyses of large national databases (7, 9, 18). Similar to the study by Washburn (9), we used the CR method to evaluate the rate and predictors of dropout from the waiting list rather than the Kaplan-Meier method used in a number of previous studies (4, 13, 19). The CR method more accurately estimates cumulative incidence compared to the Kaplan-Meier method where censored and transplanted patients are treated the same (both are censored) overestimating cumulative incidence.

In summary, the present study suggests that a combination of tumor characteristics and complete response to the first LRT defines a subgroup with a very low waitlist dropout risk of 1.3% within 1 year and 1.6% within 2 years. The vast majority of these patients does not derive immediate benefit from LT and should not receive the same listing priority as other patients with T2 HCC. Under the current climate in which demands for organs far exceeding supply, and HCC patients are advantaged in the organ allocation scheme, our results may have important implications for the organ allocation policy for HCC.

Abbreviations

MELD	Model for End Stage Liver Disease
UNOS	United Network for Organ Sharing
LT	liver transplantation
HCC	Hepatocellular carcinoma
LRT	loco-regional therapy
TACE	transarterial chemoembolization
RFA	radiofrequency ablation
AFP	alpha-fetoprotein
CR	competing risks
CPT	Child-Pugh-Turcotte

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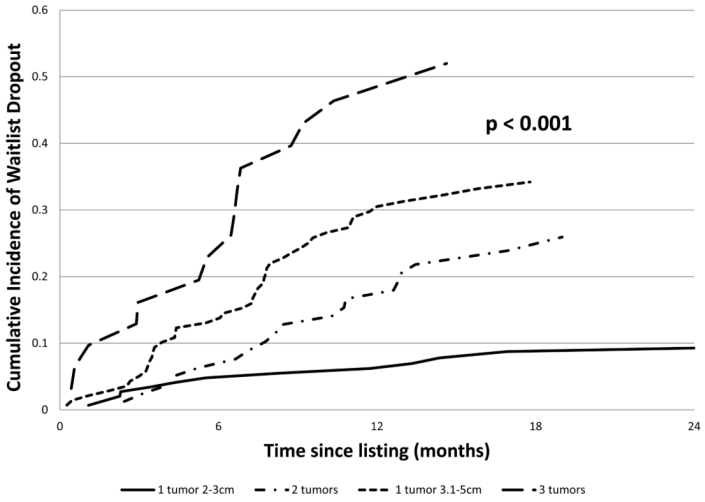
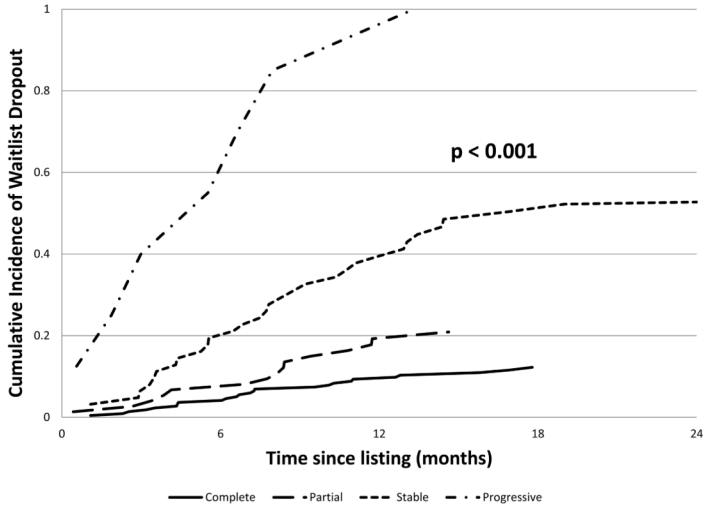
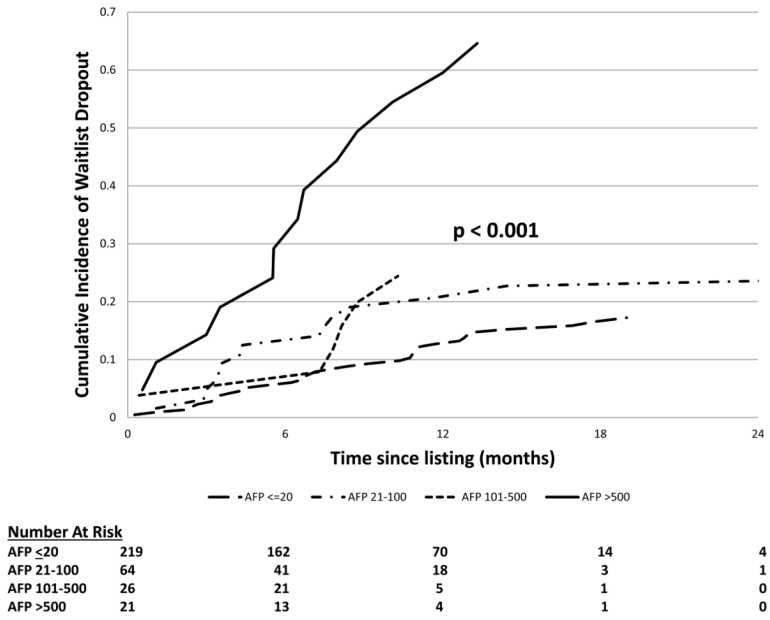


Number At Risk					
1 tumor 2-3cm	147	108	52	10	2
2 tumors	80	56	21	2	0
1 tumor 3.1-5cm	140	98	37	7	3
3 tumors	31	21	4	1	0



Number At Risk					
Complete Response	220	170	74	13	3
Partial Response	75	56	19	3	0
Stable Disease	63	40	19	4	2
Progressive Disease	8	3	1	0	0



Number At Risk					
AFP ≤20	219	162	70	14	4
AFP 21-100	64	41	18	3	1
AFP 101-500	26	21	5	1	0
AFP >500	21	13	4	1	0

Figure 1.

Cumulative incidence of waitlist dropout due to tumor progression or death by **(A).** Tumor size **(B).** Response to first loco-regional therapy received based on modified RECIST criteria and **(C).** Alpha-fetoprotein after first loco-regional therapy received.

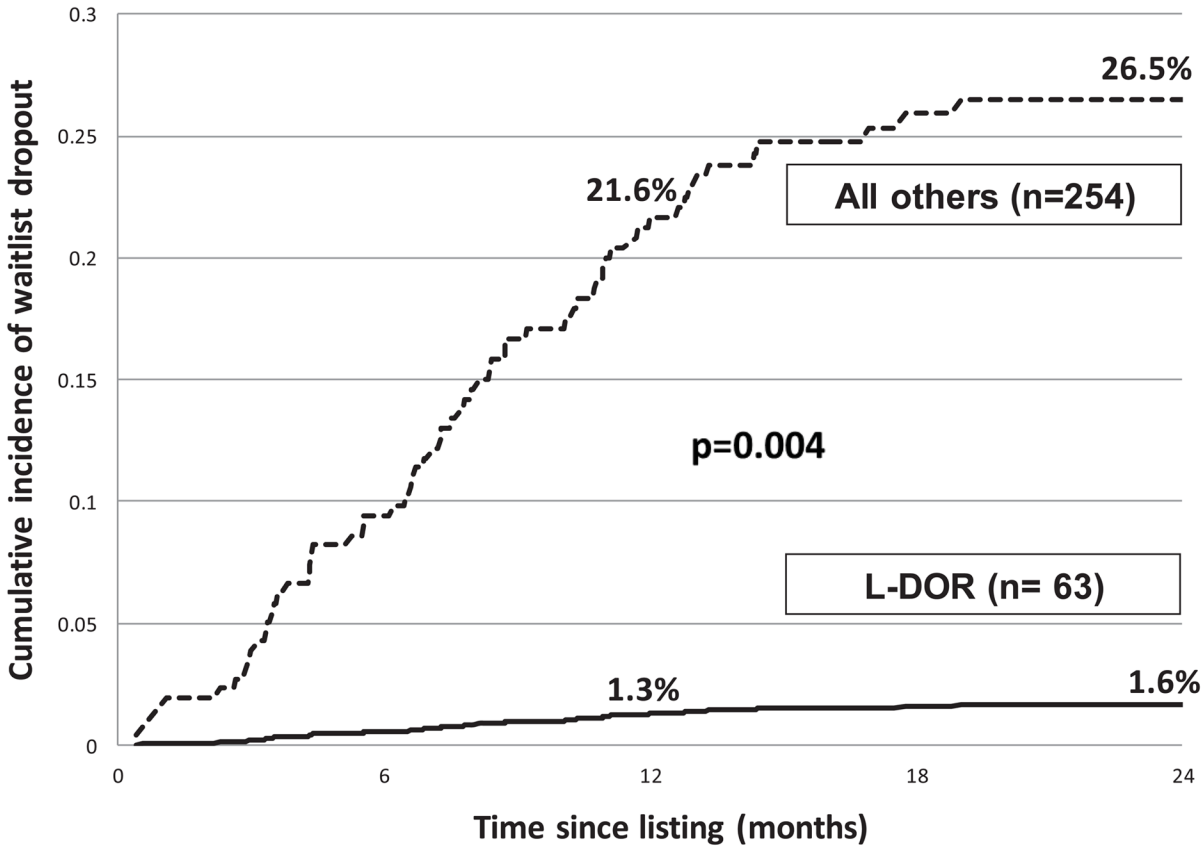


Figure 2.

The cumulative incidence of waitlist dropout due to tumor progression or death by dropout risk groups (competing risks). The low-risk group (L-DOR) meets the following criteria: a single tumor 2–3cm, a complete response to first loco-regional therapy, and an alpha-fetoprotein ≤20 ng/ml after first loco-regional therapy received.

Table 1

Baseline Characteristics of the Study Population (n=398)

Median Age (yrs)	57 (range 21–77)	
		Number (%)
Male gender		306 (76.9)
Race/Ethnicity		
	Caucasian	170 (42.7)
	Asian	125 (31.4)
	Hispanic	72 (18.1)
	African American	24 (6.0)
	Other	7 (1.8)
Etiology of Liver Disease		
	HCV	241 (60.6)
	HBV	97 (24.4)
	EtOH	26 (6.5)
	NAFLD	21 (5.3)
	Other	13 (3.3)
MELD Score at listing	11 (range 6–27)	
	MELD <15	308 (77.4)
	MELD ≥15	90 (22.6)
Child Pugh Class		
	A	186 (46.7)
	B	165 (41.5)
	C	47 (11.8)
AFP at listing (ng/ml) (n=397)	13 (IQR 5–81)	
	≤20	229 (57.8)
	20–100	80 (20.1)
	101–300	38 (9.6)
	301–500	15 (3.8)
	501–1000	9 (2.2)
	>1000	26 (6.5)
Tumor Size and Number at Diagnosis		
	1 lesion 2–3cm	147 (36.9)
	1 lesion 3.1–5cm	140 (35.2)
	2 lesions	80 (20.1)
	3 lesions	31 (7.8)

Table 2

Number of Loco-regional Treatments and Radiographic/Alpha-fetoprotein Response to First Loco-regional Treatment

Number of LRT Received (n=398)		**Number (%)**
	0	14 (3.5)
	1	191 (48.0)
	2	104 (26.1)
	3	54 (13.6)
	>3	35 (8.8)
Type of 1st LRT Received (n=384)		
	TACE	275 (71.7)
	RFA	105 (27.3)
	PEI	4 (1.0)
Response to 1st LRT by Modified RECIST criteria (n=364)		
	Complete Response	219 (60.2)
	Partial Response	86 (23.6)
	Stable Disease	49 (13.5)
	Progressive Disease	10 (2.7)
AFP before 1st LRT (ng/ml) (n=359)	18.0 (IQR 6–102)	
	≤20	186 (51.8)
	20–100	82 (22.9)
	101–300	31 (8.6)
	301–500	17 (4.7)
	501–1000	15 (4.2)
	>1000	28 (7.8)
AFP after 1st LRT (ng/ml)(n=330)	9.5 (IQR 4.6–37)	
	≤20	218 (66.1)
	20–100	65 (19.7)
	101–300	19 (5.8)
	301–500	7 (2.1)
	501–1000	9 (2.7)
	>1000	12 (3.6)

Table 3

Univariate Analysis of Predictors of Dropout Due to Tumor Progression or Death by Competing Risks

	Univariate SHR (95% CI)	p-value
Patient Characteristics at Listing		
Age (per year)	0.98 (0.96–1.01)	0.21
Female Gender	0.93 (0.57–1.52)	0.78
Etiology of liver disease (vs HCV)		
HBV	0.73 (0.44–1.21)	0.22
Others	0.81 (0.44–1.5)	0.5
MELD (per point)	1.04 (1.01–1.09)	0.049
Child's C vs A	1.65 (0.87–3.12)	0.13
Child's B vs A	1.20 (0.77–1.86)	0.42
Tumor Characteristics at Listing		
3 lesions vs 1 lesion 2–3cm	7.76 (3.63–16.58)	<0.001
1 lesion 3.1–5cm vs 1 lesion 2–3cm	4.31 (2.32–8.01)	<0.001
2 lesions vs 1 lesion 2–3cm	2.85 (1.42–5.72)	0.003
AFP (ln)	1.21 (1.11–1.32)	<0.001
AFP>1000 vs ≤1000	2.59 (1.42–4.72)	0.002
AFP>500 vs ≤500	3.42 (2.03–5.74)	<0.001
AFP>300 vs ≤300	2.35 (1.43–3.86)	0.001
AFP>100 vs ≤100	2.01 (1.31–3.09)	0.001
AFP>20 vs ≤20	1.91 (1.26–2.88)	0.002
Type of first LRT (versus TACE)		
RFA	1.10 (0.67–1.8)	0.72
Percutaneous ethanol injection	1.30 (0.15–11.36)	0.82
Radiographic and AFP Response to first LRT		
Partial Response vs Complete Response	1.86 (0.98–3.54)	0.06
Stable Disease vs Complete Response	5.75 (3.42–9.66)	<0.001
Progressive Disease vs Complete Response	25.62 (12.03–54.54)	<0.001
AFP (ln) after 1st LRT	1.29 (1.16–1.44)	<0.001
AFP>1000 vs ≤1000 after 1st LRT	4.05 (1.82–9.00)	0.001
AFP>500 vs ≤500 after 1st LRT	4.93 (2.70–8.98)	<0.001
AFP>300 vs ≤300 after 1st LRT	3.28 (1.79–6.01)	<0.001
AFP>100 vs ≤100 after 1st LRT	2.78 (1.64–4.72)	<0.001
AFP>20 vs ≤20 after 1st LRT	2.16 (1.35–3.46)	0.001

Table 4A

Multivariate Analysis of Predictors of Dropout Due to Tumor Progression or Death by Competing Risks (entire cohort)

	Multivariate SHR (95% CI)	p-value
3 lesions vs 1 lesion 2–3cm	8.68 (3.25–23.19)	<0.001
1 lesion 3.1–5cm vs 1 lesion 2–3cm	5.10 (2.28–11.41)	<0.001
2 lesions vs 1 lesion 2–3cm	5.03 (2.10–12.04)	<0.001
Lack of complete response to 1st LRT	3.08 (1.78–5.35)	<0.001
AFP>20 vs ≤20 after 1st LRT	1.87 (1.13–3.10)	0.02

Table 4B

Multivariate Analysis of Predictors of Dropout Due to Tumor Progression or Death by Competing Risks, after excluding patients with hepatitis B

	Multivariate SHR (95% CI)	p-value
3 lesions vs 1 lesion 2–3cm	5.81 (3.25–23.19)	0.001
1 lesion 3.1–5cm vs 1 lesion 2–3cm	3.71 (1.64–8.40)	0.002
2 lesions vs 1 lesion 2–3cm	3.06 (1.17–7.98)	0.02
Lack of complete response to 1st LRT	2.69 (1.44–5.0)	0.002
AFP>20 vs ≤20 after 1st LRT	2.33 (1.31–4.13)	0.004

Table 5

Loco-regional therapy and Histopathologic Characteristics in Explanted Liver following Liver Transplantation between the Low Risk group (n=63) and all other patients (n=254)

Characteristic	Low Risk Dropout n (%)	All others n (%)	p-value
Listing MELD >= 15	10 (15.9)	45 (17.7)	0.73
CTP score			
A	34 (54.0)	132 (52.0)	0.66
B	28 (44.4)	97 (38.2)	0.36
C	1 (1.6)	25 (9.8)	0.03
Number LRT			
1	52 (82.5)	114 (44.9)	<0.001
2	7 (11.1)	80 (31.5)	0.001
3	2 (3.2)	37 (14.6)	0.01
>3	2 (3.2)	23 (9.1)	0.12
Explant Characteristics			
Pathologic Stage	n=57	n=167	
No residual tumor	35 (61.4)	59 (35.3)	0.001
T1	3 (5.3)	15 (9.0)	0.02
T2	17 (29.8)	57 (34.1)	0.22
>T2	2 (3.5)	36 (21.6)	0.04
Vascular Invasion	n=57	n=167	
Yes	2 (3.5)	8 (4.8)	0.69
Histologic Grade	n=56	n=162	
Completely Necrotic	34 (60.7)	55 (34.0)	<0.001
Well Differentiated	6 (10.7)	45 (27.8)	0.009
Moderately Differentiated	12 (21.4)	58 (35.8)	0.047
Poorly Differentiated	4 (7.1)	4 (2.5)	0.11