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Downstaging of Hepatocellular Cancer before Liver Transplant: Long-term Outcome compared to Tumors within Milan Criteria

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Abstract

We report long-term intention-to-treat outcome of 118 patients with hepatocellular carcinoma (HCC) undergoing down-staging to within Milan/UNOS T2 criteria before liver transplantation (LT) since 2002, and compare the results with 488 patients listed for LT with HCC meeting T2 criteria at listing in the same period. The down-staging subgroups include 1 lesion >5 cm and ≤8 cm (n=43), 2 or 3 lesions at least one >3 cm and ≤5 cm with total tumor diameter ≤8 cm (n=61), or 4 to 5 lesions each ≤3 cm with total tumor diameter ≤8 cm (n=14). In the down-staging group, 64 patients (54.2%) had received LT, and 5 (7.5%) developed HCC recurrence. Two of the 5 patients with HCC recurrence had 4–5 tumors at presentation. The 1- and 2-year cumulative probabilities for dropout (competing risk) were 24.1% and 34.2% in the down-staging group, versus 20.3% and 25.6% in the T2 group (p=0.04). The Kaplan-Meier 5-year post-transplant survival and recurrence-free probabilities were 77.8% and 90.8%, respectively, in the down-staging group, versus 81% and 88%, respectively, in the T2 group (p=0.69 and p=0.66, respectively). The 5-year intention-to-treat survival was 56.1% in the down-staging group, versus 63.3% in the T2 group (p=0.29). Factors predicting dropout in the down-staging group included pre-treatment alpha-fetoprotein ≥1000 ng/mL (multivariate HR 2.42, p=0.02) and Child's B versus Child's A cirrhosis (multivariate HR 2.19, p=0.04). Conclusion: Successful down-staging of HCC to within T2 criteria was associated with a low rate of HCC recurrence and excellent post-transplant survival, comparable to those meeting T2 criteria without down-staging. Due to the small number of patients with 4–5 tumors, further investigations are needed to confirm the efficacy of down-staging in this subgroup.

Keywords

Hepatocellular carcinoma; down-staging; liver transplantation; local regional therapy; alpha-fetoprotein

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Once considered a relative contraindication to liver transplantation (LT), HCC now accounts for 20–30% of all LT performed in the United States (1). The success of LT as a curative treatment for HCC is largely attributed to improved candidate selection using restrictive criteria based on tumor size and number (2, 3). A 5-year post-transplant patient survival of 75 to 80% can now be achieved in many transplant centers (4, 5). In the United States, the Milan criteria (3) have been adopted by United Network for Organ Sharing (UNOS) in granting priority listing status for LT under the Model for End Stage Liver Disease (MELD) organ allocation system since 2002. Under the UNOS system, HCC within Milan criteria is divided into T1 (1 lesion <2 cm) and T2 (1 lesion 2–5 cm or 2–3 lesions ≤3 cm) stage. Only patients with T2 HCC, but not T1 HCC, are now eligible for priority listing for LT.

With the success of LT for early stage HCC, modest expansion beyond Milan criteria have been proposed to increase eligibility for LT. The University of California, San Francisco (UCSF) criteria (6) have been independently tested in two retrospective studies based on pre-transplant imaging, showing post-transplant survival that was only slightly below that of Milan criteria (7, 8). More recently, results of a large registry data based on explant pathology have led to the proposal of the “up-to-seven” criteria, associated with an estimated 5-year post-transplant survival of about 60% (9). Nonetheless, severe organ shortage limits broader application of expanded criteria due to its potential adverse impact on other non-HCC patients on the waiting list (4, 5, 10). Since local regional therapies (LRT), including trans-arterial chemoembolization (TACE) or radiofrequency ablation (RFA), are frequently used as a bridge to LT, the effects of LRT also need to be accounted for in evaluating outcome using expanded criteria for LT.

Tumor down-staging is a process involving expanded criteria and the effects of LRT. It is defined as reduction in the size of tumor using LRT specifically to meet acceptable criteria for LT (11). In principle, down-staging serves as a tool to select a subgroup of patients with HCC initially exceeding transplant criteria but will likely do well after LT (11–13). A recent international consensus conference (4) supports down-staging of HCC if it achieves survival after deceased donor LT that is the same as patients with HCC meeting Milan criteria without requiring down-staging.

We previously reported the intentional-to-treat outcome of the first 61 consecutive patients treated under the UCSF down-staging protocol (12). Despite the encouraging results, the sample size was relatively small and the follow-up was short. In this ongoing prospective study, we evaluated the long-term intention-to-treat outcome of a larger cohort of consecutive patients with HCC undergoing down-staging of HCC to within T2 criteria. We also compared the outcomes after down-staging with a group of consecutive patients with T2 HCC at initial presentation who were listed for LT over the same time period.

METHODS

Down-staging Protocol

The present study included consecutive patients enrolled in the down-staging protocol from March 2002 to January 2012, with a minimum follow-up of 6 months after the first down-staging treatment. Eligibility criteria for down-staging based on tumor diameter and number

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are summarized in Table 1. Diagnostic imaging included quadruple-phase spiral computed tomography (CT) (General Electric Healthcare, Madison, WI) or magnetic resonance imaging (MRI) with gadolinium contrast (Optima MR360 1.5T, General Electric Healthcare, Madison, WI). Gadoxetic acid was not used. The diagnosis of HCC for a lesion ≥1cm was based on either CT or MRI showing arterial phase enhancement and washout during the delayed images according to the 2005 American Association for the Study of Liver Disease (AASLD) guidelines (14), and these criteria were retrospectively evaluated for patients prior to 2005. The diagnosis of HCC could also be based on interval growth by ≥3mm over a period of 6 months with the same imaging technique. Hepatic nodules <1 cm were not counted as HCC. Percutaneous biopsy was not routinely performed for the diagnosis of HCC.

All patients underwent CT or MRI of the abdomen 1 month after each LRT for down-staging, and at a minimum of every 3 months. Imaging criteria for successful down-staging included a decrease in tumor size to within T2 criteria, or complete tumor necrosis with no contrast enhancement. Response to treatment was based on radiographic measurements of the maximal diameter of viable tumors that enhanced on CT or MRI, not including the area of necrosis (15). If there were multiple areas of residual tumor within a solitary nodule, then the entire nodule was considered in the staging process. Additional treatments were given with the intention of achieving complete necrosis of the entire tumor nodule. In a patient with more than 3 nodules, successful down-staging requires complete necrosis of one or more nodules, equivalent to obliteration of the tumors, so that there are no more than 3 nodules with viable tumors, none exceeding 3 cm to meet T2 criteria. Treatment was intended to achieve complete necrosis of all tumor nodules while awaiting LT. A minimum observation period of 3 months after down-staging was required before LT. In the event of hepatic decompensation after LRT, the patient is not eligible for LT unless the criteria for successful down-staging are met (Table 1).

Following successful down-staging of HCC, patients were listed with MELD priority upon approval by the regional UNOS review board. In April 2006, the UCSF down-staging protocol was incorporated into the UNOS Region 5 policy, in which patients were eligible for HCC-MELD exception points for LT after successful down-staging to within T2 criteria without the need for individual petition for approval. From March 2002 to April 2006, 28 other patients underwent LT using expanded UCSF criteria (6) under a separate investigation protocol, as the role and benefits of LRT were uncertain at the time. There were no specific guidelines dictating which of these protocols to use, other than the fact that some patients had HCC beyond the expanded UCSF criteria but within the down-staging inclusion criteria. After April 2006, all patients exceeding T2 criteria but within UCSF criteria were also included in the down-staging protocol.

Criteria for down-staging failure and exclusion from LT are summarized in Table 1. Even if there was evidence of tumor progression (increase in tumor diameter or new lesion), they were not excluded from LT as long as the tumor maximal diameter and numbers were within the inclusion criteria for down-staging. There was no time limit for completing down-staging.

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Control Group with T2 HCC

A retrospective component of this study was the collection of data in a control group of patients with HCC meeting T2 criteria without requiring down-staging. These were consecutive patients with T2 HCC at the outset who were listed with MELD exception for LT from March 2002 to August 2011, with a minimal follow-up of 6 months from LT listing among survivors. The baseline characteristics, LRT, intention-to-treat outcome as well as post-transplant outcomes were compared between the down-staging and the T2 groups. The criteria for tumor staging and exclusion from LT are the same as the down-staging group (Table 1).

Tumor-directed Therapy

TACE regimen consisted of doxorubicin hydrochloride (25 mg), cisplatin (50 mg), and mitomycin C (10 mg) dissolved in 10 mL of Omnipaque 350 (Amersham Health, Princeton NJ) and mixed in a 50–50 emulsion with thiodized oil (Ethiodol, Laboratoires Guerbet, Roissy, France). After administration of the emulsion, the targeted hepatic artery branch was embolized to stasis with a gelatin sponge slurry (Gelfoam, Pharmacia Upjohn, Kalamazoo, MI). The dose of doxorubicin was reduced to 12.5 mg for patients with a serum bilirubin level > 3 mg/dL; cisplatin was withheld for patients with a serum creatinine level > 1.2 mg/dL; and patients with a white blood cell count < 3000/mL or a platelet count < 60,000/mL did not receive mitomycin C. We did not start using TACE with drug-eluting beads until after 2012, and thus this technique was not used in this study. If patients treated with TACE were found to have vascular tumor blush not corresponding to lesion on imaging or corresponding to a nodule without typical radiographic features for HCC, they were treated with TACE. However, the staging of HCC was based on imaging and not by angiographic findings in this study.

Percutaneous RFA was performed under CT guidance and under general anesthesia using one to three radio frequency probes (Cool- tip RF Ablation System E-series, Covidien, Mansfield, MA). Ablations were performed in 6 to 12 minute cycles to create a 5 mm to 10 mm ablative margin of normal tissue surrounding the targeted lesion. Percutaneous ethanol injection (PEI) involved directing a 22-gauge 10 cm, 15 cm, or 20 cm length needle (Cook Medical, Bloomington, IN) into the tumor under ultrasound or CT guidance, and 5 to 20 mls of dehydrated ethanol (Akorn Pharmaceuticals, Lake Forest, Ill) were injected at a rate not exceeding 2 mls/minutes until complete or near-complete coverage of the lesion.

Histopathologic Analysis

Explant histopathologic features evaluated included maximal tumor diameter, number of tumor nodules, histologic grade of differentiation based on the Edmondson and Steiner criteria (grade 1, well differentiated; grade 2, moderately differentiated; grade 3, poorly differentiated) (16), and the presence or absence of micro- or macro-vascular invasion, based on standardized reporting during the entire study period. Pathologic tumor staging was based on the UNOS TNM staging system (5). The maximal diameter and number of only viable tumors were considered. For example, if the explant liver showed a 4 cm completely necrotic nodule with no viable tumor and a 1-cm nodule with HCC, the pathologic tumor stage in this patient would be T1 based on only the 1-cm HCC.

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Statistical Analysis

A chi-squared, t test or Mann-Whitney U test was used to compare differences between subgroups. The cumulative probabilities of dropout were estimated and compared using the competing risk method by Fine and Gray (17). Patients were evaluated from date of down-staging treatment or LT listing in the T2 group until dropout due to HCC progression or the competing events of LT or non-HCC related dropout or death. Survival function was estimated using the Kaplan-Meier method and compared using the log-rank test. Competing risk regression was used to evaluate predictors of cumulative incidence of dropout. Variables with a p-value of < 0.1 in univariate analysis were included in the multivariate model. Competing risk analyses were performed using Stata 1C/11.1 (StataCorp, College Station, TX).

RESULTS

Baseline characteristics

A total of 122 patients were enrolled in the down-staging protocol during the study period. Among them, 3 received live donor LT after successful down-staging, and 1 had violation of protocol by receiving decreased donor LT < 3 months after successful down-staging. There 4 patients were excluded from our analysis, and the remaining 118 patients comprised the study cohort. The baseline characteristics of these 118 patients in the down-staging group and the 488 patients in the T2 group are summarized in Table 2. The two groups were not significantly different in age, gender, etiologies of liver disease, Child-Turcotte-Pugh (CTP) scores, and baseline alpha-fetoprotein (AFP) levels. By definition, all patients in the down-staging cohort received LRT, while 16 of 488 (3.3%) in the T2 group did not receive LRT before LT (p=0.046). Compared to the T2 group, a significantly lower percentage of patients in the down-staging group received only a single session of LRT, and a significantly greater proportion of patients in the down-staging group received more than 3 LRT sessions (p<. 001) (Table 2). Within the down-staging group, there were 43 with 1 tumor, 61 with 2–3 tumors, and 14 with 4–5 tumors. None of the patients in this study were listed or underwent LT due to liver failure and not HCC.

There were 8 patients with multifocal disease in whom the diagnosis of HCC was based on interval growth of ≥3mm in 9 nodules ranging from 1.6 to 2.1 cm in maximal diameter (6 hypovascular and 3 hypervascular). All these nodules were treated with RFA or PEI. Among the 6 patients who ultimately underwent LT (3 with 2 lesions, 1 with 2 lesions, and 2 with 4 lesions), none had complete necrosis of all the tumor nodules.

Intention-to-treat outcome

The intention-to-treat outcome of the down-staging group is summarized in Figure 1. Down-staging was successful in 77 patients (65.3%). At last follow-up, 64 patients (54.2%) had received LT, and 9 patients were still awaiting LT. The median time from first down-staging treatment to LT was 9.8 months (range 4.8 to 25 months), which was significantly longer than the median waiting time of 8.0 months (range 0.5 to 20.1 months) in the T2 group (p=0.001). Tumor down-staging failed in 41 patients (34.7%) because of tumor progression in 33 patients, dropout due to other reasons in 3 patients, and death without LT in 5 patients

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(Figure 1). The median time from first down-staging treatment to dropout was 8.2 months (range 1.2 to 24.2 months).

Among the 488 patients in the T2 group, 332 (68%) were transplanted, 121 (24.5%) had dropped out, and 8 (1.6%) were still waiting for liver transplant. In addition, follow-up was censored in 27 patients (5.5%) as a result of exclusion from LT due to psychosocial or other medical reasons unrelated to HCC or liver disease.

The intention-to-treat survival at 1 and 5 years was 86.0% and 56.1%, respectively, in the down-staging group, versus 85.4% and 63.3%, respectively, in the T2 group (p=0.29) (Figure 2). Using competing risk analysis, the cumulative probabilities of dropout at 3 months, 6 months, 1 and 2 years were 5.9%, 11.9%, 24.1% and 34.2%, respectively, in the down-staging group, compared to 4.9%, 10.5%, 20.3% and 25.6%, respectively, in the T2 group (p=0.04) (Figure 3).

Post-transplant survival and HCC recurrence

In the down-staging group, the median post-transplant follow-up was 3.8 years (range 0.2 to 9.1 years), during which 5 of 64 patients (7.5%) developed HCC recurrence. One of these patients had a solitary nodule with complete tumor necrosis found in the liver explant, but had tumor involvement within a small lymph node under the diaphragm. The median post-transplant follow-up in the T2 group was 3.6 years (range 0.1–9.3 years) (p=0.45 compared to down-staging group). The Kaplan-Meier 1- and 5-year post-transplant survival was 93.4% and 77.8% in the down-staging group, versus 94.3% and 81%, respectively, in the T2 group (p=0.69) (Figure 4). The respective 1-and 5-year recurrence-free probabilities were 95.0% and 90.8% in the down-staging group, and 96.1 and 88.0% in the T2 group (p=0.66).

Outcome of Down-staging According to Subgroups

We also performed a separate analysis of the 3 down-staging subgroups: 1 tumor (n=43), 2–3 tumors (n=61), and 4–5 tumors (n=14) (Supplemental Figures 1a, 1b, and 1c). The 1- and 5-year intention-to-treat survival was 90.2% and 60.6% for 1 lesion, 81.7% and 52.5% for 2–3 lesions (p=0.32 versus 1 lesion), and 92.8% and 54.8% for 4–5 lesions (p=0.76 versus 1 lesion, p=0.29 versus 2–3 lesions). The 1- and 2-year cumulative probabilities of dropout by competing risk analysis were 23.9% and 34.3% for 1 lesion, 26.6% and 37.9% for 2–3 lesions (p=0.6 versus 1 lesion); and 14.3% and 14.3% for 4–5 lesions (p=0.75 versus 1 lesion, p= 0.49 versus 2–3 lesions). The 1- and 5-year post-LT survival was 95% and 81.6% for 1 lesion, 93.8% and 73.8% for 2–3 lesions (p=0.49 versus 1 lesion), and 85.7% and 85.7% for 4–5 lesions (p=0.69 versus 1 lesion, p=0.56 versus 2–3 lesions). Among the 5 patients who developed recurrence, 3 of these patients had 2–3 tumors on presentation, and the other 2 had 4–5 tumors, and none had a solitary tumor.

Explant Histopathologic Characteristics

Explant histopathologic characteristics of the downs-staging and T2 groups are summarized in Table 3. Complete tumor necrosis with no residual tumor was observed in 26 (40.6%) patients in the down-staging group. Among the subgroups, complete tumor necrosis was found in 15 of 43 patients (34.9%) with 1 lesion, 10 of 61 patients (16.4%) with 2–3 lesions

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(p= 0.03 versus 1 lesion), and 1 of 14 patients (7.1%) with 4–5 lesions (p= 0.04 versus 1 lesion). In 28 patients (43.7%), the tumors were down-staged to within T1 (15.6%) or T2 (28.1%) criteria. Tumor under-staging to beyond T2 criteria was observed in 10 (15.7%) patients, including one with macro-vascular invasion (T4b). Only one patient had micro-vascular invasion, and one patient had macro-vascular invasion. Among 40 patients with viable tumors in the explant, all had either well differentiated (40.9%) or moderately differentiated HCC (51.9%), and none had poorly differentiated tumor grade. There were no statistically significant differences between the down-staging and the T2 groups in the all the histologic characteristics (Table 3).

Predictors of Dropout

By competing risk analysis, univariate and multivariate predictors of the cumulative incidence of dropout in the down-staging group and the T2 group are summarized in Table 4 and Table 5, respectively. In the down-staging group, baseline pre-treatment AFP ≥1000 ng/mL (HR 2.42, p=0.02) and Child's B versus Child's A cirrhosis (HR 2.19, p=0.04) were statistically significant as predictors of dropout in multivariate analysis. Among 14 patients with baseline pre-treatment AFP ≥ 1000 ng/dL, 8 of 14 had dropout, 5 underwent LT after successful down-staging, and 1 was excluded from LT due to psychosocial reasons despite successful down-staging. All 5 patients who underwent LT had significant decrease in AFP (range 2.2 to 32.1 ng/mL) obtained within 3 months prior to LT. One of these 5 patients developed HCC recurrence after LT. No patients had a rise in the AFP from < 1000 to ≥ 1000 ng/dL before LT.

DISCUSSION

The concept of applying LRT to reduce the size of HCC to facilitate resection or LT was first tested by Majno and colleagues from Hospital Paul Brousse, France (18). A number of more recent studies have formally evaluated down-staging of HCC (11, 12, 19–24), and the majority of these studies have used Milan criteria as the endpoint for down-staging (12, 19–22). Down-staging of HCC has been identified as a priority for research in the field of LT for HCC in a National Cancer Institute consensus conference (25). Up to this point, however, the majority of published data are limited by the small sample size and a short duration of follow-up to fully assess the risk of HCC recurrence after LT; and the lack of a comparison group without down-staging (11).

The present study included almost twice the sample size as the last published series (12) with longer post-transplant follow-up. Our results suggest that down-staging of tumors initially exceeding T2 but meeting our inclusion criteria can achieve post-transplant survival and recurrence-free probability that are not significantly different compared to that in the group meeting T2 criteria without down-staging. The cumulative incidence of dropout in the down-staging group was significantly higher than the T2 group, likely related to a greater initial tumor burden. Nevertheless, we feel that the 5-year intention-to-treat survival of 56% in the down-staging group is acceptable, especially in light of the fact that our region has one of the longest waiting times in the country. It does not appear that the success of tumor down-staging is confined to one particular subgroup based on the number of tumors.

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However, there are only 14 patients in the subgroup with 4–5 lesions and 2 of the 5 cases of HCC recurrence occur in this subgroup. Despite this limitation, the overall low rate of HCC recurrence after LT and the very low incidence of unfavorable explant tumor histologic characteristics (poorly differentiated grade or vascular invasion) support the notion that down-staging serves as an additional selection tool for tumors with more favorable biology and better prognosis as assessed by response to LRT (11, 13). In this context, a minimal observation period from successful down-staging to LT is required. This observation period is 3 months in our protocol, but the optimal length of this period of observation for tumor biology is unknown (5, 11). This concept has been filtered into the "ablate and wait" strategy for HCC within or beyond Milan criteria (26).

Only one other study (19) has provided inclusion criteria for down-staging. Many studies are limited by the small sample size, with 20 or fewer patients undergoing LT after down-staging, and the short duration of follow-up (20–24). We believe that there are upper limits in tumor size and number beyond which down-staging is not likely to be successful and the outcome may be significantly worse. In the Bologna study involving 48 patients undergoing tumor down-staging (19), the inclusion criteria were 1 lesion ≤ 6 cm, 2 tumors each ≤ 5 cm, and 3 to 5 tumors each ≤ 4 cm with the sum of maximal diameters ≤ 12 cm. The 3-year disease-free survival after LT was 71% among 32 patients who underwent LT; and 18% had HCC recurrence. The more liberal upper size limits for 3 or more tumors in the Bologna study when compared to our inclusion criteria may explain their higher recurrence rate. In the present study, the small number of patients with 4–5 lesions precludes drawing firm conclusions about the efficacy of down-staging in this subgroup. In fact, a recent US national conference on HCC proposed establishment of uniform inclusion criteria for down-staging to facilitate future research in this area (5). The proposed criteria for eligibility for down-staging were modified from the UCSF down-staging protocol - 1 lesion ≤ 8 cm, 2–3 tumors each ≤ 5 cm with the sum of the maximal tumor diameters ≤ 8 cm; excluding those with 4 or 5 lesions (5).

The type of LRT in this study was determined on a case-by-case basis in a weekly multi-disciplinary tumor board. There is no evidence that one type of LRT is clearly superior to another (11). A recent report has suggested that there are angiographic and other imaging features that predict response to TACE, which may help guide an optimal strategy for bridging patients to LT (27). Consequently, an individualized approach to the choice of LRT based on clinical and tumor characteristics may offer the best chance of successful down-staging prior to LT.

A baseline AFP ≥1000 ng/mL was identified to be a predictor of dropout in multivariate competing risk analysis in the down-staging group and the control group with T2 HCC. Previous studies have shown an association between high AFP and the risk of dropout from the transplant waiting list (5, 28). High AFP has also been shown in a plethora of studies to be predictive of worse prognosis after LT (29). Although the best AFP cut-off in predicting prognosis after LT is still subject to debate, an AFP >1000 ng/mL was shown in 2 recent studies to be associated with worse outcome after LT for HCC within Milan criteria (30, 31). The U.S. national conference proposed adding AFP > 1000 ng/mL as an exclusion criterion for LT unless the AFP level decreases to < 500 ng/mL after down-staging treatments (5).

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Recent data have suggested that progressive disease by mRECIST criteria predicts poor post-transplant outcome for HCC within and beyond Milan criteria (32). It is possible that tumors could be successfully "down-staged" to meet transplant criteria and yet still exhibited tumor "progression" by mRECIST criteria, often as a result of the development of new lesions. In the present study, only 3 patients in the down-staging group exhibited this phenomenon, and 1 of the 3 developed tumor recurrence after LT. More data are needed to determine if tumor progression should result in exclusion from LT, or deferring LT until tumor control is achieved with additional LRT.

There are several limitations of our study. First, this is a single institutional study, and the generalizability of our results may be questioned. The second limitation relates to imaging diagnosis of HCC. The AASLD guidelines for HCC diagnosis (14) were retrospectively evaluated in patients enrolled prior to 2005, and the use of interval growth of ≥3mm within a period of 6 months as a diagnostic criterion has not been validated. Furthermore, there are limitations in using lipiodol accumulation after TACE in defining tumor necrosis and response to down-staging (33). Third, there were additional patients who underwent LT using expanded UCSF criteria (6) under a separate investigation protocol at the same time as the down-staging protocol prior to 2006, and this raises the concern of a selection bias for down-staging. Finally, only a small proportion of our patients in the present study had advanced Child's C cirrhosis, and this raises the possibility of a referral bias. Our results call into question the safety and benefits of down-staging in patients with advanced decompensated cirrhosis. In this regard, there is a need for further refinements of the selection criteria for down-staging. There is obviously a limit in the severity of liver disease beyond which down-staging should not be applied due to a high risk of hepatic decompensation or death before meeting criteria for successful down-staging to be eligible for LT. The 3 deaths in the present study as a result of hepatic decompensation following down-staging treatments highlights the importance of counselling patients regarding the risks of undergoing down-staging of HCC to meet criteria for LT.

In conclusion, we report excellent long-term post-transplant outcome after successful down-staging of HCC prior to LT using well defined inclusion criteria based on tumor size and number. We have further demonstrated that down-staging of HCC achieves post-transplant and intention-to-treat outcomes that are similar to that of patients with HCC initially meeting UNOS T2 criteria receiving priority listing for LT, thus meeting the expectations recommended in a recent international consensus conference (4). Due to the small number of patients with 4–5 tumors, further investigations are needed to confirm the efficacy of down-staging in this subgroup. In spite of this and other limitations of the present study, the overall low rate of HCC recurrence after LT and the very low incidence of either poorly differentiated grade or micro-vascular invasion in the liver explant support the role of down-staging in the selection of patients with tumors of more favorable biology that respond to LRT and also do well after LT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

HCC	hepatocellular carcinoma
LT	liver transplantation
UNOS	United Network for Organ Sharing
MELD	Model for End Stage Liver Disease
UCSF	University of California, San Francisco
LRT	local regional therapy
TACE	transarterial chemoembolization
RFA	radiofrequency ablation
CT	computed tomography
MRI	magnetic resonance imaging
AASLD	American Association for the Study of Liver Disease (AASLD)
PEI	percutaneous ethanol injection
CTP	Child-Turcotte-Pugh
AFP	alpha-fetoprotein

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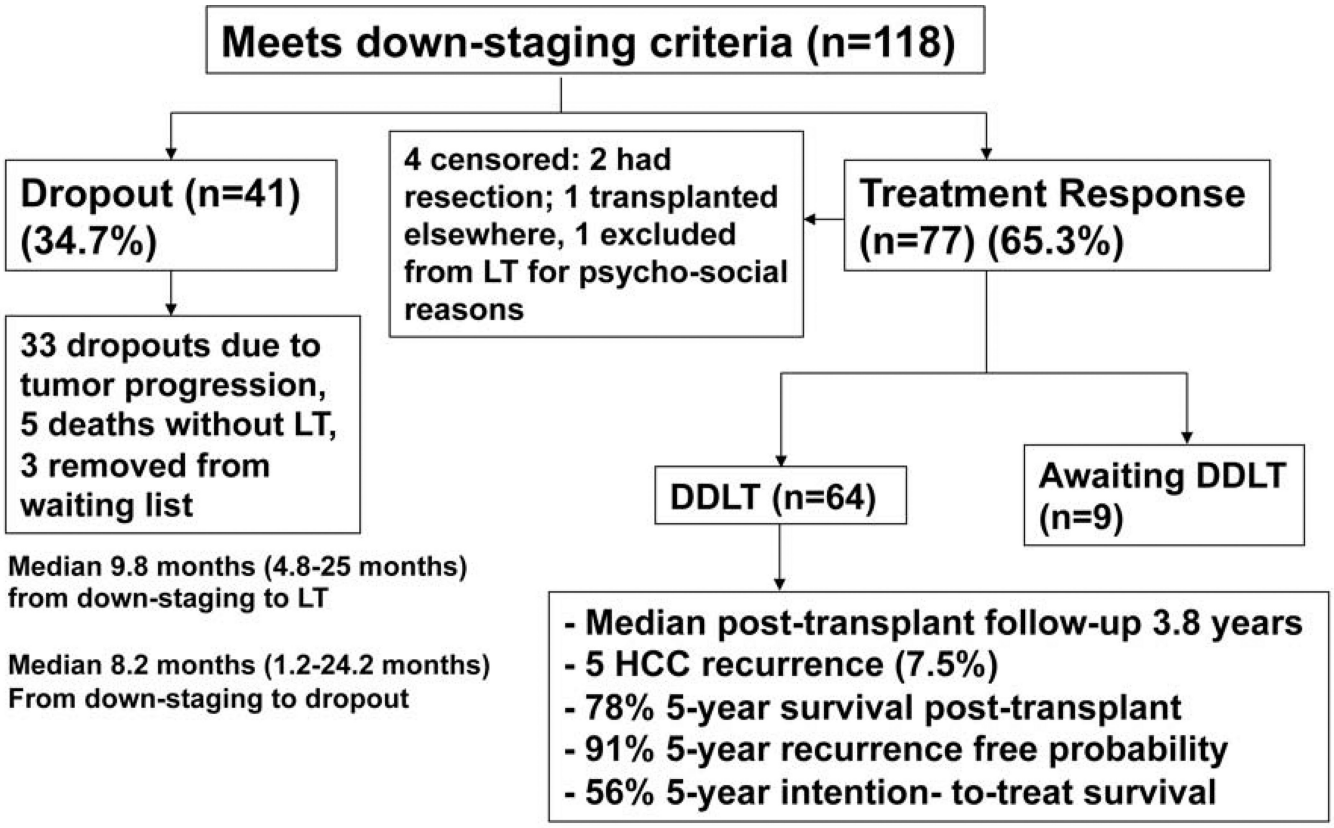

Figure 1. Summary of the intention-to-treat outcome of the 118 patients enrolled in the down-staging protocol

Abbreviations: LT, liver transplant; HCC, hepatocellular carcinoma; DDLT, deceased donor liver transplant

An additional 3 patients who underwent live donor liver transplant and one patient who had violation of protocol (< 3 months of observation before liver transplant) were excluded from analysis

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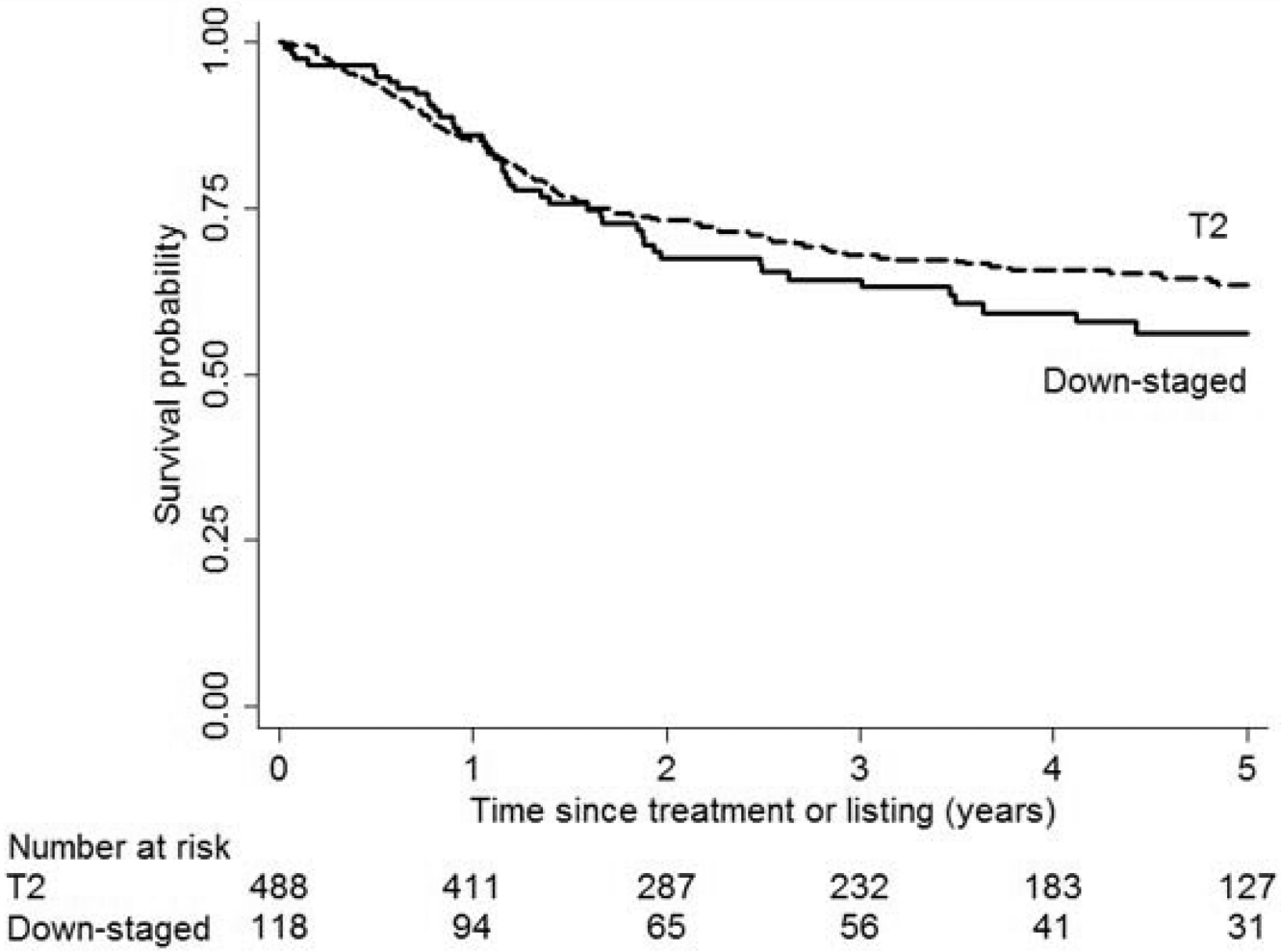

Figure 2. Kaplan-Meier intention-to-treat survival probabilities of the down-staging group and the T2 group

Time zero represents the first down-staging treatment in the down-staging group, and the time of listing for liver transplant in the T2 group. The difference in survival was not statistically significant (p=0.29)

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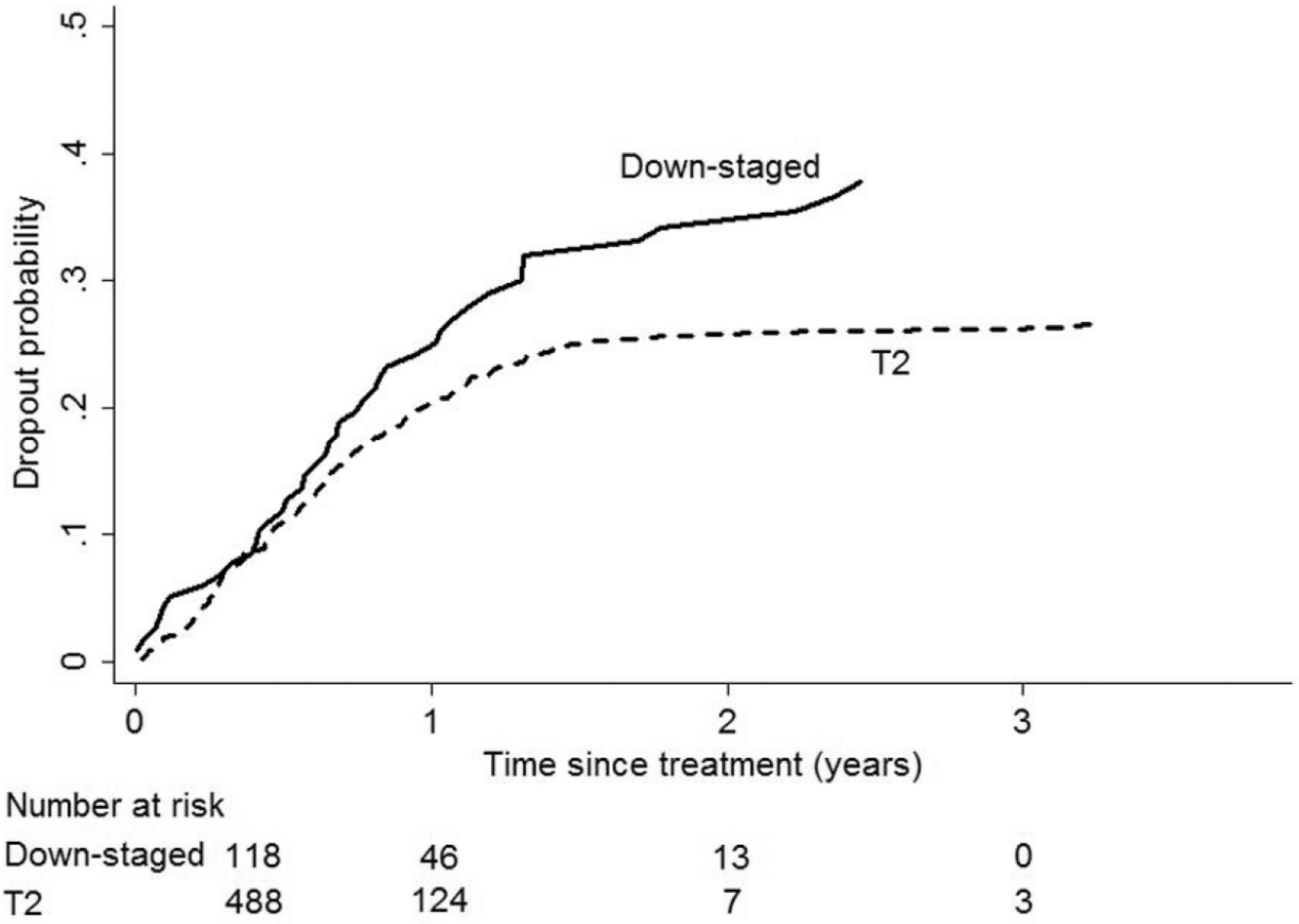

Figure 3. Competing risk analysis of the probabilities of dropout from the waiting list in the down-staging group and the T2 group

Time zero represents the first down-staging treatment in the down-staging group, and the time of listing for liver transplant in the T2 group. The difference in the probabilities of dropout was statistically significant (p=0.04)

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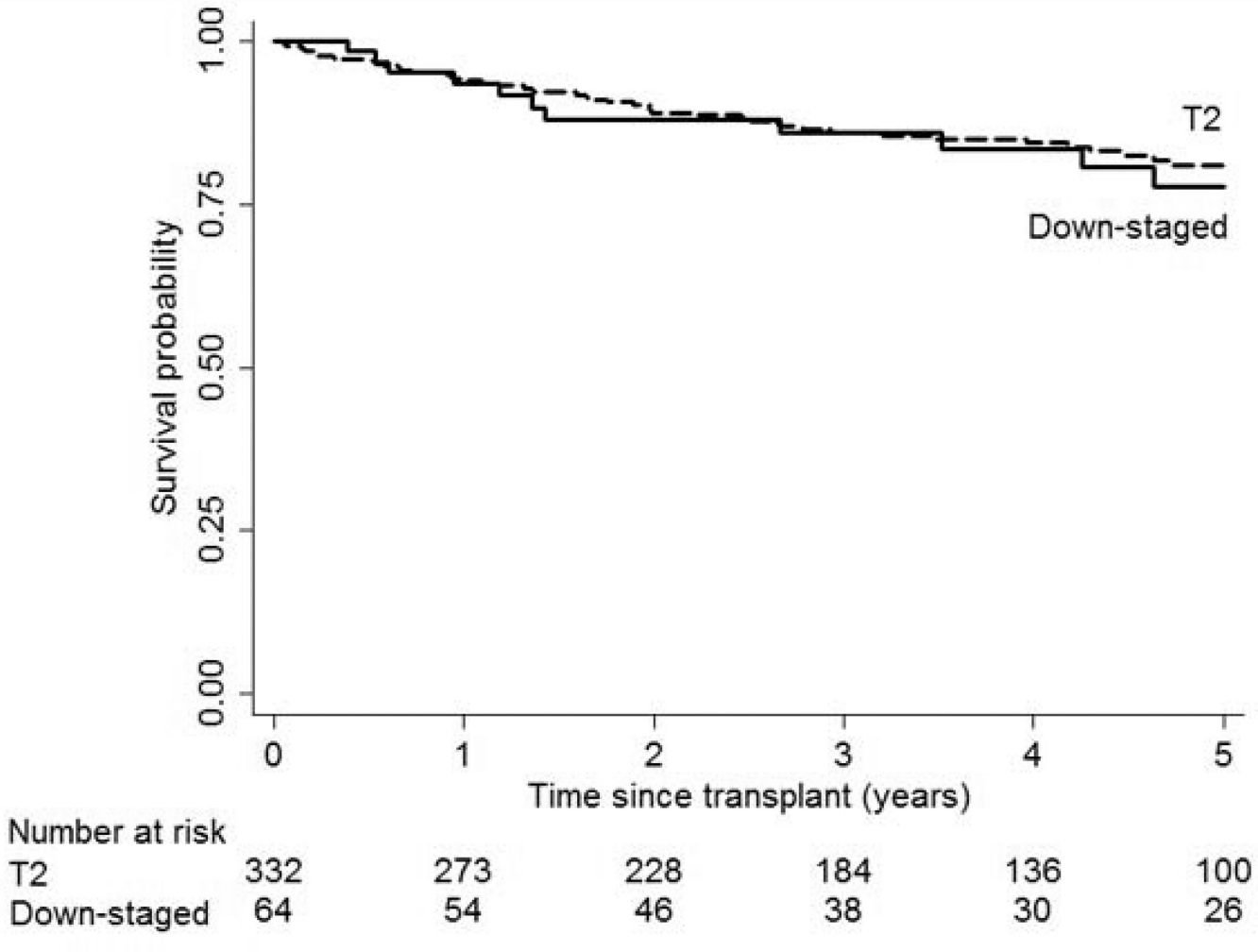

Figure 4. Kaplan-Meier post-transplant survival probabilities of the down-staging group and the T2 group

Time zero represents the date of liver transplant in both groups. The difference in survival was not statistically significant (p=0.69)

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Table 1

UCSF Down-staging Protocol

Inclusion Criteria

HCC exceeding UNOS T2 criteria but meeting one of the following criteria:

1. Single lesion ≤ 8 cm
2. 2 or 3 lesions each ≤ 5cm with the sum of the maximal tumor diameters ≤ 8 cm.
3. 4 or 5 lesions each ≤ 3cm with the sum of the maximal tumor diameters ≤ 8 cm.

Absence of vascular invasion based on cross-sectional imaging

Criteria for successful down-staging

1. Residual tumor(s) within UNOS T2 criteria for deceased donor liver transplant and to within UCSF criteria for live donor liver transplant.*
2. In patients with 4 or 5 tumors, successful down-staging requires obliteration (complete necrosis) of at least 1–2 tumor(s) so that there will be no more than 3 lesions with viable tumor each ≤ 3 cm to meet UNOS T2 criteria.

Criteria for down-staging failure and exclusion from liver transplant

1. Progression of tumor(s) to beyond inclusion criteria for down-staging based on tumor size and number.
2. Invasion of a major hepatic vessel based on cross-sectional imaging or Doppler ultrasonography of the abdomen.
3. Lymph node involvement by tumor or extra-hepatic spread of tumor.

Additional Guidelines

1. A minimal observation period of 3 months between down-staging and liver transplant is required.
2. A patient with acute hepatic decompensation after down-staging treatment is not eligible for liver transplant unless criteria for successful down-staging and minimal observation period are met.

* UCSF criteria – 1 lesion ≤ 6.5 cm, 2–3 lesions each ≤ 4.5 cm with the sum of the maximal tumor diameters ≤ 8 cm.

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Table 2

Baseline Characteristics of the Down-staging group and T2 group*

	Down-staging group (n=118)	T2 group (n=488)	p-value
Age (median, range)	59 (36–74)	57 (21–77)	0.04
Male (n, %)	97 (82.2%)	377 (77.2%)	0.26
Liver Disease (n, %)			
HCV	66 (56%)	297 (60.9%)	0.33
HBV	32 (27.0%)	123 (25.2%)	0.67
Others	20 (17%)	68 (13.9%)	0.40
CTP score			
5–6 (Child's A)	67 (57%)	240 (49.2%)	0.14
7–9 (Child's B)	38 (32%)	194 (39.7%)	0.13
10–15 (Child's C)	13 (11%)	54 (11.1%)	0.99
AFP ng/dL (median, range)	22.6 (2.1–10,300)	18 (1.3–36,000)	0.06
< 10	37 (31%)	189 (39%)	0.14
10–99	44 (37%)	154 (32%)	0.23
100–499	16 (14%)	87 (17.8%)	0.27
500–999	7 (6%)	20 (4.1%)	0.39
>=1000	14 (12%)	38 (7.8%)	0.16
HCC number; mean size (cm) ± SD			
1	43 (36.1%); 6.3 ± 0.7	331 (67.8%); 3.12 ± 0.87	<.001 <.001
2	45 (37.7%); 4.2 ± 0.7	107 (21.9%); 2.36 ± 0.51	<.001 <.001
3	16 (14.8%); 4.1 ± 0.6	50 (10.2%); 2.23 ± 0.42	0.3 <.001
4	12 (9.8%); 2.4 ± 0.5	--	n/a
5	2 (1.6%); 2.2 ± 0.2	--	n/a
Types of LRT**			
TACE only	49 (41.5%)	227 (47%)	0.33
RFA only	13 (11%)	53 (11.2%)	0.96
PEI only	0	6 (1.3%)	0.23
Combination	50 (42.3%)	186 (38%)	0.39
Resection***	6 (5.1%)	-	n/a
Number of LRT			
0	0	16 (3.3%)	0.046
1	32 (27%)	230 (47.1%)	<.001
2	32 (27%)	131 (26.8%)	0.95

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	Down-staging group (n=118)	T2 group (n=488)	p-value
3	25 (21%)	68 (13.9%)	0.0498
>3	29 (25%)	43 (8.8%)	<.001

Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; CTP, Child-Turcotte-Pugh; AFP, alpha-fetoprotein; LRT, local regional therapy; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection.

* Baseline characteristics in the down-staging group were obtained before the first down-staging treatment. Baseline characteristics in the T2 group were obtained before priority listing for LT.

** In the down-staging group, 13 patients had 14 sessions of laparoscopic or open RFA only, 49 patients had 131 TACE treatments only, 11 patients had 48 treatments with TACE +PEI, 22 patients had 80 TACE+ percutaneous RFA, and 17 patients had 48 sessions of laparoscopic RFA + TACE.

*** Resection as a down-staging treatment was used in 6 patients before 2005. Among these 6 patients, one developed post-operative respiratory failure and subsequently died of multi-organ failure without LT. One patient had micro-vascular invasion in the resection specimen and was no longer considered for LT and was counted as down-staging failure/ dropout. One patient was listed for LT after resection, but subsequent petition for extension of MELD priority status for denied, and follow-up was censored at that point. Three patients underwent LT, and 2 of these received RFA of additional lesion at the time of resection.

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Table 3

Explant histologic characteristics in the Down-staging group and the T2 Group

	Down-staging group (n=64)	T2 group (n=332)	p-value
Pathologic Tumor Stage			
Complete Necrosis (no viable tumor)	26 (40.6%)	133 (40.1%)	1.0
T1*	10 (15.6%)	29 (8.7%)	0.11
T2	18 (28.1%)	115 (34.6%)	0.39
T3	4 (6.3%)	24 (7.2%)	1.0
T4a (≥ 4 lesions)	5 (7.8%)	29 (8.7%)	1.0
T4b (macro-vascular invasion)	1 (1.6%)	2 (0.6%)	0.41
Histologic Grade of Differentiation**	**N=38**	**N=199**	
Well-differentiated	13 (34.2%)	79 (39.7%)	0.59
Moderately-differentiated	25 (65.8%)	103 (51.8%)	0.15
Poorly-differentiated	0	17 (8.5%)	0.08
Vascular invasion	**N=64**	**N=332**	
Micro-vascular	1 (1.6%)	18 (5.4%)	0.33
Macro-vascular	1 (1.6%)	2 (0.6%)	0.41

* In 6 of these 10 cases, the T1 tumor in the explant represents a small satellite nodule discovered in the explant that were either indeterminate or not seen on imaging prior to liver transplant. In the other 4 cases, the T1 tumor represents residual disease in patients with known multi-focal HCC.

** The histologic grade of differentiation could not be determined in 26 patients in the down-staging group and 133 patients in the T2 group who had complete tumor necrosis and no viable tumors in the explant.

Three patients had resection as a down-staging procedure before LT. One had two satellite nodules (0.9 cm and 0.6 cm) found in the explant, the other two had resection as well as RFA of a second lesion at the same time as resection. The explant showed complete necrosis of the RFA-treated site in one patient, and small residual tumor in a > 85% necrotic nodule in the other patient.

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Table 4

Univariate and Multivariate Competing Risks Analyses of Predictors of Dropout in the Down-staging group

Univariate Analysis		
Predictor Variables	**Sub-Hazard ratio (95% CI)**	**P-value**
Diagnosis of Liver Disease		
HBV (vs. HCV)	1.29 (0.60–2.74)	0.51
Others (vs. HCV)	2.12 (1.04–4.28)	***0.04***
Child's class cirrhosis		
B (vs. A)	1.82 (0.96–3.47)	0.07
C (vs. A)	1.66 (0.61–4.51)	0.32
AFP		
≥ 10 (vs. < 10)	0.99 (0.54–1.83)	0.98
≥ 100 (vs. < 100)	1.68 (0.89–3.16)	0.11
≥ 300 (vs. < 300)	1.91 (0.96–3.8)	0.07
≥ 400 (vs. < 400)	1.54 (0.75–3.18)	0.24
≥ 500 (vs. < 500)	1.56 (0.72–3.35)	0.26
≥ 1000 (vs. < 1000)	2.38 (1.06–5.35)	***0.04***
Types of LRT		
TACE (vs. RFA)	1.26 (0.41–3.9)	0.68
Combination Treatment (vs. RFA)	0.94 (0.30–2.94)	0.92
Number of lesions		
2–3 (vs. 1)	1.06 (0.51–2.18)	0.88
4–5 (vs. 1)	1.53 (0.62–3.76)	0.35
Diameter of largest lesion (per 1 cm increase)	1.04 (0.84–1.28)	0.69
Multivariate Analysis:		
Predictor Variables	**Hazard ratio (95% CI)**	**P-value**
Child's class cirrhosis		
B (vs. A)	2.19 (1.04–4.64)	0.04
C (vs. A)	1.66 (0.61–4.51)	0.31
AFP ≥ 1000 ng/mL	2.42 (1.16–5.05)	***0.02***

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; LRT, local regional therapy; TACE, transarterial chemoembolization; RFA, radiofrequency ablation.

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Table 5

Univariate and Multivariate Competing Risks Analyses of Predictors of Dropout in the control group

Univariate Analysis		
Predictor Variables	**Sub-Hazard ratio (95% CI)**	**P-value**
Diagnosis of Liver Disease		
HBV (vs. HCV)	0.79 (0.51–1.22)	0.29
Others (vs. HCV)	0.80 (0.46–1.38)	0.42
Child's class cirrhosis		
B (vs. A)	1.26 (0.86–1.84)	0.23
C (vs. A)	1.51 (0.84–2.70)	0.17
AFP		
≥ 100 (vs. < 100)	2.28 (1.59–3.25)	***<0.001***
≥ 300 (vs. < 300)	2.37 (1.59–3.52)	***<0.001***
≥ 400 (vs. < 400)	3.09 (2.07–4.60)	***<0.001***
≥ 500 (vs. < 500)	3.25 (2.16–4.89)	***<0.001***
≥ 1000 (vs. < 1000)	2.43 (1.48–3.98)	***<0.001***
Types of LRT		
TACE (vs. RFA)	0.83 (0.43–1.60)	0.57
Combination Treatment (vs. RFA)	1.26 (0.66–2.41)	0.48
Number of lesions		
2 (vs. 1)	1.09 (0.70–1.70)	0.70
3 (vs. 1)	3.45 (2.18–5.46)	***<0.001***
4 (vs. 1)	NA	NA
5 (vs. 1)	NA	NA
Diameter of largest lesion (per 1 cm increase)	1.30 (1.07–1.58)	***0.009***
Multivariate Analysis:		
Predictor Variables	**Hazard ratio (95% CI)**	**P-value**
AFP ≥ 1000 ng/mL	1.85 (1.11–3.07)	***0.02***
Number of lesions		
2 (vs. 1)	1.71 (1.04–2.81)	***0.04***
3 (vs. 1)	5.67 (3.26–9.86)	***<0.001***
Diameter of largest lesion (per 1 cm increase)	1.70 (1.35–2.13)	***<0.001***

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; LRT, local regional therapy; TACE, transarterial chemoembolization; RFA, radiofrequency ablation.