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ORIGINAL ARTICLE

Downstaging Advanced Hepatocellular Carcinoma to the Milan Criteria May Provide a Comparable Outcome to Conventional Milan Criteria

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Abstract
Background and Aims Many hepatocellular carcinoma (HCC) patients met the appropriate criteria and accepted liver transplantation after successful downstaging therapies; however, the outcome in these patients is unclear. We aim to compare the outcome of patients meeting the Milan criteria at the beginning and after successful downstaging therapies.
Patients and Methods Between July 2001 and January 2013, 112 patients were diagnosed with early-stage HCC that met the Milan criteria. Of these patients, 58 patients did not meet the Milan criteria initially but did after successful downstaging therapies. We retrospectively collected and then compared the baseline characteristics, postoperative complications, survival rate, and tumor recurrence rate of these two groups. Kaplan–Meier analyses were used to estimate the long-term overall survival and tumor-free survival in these patients.
Results No significant differences were observed between the two groups with respect to baseline donor and recipient characteristics. The downstaging Milan group showed similar tumor characteristics compared to the conventional Milan group, except the downstaging group had better tumor histopathologic grading (P=0.027). The 1-, 3-, and 5-year overall survival rates were comparable at 91.4, 82.8, and 70.7 %, respectively, in the downstaging Milan criteria and 92.0, 85.7, and 74.1 %, respectively, according to the initial Milan criteria (P=0.540). The 1-, 3-, and 5-year tumor-free survival rates between the two groups were not statistically significant (P=0.667).
Conclusion Successful downstaging therapies can provide a comparable posttransplantation overall survival and tumor-free survival rates after liver transplantation.

Keywords Liver · Transplant · Downstage · Hepatocellular carcinoma

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Abbreviations

LT	Liver transplantation
LDLT	Living donor liver transplantation
DDLT	Deceased donor liver transplantation
HCC	Hepatocellular carcinoma
TACE	Transarterial chemoembolization
RAF	Radiofrequency ablation
EI	Alcohol injection
TACI	Transarterial chemoinfusion
AFP	Alpha fetoprotein
HBV	Hepatitis B virus
HCV	Hepatitis C virus
MELD	Model for end stage liver disease
mRECIST	Modified version of the Response Evaluation Criteria in Solid Tumors

BMI Body mass index
HBcAb Hepatitis B core antibody

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide[1] and the third most common cause of cancer deaths.[2,3] The disease is responsible for about one million deaths per year, and the burden is heavier in China because of the high prevalence of hepatitis B virus infections. China accounts for 55 % of all HCC cases worldwide.[4,5] Fortunately, liver transplantation (LT) is currently an established therapy for small, early-stage HCC by removing both the tumor and the organ at risk for developing future malignancy.[6] The early series of LT was reserved mainly for patients with extensive tumor burden, which was not amendable to surgical resection.[7,8] This approach demonstrated disappointing results (survival of <40 % at 5 years) due largely to tumor recurrence.[9,10] However, in 1996, Mazzaferro and colleagues[11] demonstrated superior outcomes for patients with early-stage HCCs, which led to the development of the Milan criteria (single tumor, ≤5 cm, or multiple tumors, ≤3 nodules, ≤3 cm). These criteria have been accepted worldwide and have resulted in the consistent selection of patients with HCC for LT. Because some patients beyond the Milan criteria have negative histological factors, expanded criteria such as the University of California, San Francisco (UCSF) criteria[12] and the Chengdu and Hangzhou criteria in China[5,13] have been proposed; however, the Milan criteria are still the most commonly recognized inclusion criteria for HCC LT.[2]

Most HCC cases are diagnosed first as advanced cases due to the lack of routine screening, especially in China.[14] For advanced HCC, LT yields a disappointing survival rate (5-year range, 18 to 32 %), mainly because of tumor recurrence.[15,16] Downstaging of HCC to meet Milan criteria is an attractive alternative to simply expanding the tumor size limits in the absence of pre-transplantation locoregional therapy.[17] Various pre-transplantation therapies such as liver resection, radiofrequency ablation (RFA), Transarterial chemoembolization (TACE), ethanol injection (EI), high-intensity focused ultrasound (HIFU), and gamma knife radiosurgery are locoregional therapies currently used in advanced HCC downstaging. While there is no consensus about whether downstaging of HCC to within the Milan criteria followed by transplantation has a beneficial outcome, several studies have reported comparable overall and tumor-free survival rates between patients initially meeting the Milan criteria and those downstaged to fall within it.[18–20] Other published studies showed better posttransplant outcomes in downstaged patients.[21,22] Yao et al.[23] found that the downstaging process allows for selection of tumors with more favorable biology that will likely respond to downstaging therapies and will also do well following LT. Some also believe that even if an 8-cm tumor could be successfully downsized to <5 cm (meeting Milan criteria), the risk of tumor recurrence after LT may still be the same as that of an 8 cm HCC lesion.[17] Currently, whether overall and disease-free survivals of downstaged patients are equivalent to those in patients initially meeting the Milan criteria is still a source of controversy. Thus, in our study, we performed a retrospective analysis comparing the outcome of patients meeting the Milan criteria at the beginning and the outcome of patients included in the downstaging protocol.

Patients and Methods

Study Design and Patient Population

From July 2001 to January 2013, we retrospectively collected data from 170 patients receiving LT for HCC. Of those patients, 112 were diagnosed with early-stage HCC that met the Milan criteria at the beginning and 58 were advanced HCC patients accepting LT even though the initial HCCs were out of the Milan criteria but fell within it after various downstaging therapies. Patients whose HCC progress to advanced HCC were excluded from the initial Milan group. The diagnoses of HCC were made following the EASL and the AASLD guidelines.[24,25] Then, we compared liver transplantation outcomes between the two groups, including overall survival and recurrence rate. All of the data come from “the China Liver Transplant Registry System”.

Downstaging Protocol

The downstaging protocol has been described in detail in our previous report.[5] The inclusion criteria for downstaging were based on the tumor number and diameter. We applied the modified UCSF downstaging inclusion criteria (a single tumor with a diameter of up to 8 cm; two to three tumors with individual diameters of up to 5 cm; and a total diameter of up to 8 cm)[26] for enrolling the advanced HCC patients. TACE, RAF, resection, HIFU, and gamma knife radiosurgery were introduced as downstaging therapies in our study. The types and numbers of treatments were tailored to each patient according to the tumor characteristics, location, liver function, and response. Combined therapy was necessary for complicated or recurrent disease. Salvage hepatectomy and radiofrequency ablation were the first choices for a single lesion, TACE was considered to be the most effective way to control multiple tumors, RFA was used for small lesions in the remnant liver after salvage hepatectomy or recurrence, and HIFU and gamma knife radiosurgery were

recommended to patients as a supplementary treatment to other locoregional therapies.

Bimonthly CT or MRI scans were assessed by two investigators using a modified version of the Response Evaluation Criteria in Solid Tumors (mRECIST) for HCC.[27,28] The mRECIST for HCC takes into account the induction of intratumoral necrotic areas in estimating the decrease in viable tumor load rather than just a reduction in overall tumor size (modified WHO criteria or standard Response Evaluation Criteria in Solid Tumors (RECIST)). When the tumor met the UCSF criteria for transplantation, the patient was advised to receive LT as soon as possible. All of the imaging evaluations were performed up to the time of transplantation. Patients whose tumors progressed while they were awaiting LT, even with initial successful downstaging therapies, were not considered successful cases.

Statistical Analysis

Descriptive statistics were expressed as proportions (percent) for categorical variables, and mean ± standard deviation or median and range were used for continuous variables. Comparisons were analyzed using the chi-square test for categorical variables and Student's *t* test for continuous variables if normality was observed or the Wilcoxon rank-sum testing in other cases. The overall survival and tumor-free survival were estimated using the Kaplan–Meier method. $P<0.05$ was considered statistically significant in all analyses.

Results

Baseline Recipient Characteristics

The baseline clinical characteristics of the two recipient groups in our study are summarized and compared in Table 1. No significant difference was observed between patient features among the two groups. The most common etiology of liver disease was hepatitis B for both groups, followed by hepatitis C. The majority of patients (94.1 %) had a Child score <10 (class A or B) before downstaging, and the MELD score of the two groups also showed no difference. Most of the patients (77.6 %) accepted deceased donor liver transplantation, but there were 14 cases (24.1 %) in the downstaging Milan group and 24 cases (21.4 %) in the initially Milan group who accepted living donor liver transplantation. Donor characteristics of these two groups also showed no significant difference. But the mean waiting time in the downstaging Milan group was significantly longer than that in the initially Milan group (168.5 versus 21.5 days, $P=0.000$)

Locoregional Therapy for Tumor Downstaging

Locoregional treatments used for downstaging in our study are shown in Table 2. TACE was the most common single treatment, followed by resection. Five patients accepted percutaneous RFA and two patients accepted open-access RFA for the location of the HCC targets. Most of these patients (82.8 %) only required a single downstaging therapy before their tumors met the Milan criteria, but ten cases required combined therapies. The most common combined therapies were resection and postoperative TACE. One patient accepted resection for a large target and RFA for the remaining small targets. Three TACE treatments were performed after LT. HIFU and gamma knife radiosurgery were used in some patients due to their clinical needs. The mean number of downstaging therapies per patient for theses 58 patients was 1.6±0.4.

Tumor Characteristics

Individual tumor characteristics before transplantation and in the liver explants are summarized in Table 3. Downstaging therapies achieved complete tumor necrosis without residual HCC found in the liver explant in two patients in the downstaging therapies group. There was no significant difference between the two groups in the number of targets or tumor diameter. However, two new tumor targets in the downstaging Milan group and three new tumor targets in the initially Milan group were found in the liver explants. The alpha fetoprotein (AFP) level also showed no difference between the two groups that accepted LT ($P=0.470$). For the downstaging Milan group, the AFP level after downstaging was 1,085.7± 2,415.3, which was higher than the initial level (1,438.2± 1,743.6); however, this reduction did not reach statistical significance ($P=0.135$). The grade of tumor differentiation could not be determined in the two patients with complete tumor necrosis. Tumors were well differentiated in 29 patients, moderately differentiated in 19 patients, and poorly differentiated in only eight patients. These eight patients had tumors that were better differentiated than those in the initially Milan group ($P=0.027$)

Overall and Tumor-Free Survival Rates

The median post-LT follow-up was 35.1±19.9 months for the downstaging Milan group and 39.2±20.6 months for the initially Milan group ($P=0.212$). There was no significant difference in the overall post-LT survival rate and tumor-free survival rate between the downstaging Milan group and initially Milan group (Figs. 1 and 2). Overall 1-, 3-, and 5-year survival rates were 91.4, 82.8, and 70.7 %, respectively, for the patients meeting the Milan criteria after successful downstaging therapies and 92.0, 85.7, and 74.1 %,

Table 1 Baseline characteristics of the two groups of recipients and donors

	Downstaging Milan group n=58	Initially Milan group n=112	P value
Age (years)	47.6±9.4	47.3±9.3	0.270
Sex (M/F)	48:10	93:19	0.934
Weight (kg)	67.4±9.6	67.0±9.2	0.438
Height (cm)	166.0±8.5	164.6±9.1	0.353
BMI (kg/m^2)	23.0±2.3	23.1±2.2	0.769
Etiology			
HBV	51	102	0.598
HCV	3	4	0.836
HBV and HCV	2	2	0.932
No hepatic virus	2	4	0.252
MELD score	12.5±6.3	12.3±5.4	0.336
Child score (A/B/C)	40/15/3	70/25/7	0.085
Donor age	36.1±8.7	34.5±8.0	0.732
Donor gender	28:30	42:70	0.804
Donor BMI (kg/m^2)	23.1±2.3	22.4±2.7	0.000
Donor HBcAb (+/−)	5/53	11/101	
LDLT/DDLT	14/44	24/88	
Mean waiting time (days)	168.5±85.4	21.5±11.3	

LDLT living donor liver transplantation, *DDLT* deceased ?donor liver transplantation, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *MELD* model for end stage liver disease, *BMI* body mass index, *HBcAb* hepatitis B core antibody

respectively, for the recipients whose HCC met the Milan criteria initially (P=0.540) (shown in Fig. 1). During the post-LT follow-up, 12 patients (20.7 %) in the downstaging Milan criteria group developed HCC recurrence at a median of 25.8 (range 8–49)months after LT, and 23 patients (20.5 %) in the initially Milan criteria group developed HCC recurrence at a median of 27.1 (range 5–49)months. The overall 1-, 3-, and 5-year tumor recurrence-free rates were 87.9, 75.9, and 63.8 %, respectively, for the downstaging Milan criteria group and 87.5, 81.3, and 66.1 %, respectively, for the initially Milan criteria group (P=0.667) (shown in Fig. 2). The causes of post-LT death were tumor recurrence (25 cases, 64.1 %), infection (5 cases, 12.8 %), organ failure (5 cases, 12.8 %), rejection (3 cases, 7.7 %), and vascular complications (1 case, 2.6 %). Eight patients who developed HCC recurrence after LT are currently alive.

For the 58 patients who accepted pre-LT downstaging therapies, 26 patients accepted resection or resection plus other therapies. Overall 1-, 3-, and 5-year survival rates were 92.3, 84.6, and 73.1 %, respectively, for the 26 patients and 90.6, 81.3, and 78.1 %, respectively, for the remanent 32 patients (P=0.813). And the overall 1-, 3-, and 5-year tumor recurrence-free rates were 88.5, 76.9, and 73.1 %, respectively, for the 26 patients and 87.5, 75, and 68.8 %, respectively, for the remanent 32 patients (P=0.869).

Table 2 Protocol for downstaging therapies for the 58 patients

Protocol for downstaging therapies	Number of patients (number of treatments)
TACE only	24 (42)
Resection	17 (18)
RFA (percutaneous/open access)	5/2 (7/2)
Resection + TACE	5 (11)
Resection + open-access RFA	2 (4)
Resection + γKnife	1 (3)
TACE + HIFU	1 (2)
Resection + RFA + TACE	1 (5)

TACE transcatheter arterial chemoembolization, *RFA* radiofrequency ablation, *HIFU* high-intensity focused ultrasound, *γKnife* gamma knife radiosurgery

Discussion

Although extending the HCC criteria for LT remains a controversial issue, it is generally accepted that some patients with tumors exceeding the Milan criteria would also benefit from LT with a comparable risk of tumor recurrence after LT.[17,29,30] Although the RECIST[18,31] and other criteria[22] have been used to define the response to tumor downstaging, most of the published reports[17,30,32,33] have used the Milan criteria as the endpoint of downstaging. In our current study, we defined the Milan criteria as the endpoint of downstaging. The concept of applying locoregional therapies to reduce the size of HCC tumors and to thus facilitate resection or LT was first introduced and tested by

Table 3 Tumor characteristics of the two groups of recipients before transplantation

	Downstaging Milan group n=58	Initially Milan group n=112	P value
Target number (0/1/2/3)	2/35/15/6	0/72/31/9	0.915
Total diameter per patient	4.0±1.5	3.7±1.5	0.346
AFP level (ng/ml)	1,085.7±2,415.3	1,333.78±1,363.9	0.470
Histopathologic grading (I/II/III)	29/19/8	40/41/31	0.027

AFP alpha fetoprotein

Majno et al.[34] in 1997. After that, downstaging protocols such as TACE, TACI, RFA, resection, EI, HIFU, and gamma knife radiosurgery have been widely used in patients whose HCC exceeds the Milan criteria.[5,17,29–34] And the type of downstaging therapy did not affect the outcome of LT. However, controversy still surrounds the effectiveness and feasibility of downstaging therapies for HCC LT. Some have reported that the proposed downstaging criteria provide a comparable outcome to the conventional Milan criteria,[23,30] while some reports indicate that patients who are successfully downstaged and undergo LT may have a higher recurrence-free survival rate.[35] However, Liovet et al.[36] have reviewed the literature and found that the results of published studies are inconsistent and do not provide compelling evidence to accept downstaging as a standard of care. Although most of them were intention-to-treat analyses, the sample sizes of these studies were too small to provide compelling evidence for accepting downstaging therapies.[17,30] Consequently, the impact of successful downstaging on the outcome of LT is still unknown. This large-volume retrospective study aims to analyze the outcomes of downstaging therapies prior to LT in patients with HCC exceeding the Milan criteria.

Downstaging treatments can be defined as decreasing the tumor burden so that the acceptable criteria for LT are met in patients whose initial tumor size and number exceed these criteria. Another function of downstaging therapies was the selection of patients whose tumors have a more favorable biology, respond well to treatment, and also may do well after LT.[33] In Yao's intention-to-treat analysis,[17] downstaging treatments achieved complete tumor necrosis with no residual tumor in 13 patients. Tumor differentiation in only one patient was poor, as evidenced by biopsy prior to LT. In the other 22 patients with residual HCC in the explant, the grade of tumor differentiation was moderate in 13 patients and well differentiated in the remaining nine patients. None had poorly differentiated tumors. In our study, although eight patients in the downstaging group had poor tumor differentiation, the histopathologic grading was better in the downstaging Milan group than that in the initially Milan group, especially for more well differentiation and much less poor differentiation. The selection concept was highlighted by Otto et al.[21] who found that

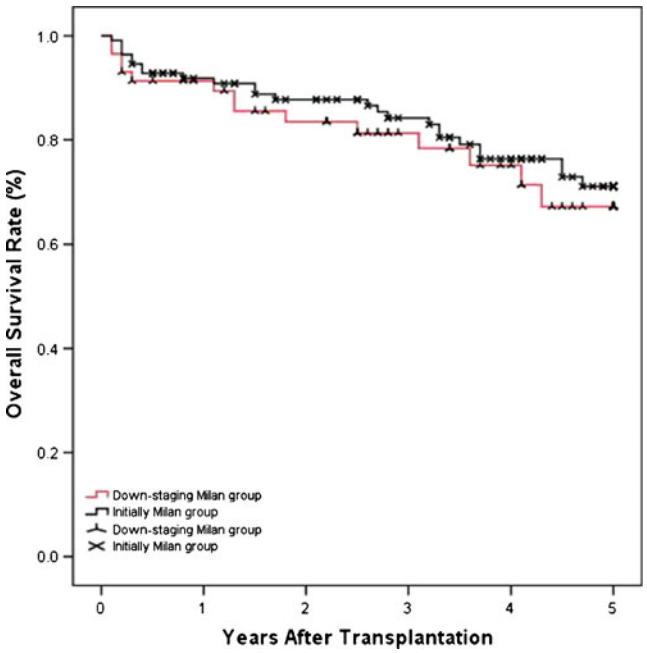

Fig. 1 The overall survival rate comparison between two groups (P=0.540)

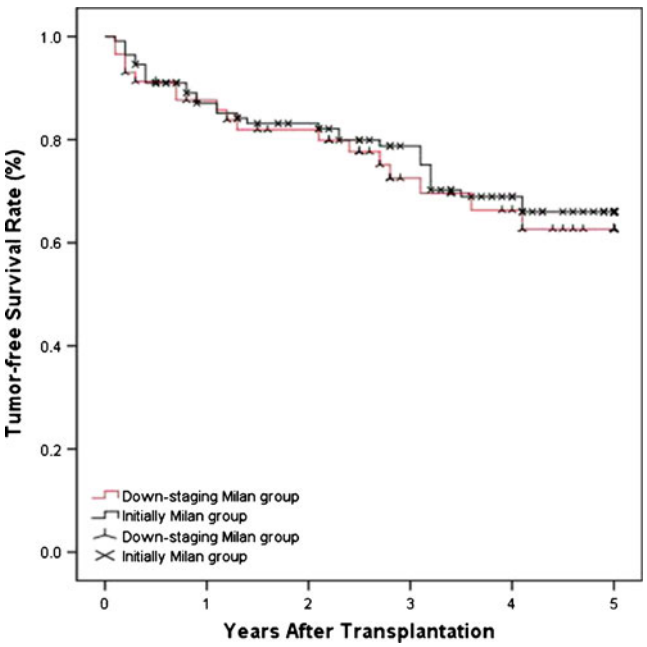

Fig. 2 The tumor-free survival rate comparison between two groups (P=0.667)

TACE was used exclusively in controlling tumor progression prior to LT in 62 patients with HCC initially exceeding Milan criteria and in 34 patients meeting Milan criteria and suggested that a sustained response to TACE is a better selection criterion for LT than the initial assessment of tumor size or number. Thus, HCC downstaging may allow for the selection of patients whose tumors have a more favorable biology, respond well to treatment, and may also do well after LT.

Liver transplantation was successfully performed in larger tumors after downstaging. We observed no significant difference in the posttransplantation overall survival and HCC recurrence-free survival rate between the two groups. Most of the published reports show that the posttransplant survival rates for patients with downstaged tumors should be comparable to or only slightly below those achieved by patients with HCC meeting the Milan criteria before LT.[33] The proposed 5-year posttransplant survival rate after downstaging therapies was 60–70 %. We reported the overall 5-year survival rate after successful downstaging therapies to be 70.7 %, which was slightly lower than for the patients without any pre-LT therapies (74.1 %). In the study by Yao et al.,[17] 35 patients underwent LT after downstaging therapies, and the 1- and 4-year posttransplantation survival rates were 96.2 and 92.1 %, respectively. None had HCC recurrence after a median posttransplantation follow-up of 25 months. However, Ravaioli et al.[30] reported that the 5-year survival rate computed from the evaluation of LT was only 56 %. The main cause of this marked difference was the small sample size in these studies. In our study, we collected the 58 cases who accepted successful downstaging therapies and, eventually, LT. Meanwhile, we compared the overall posttransplantation survival and tumor-free survival between the patients who met the Milan criteria after successful downstaging therapies and those patients who met the Milan criteria initially.

As described above, our downstaging protocol involves the selection of patients whose tumors have a favorable biology, consisting of more well-differentiated cases. Only eight cases in the downstaging group had poorly differentiated tumors. The overall and tumor-free survival rates showed no significant difference between the two study groups. These findings were consistent with Ravaioli's.[30] In his study, the downstaging group had more highly differentiated tumors, and the 1- and 3-year disease-free survival rates were comparable at 80 and 71 % in the Milan group versus 78 and 71 % in the downstaging group. The main causes of this are still unknown. Tumor differentiation level may not be an independent predictive factor for HCC recurrence and survival after LT.[37,38]

The main limitation of this study is its retrospective single-center design. However, the endpoints of the study, including the overall survival rate and tumor-free survival rate, are all objective measures. Further, the nonrandomized nature of our study was another limitation, but we believe that these data make any randomized protocol unethical. The relatively small sample size of the downstaging group also limits our conclusions. Multicenter and larger cohort studies will be implemented in our future studies.

In conclusion, patients who accepted LT and had successfully downstaged tumors that met the Milan criteria had a comparable outcome according to both the overall survival and tumor-free survival rates after LT.

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Conflict of Interest No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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