Annals of Medical Research
DOI: 10.5455/annalsmedres.2019.06.327 2019;26(8):1704-7

Original Article

Downstaging in patients with hepatocellular carcinoma: Is there real hope?

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Abstract

Aim: The conventional criteria preclude many patients with hepatocelular carcinom (HCC) from liver transplantation (LT). Recent studies reported comparable results in downstaged patients. In present study, the outcomes of patients with HCC after LT was evaluated in regard to response to a uniform downstaging protocol.

Materials and Methods: The data of 136 HCC patients who underwent LT between January 2012 and April 2018 were analysed. 82 patients who were with minimum follow-up of one year and/or who reached the end-point (recurrence and/or death) were enrolled to the study and were divided into two groups as downstaging group and initially within Milan group. We retrospectively collected and then compared the baseline characteristics, postoperative complications, survival rate, and tumor recurrence rate of patients.

Results: One of the study group included 54 (45.7%) patients within Milan criteria initially and there were 28 (23.7%) patients in the downstaging group. The disease-free survival rates were 82.1% and 87.1% in downstaging group and initially witihin Milan group, respectively (p=0.368). The overall 3-year survival rates were 82.1% and 88.9% in downstaging group and intially within Milan group, respectively (p=0.402).

Conclusion: The patients who were initially excluded according to the current conventional criteria had a chance for LT with comparable outcome according to both the overall survival and disease-free survival rates.

Keywords: Hepatocelular carcinom; liver transplantation; downstaging.

INTRODUCTION

The most commonly used acceptance criteria for liver transplantation (LT) in patients with hepatocellular carcinoma (HCC) are still the Milan criteria. However, numerous expanded criteria, including comparable results in patients within the Milan criteria, have been offered to selected patients with HCC beyond the Milan criteria (1,2).

Tumour downstaging in HCC patients is a process involving expanded criteria for LT and also the impacts of locoregional therapy (LRT). Downstaging may be considered a selection criterion for patients with HCC who are initially outside the accepted listing criteria (mostly the Milan criteria) for LT (3,4). This is because successful downstaging induces a reduction in tumour burden that brings patients within conventional LT criteria. Responses to downstaging may also provide a prognostic estimation about favourable tumour biology. Radiofrequency ablation (RFA) and transarterial chemoembolisation (TACE) are the most-used procedures in HCC downstaging. RFA is preferred for HCC lesions under 3 cm; for multiple tumours (more than three lesions) or single tumours larger than 3 cm, TACE is recommended (5,6).

Although several series have shown encouraging outcomes in downstaged patients, there is not a standardised downstaging protocol in the literature (5). We aim to evaluate post-transplantation outcomes in downstaged patients under a uniform downstaging protocol.

MATERIAL and METHODS

This study was designed as a retrospective study and approved by the local ethics committee with protocol number 2018-17/4. We evaluated the data of 136 HCC patients who underwent LT between January 2012 and

Received: 16.06.2019 **Accepted:** 26.07.2019 **Available online:** 28.08.2019
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April 2018 in our center. Patients who underwent the minimum follow-up of 1 year and/or who reached the end-point (recurrence and/or death) were enrolled in the study.

LRTs (mostly TACE) were performed in patients other than Milan criteria patients according to a uniform downstaging protocol. Some of the patients who were within the Milan criteria at the beginning were also given LRT to prevent tumour progression while they were wait-listed. This therapy was not considered downstaging, and these patients were not included in downstaging groups.

Two groups were considered downstaging groups, and patients within the Milan criteria initially had alpha-fetoprotein (AFP) values under 400 IU/mL. The clinical and laboratory features of patients, their responses to downstaging, recurrence rates and mortality rates were evaluated. Disease-free and overall survival rates were compared. We also compared liver transplantation outcomes between the two groups, including overall survival and recurrence rates.

Downstaging Protocol

During the first application of downstaging, patients with HCC were evaluated via magnetic resonance angiography (MRa). The inclusion criteria for downstaging were based on tumour size, number of tumours and AFP values:

a. HCC without extrahepatic dissemination/metastasis
b. HCC without macrovascular invasion
c. Longest tumour diameter > 9 cm (single or multiple)
d. AFP value > 400 ng/mL (even for patients within the Milan criteria)

Mostly, TACE was used for downstaging and RFA was used for only a limited number of small tumours. The patients were assessed with MRa one month after LRTs were performed. Multiple LRTs were performed at intervals of 45 days if necessary.

Our protocol was not based on the downstaging of HCC within the Milan criteria. We have defined two types of responses to downstaging based on two criteria:

1. AFP level has dropped below 400 IU/mL (partial or complete response)

2. a. ≥ 50% reduction of the tumour size (complete response)

b. between 30% and 50% reduction of the tumour size (partial response)

Patients with AFP levels over 400 IU/mL were not accepted for LT. If their AFP levels had not decreased below 400 IU/mL following downstaging or increased above 400 IU/mL after the observation period following LRT, the downstaging was considered unsuccessful, and LT was not applied.

If a complete/partial response was obtained, our protocol mandates a minimum observation period of 3 months to ensure disease stability before proceeding with LT.

Statistical Analysis

Descriptive statistics were stated as percentages for categorical variables, and mean ± standard deviation or median and range were used for continuous variables. Comparisons were analysed 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 test (in other cases). Overall survival and tumour-free survival rates were estimated using the Kaplan-Meier method. A p-value of $p<0.05$ was considered statistically significant in all analyses.

RESULTS

The baseline clinical features of the 82 patients included in the study are summarised in Table 1. One of the study groups included 54 (45.7%) patients within the Milan criteria initially and who had AFP values under 400 IU/mL at the beginning. There were 28 (23.7%) patients in the downstaging group. Of these 28 patients, 5 patients were initially within the Milan criteria, but their AFP values were over 400 ng/mL. No significant difference was detected between the basic clinical characteristics of the two groups.

TACE was almost the only LRT in our downstaging group, except for two patients who additionally received RFA. The mean number of TACE procedures per patient for patients who underwent downstaging was 1.7±0.3.

The disease-free survival rates were 82.1% and 87.1% in the downstaging group and initially within the Milan group, respectively (p=0.368) (shown in Figure 1) at a 3-year follow-up. The overall 3-year survival rates were 82.1% and 88.9% in the downstaging group and initially within the Milan group, respectively (p=0.402) (shown in Figure 2).

Complete and partial response were obtained in 17 (60.8%) and 11 (39.2%) downstaged patients, respectively. Only 1 patient had a recurrence in patients with complete responses (5.8%), and 4 (36.3%) patients had recurrences in the partial response group. There is a significant difference between these two groups.

Table 1. Baseline features of the patients

	Initially within Milan group (54 patients)	Downstaging group (28 patients)
Age (years)	57.1±8.2	56.8±7.4
Gender (Male/Female)	46/8 (85.2%/14.8%)	23/5 (82.1%/17.9%)
MELD score	12.8±5.6	13.4±3.6
Etiology		
Hepatitis B virus	29(53.7%)	15(53.5%)
Hepatitis C virus	11(20.3%)	6(21.4%)
Criptogenic	8(14.8%)	5(17.8%)
Alcoholic	2(3.7%)	-
Hepatitis B and C virus	2(3.7%)	1(3.6%)
HCC (non-cirrhotic)	2(3.7%)	1(3.6%)
Alfa fetoprotein: mean (min-max)	12.4 IU/mL (0.7– 58)	177.5 IU/mL (1.2– 2453)

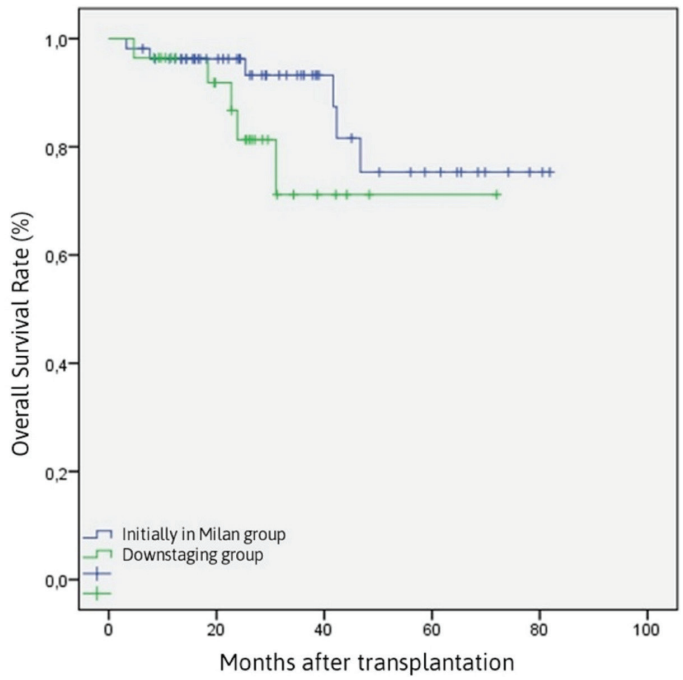

Figure 1. The overall survival rate comparison between two groups

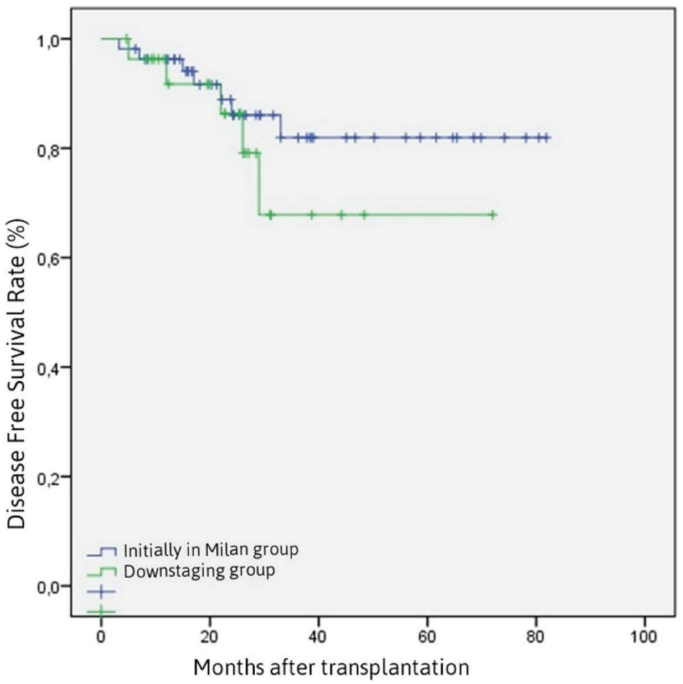

Figure 2. The disease-free survival rate comparison between two groups

DISCUSSION

Even though a considerable number of studies have reported comparable outcomes, expanding the criteria for LT in patients with HCC is still controversial. Particularly, the ethical debate on selecting HCC patients for deceased donors has caused restricted protocols for downstaging. As such, several reports have been published in recent years that have identified successful downstaging as fulfilling Milan or UCSF criteria. In spite of this, other studies have shown successful results using extended criteria, ruling out AFP level and fulfilling Milan criteria or accepting a 30%-50% decrease in the size of tumours (7,8).

It is commonly thought that some patients with tumours outside of the conventional criteria would also benefit from LT with a comparable risk of tumour recurrence. Responses to LRT are related with good outcomes after LT, and they can be useful to select patients whose tumours have a more favourable biology (9). An international, multi-centre study reported that both serum AFP values and responses to LRT were correlated with low rates of recurrence-free and overall survival (10). Also, inadequate responses to LRT were determined to be a strong predictor of excluding patients with HCC for LT in single-centre studies (8). We designated our protocol on this basis and determined a partial/complete response for downstaging in patients, even if they were not downstaged within the Milan criteria. Although the best AFP cut-off in predicting prognosis is still subject to evaluation, in our study, AFP levels must be reduced under 400 IU/mL to accept patients for LT following the downstaging protocol. Under these circumstances, our results showed that even patients with partial responses to downstaging had comparable outcomes after LT.

The literature presents no evidence about the superiority of any type of LRT. Precisely, there are limitations for RFA and TACE, which are commonly used LRTs. For tumours located close to the surface of the liver, RFA should not be preferred due to the risk of rupture of the liver capsule. The main harms of TACE are related to the ischemic damages of embolisation, such as postembolisation syndrome, the risk of liver failure and risk of arterial injury (3, 9). We preferred mostly TACE for LRT depending on the recommendations of our interventional radiology team. We experienced serious hepatic artery dissection in three patients due to TACE, and we have used the right gastroepiploic artery to reconstruct hepatic artery anastomosis. In brief, an individualised approach to selecting a type of LRT based on clinical and tumour features may provide optimal downstaging (4).

We also emphasised the importance of 3 months of observation time following successful downstaging to evaluate the stability of the disease. Some authors refer to this period as the 'test of time' to determine the nature of a tumour and to avoid its recurrence, the increase of AFP, macrovascular invasion and metastasis (8).

Yao et al. (4) reported their 10-year experience with downstaging and presented similar outcomes to those of patients presenting within conventional criteria. Chapman et al. (11) reported similar conclusions, analysing 63 downstaged patients over a 12-year period. Although most published reports support these results (12,13), controversy remains about the effectiveness of downstaging. This is because most of the reports are based on single-centre experiences with small sample sizes. In regard to this criticism, a multi-centre study

reported an 87% recurrence-free survival rate and an 80% 5-year overall survival rate (14). The overall and tumour-free survival rates showed no significant difference between the two groups in the present study.

Microvascular invasion and AFP levels are the most valuable prognostic factors to predict tumour recurrence (15,16). In the present study, none of the 7 patients who downstaged within the Milan criteria showed tumour recurrence. Five of these patients had microvascular invasion, but all of them had AFP levels under 400 ng/mL. Even then, the patients who did not downstage within the Milan criteria had significant microvascular invasion (18/21, 85.7%), and 25% of them had AFP levels over 400 ng/mL. The tumour recurrence rate was 25.1% in these patients. These results supported our downstaging protocol in regards to the aim of decreasing AFP levels under 400 ng/mL.

Study Limitations

The main limitation of this study is its retrospective, single-centre design. The small sample size of the downstaging group also limits our conclusions. However, the endpoints of the study, including the overall survival rate and the tumour-free survival rate, are all objective measures. Multi-centre studies are necessary to achieve better results.

CONCLUSION

We aimed with downstaging to select patients who had significant responses to LRT with reasonably good tumour biology. In this way, the patients who were initially excluded according to the current conventional criteria had a chance for LT with comparable outcomes according to both the overall survival and disease-free survival rates.

Financial Disclosure: There are no financial supports

Ethical approval: This study was designed as a retrospective study and approved by the local ethics committee with protocol number 2018-17/4.

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