

## Up-to-seven criteria for hepatocellular carcinoma liver transplantation: A single center analysis

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### Abstract

**AIM:** To detect whether the up-to-seven should be used as inclusion criteria for liver transplantation for hepatocellular carcinoma.

**METHODS:** Between April 2002 and July 2008, 220 hepatocellular carcinoma (HCC) patients who were diagnosed with HCC and underwent liver transplantation (LT) at our liver transplantation center were included. These patients were divided into three groups according to the characteristics of their tumors (tumor diameter, tumor number): the Milan criteria group (Group 1), the in up-to-seven group (Group 2) and the out up-to-seven group (Group 3). Then, we compared long-term survival and tumor recurrence of these three groups.

**RESULTS:** The baseline characteristics of transplant recipients were comparable among these three groups, except for the type of liver graft (deceased donor liver transplant or live donor liver transplantation). There were also no significant differences in the pre-operative  $\alpha$ -fetoprotein level. The 1-, 3-, and 5-year overall survival and tumor-free survival rate for the Milan criteria

group were 94.8%, 91.4%, 89.7% and 91.4%, 86.2%, and 86.2% respectively; in the up-to-seven criteria group, these rates were 87.8%, 77.8%, and 76.6% and 85.6%, 75.6%, and 75.6% respectively ( $P < 0.05$ ). However, the advanced HCC patients' (in the group out of up-to-seven criteria) overall and tumor-free survival rates were much lower, at 75%, 53.3%, and 50% and 65.8%, 42.5%, and 41.7%, respectively ( $P < 0.01$ ).

**CONCLUSION:** Considering that patients in the up-to-seven criteria group exhibited a considerable but lower survival rate compared with the Milan criteria group, the up-to-seven criteria should be used carefully and selectively.

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**Key words:** Up-to-seven criteria; Liver transplantation; Outcome; Hepatocellular carcinoma; Recurrence

**Core tip:** The up-to-seven criteria were introduced several years ago, but there is still no consensus about their effectiveness. Two hundred and twenty patients were divided into three groups according to the characteristics of their tumors: the 1-, 3-, and 5-year overall survival and tumor-free survival rate for the Milan criteria group were higher than that in the up-to-seven criteria group. However, the advanced hepatocellular carcinoma patients' overall and tumor-free survival rates were much lower. So considering that patients in the up-to-seven criteria group exhibited a considerable but lower survival rate compared with the Milan criteria group, the up-to-seven criteria should be used carefully and selectively.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is a major health problem worldwide and is the sixth most common cancer and the third most common cause of cancer death<sup>[1]</sup>. This disease is especially problematic for Asian countries, which have a high prevalence of hepatitis B virus (HBV) and hepatitis C virus infection<sup>[2]</sup>. Effective management of early HCC includes resection, radiofrequency ablation and liver transplantation (LT). Liver transplantation remains the best treatment for small HCC resulting from chronic liver disease, as it both removes the neoplastic lesion and eliminates the underlying disease in a single procedure. However, post-operative recurrence is still a major problem related to HCC LT. Stringent inclusion criteria have been adopted to ensure tumor free survival after LT. The first criteria for HCC LT were introduced by Mazzaferro *et al.*<sup>[3]</sup> and were named the Milan criteria: a solitary lesion of < 5 cm, or 2 to 3 nodules all < 3 cm and without microscopic vascular invasion or extrahepatic disease. Due to the favorable results that have been achieved, *i.e.*, a 5-year post-transplant survival exceeding 70% and a rate of tumor recurrence below 15%, the Milan criteria have been used as the standard selection criteria for HCC LT all over the world<sup>[4,5]</sup>. Several years later, based on greater experience, some groups argued that the Milan criteria should be expanded, as a substantial number of patients with HCC exceeding these criteria could also greatly benefit from transplantation<sup>[6-10]</sup>. The most representative set of new criteria were the University of California San Francisco criteria proposed by Yao *et al.*<sup>[6]</sup>: 1 lesion  $\leq$  6.5 cm in diameter or 2 to 3 lesions, each  $\leq$  4.5 cm in diameter, with a total diameter of  $\leq$  8 cm. Several groups argued the Milan criteria were too strict and excluded some HCC patients from LT, despite the possibility of benefit, and that the criteria should be expanded. Therefore, the Milan group (Mazzaferro *et al.*<sup>[11]</sup>) attempted to expand the Milan criteria and create a new set called the up-to-seven criteria (new Milan criteria): hepatocellular carcinomas with seven as the sum of the size of the largest tumor (in cm) and the number of tumors. In Milan group's study, the up-to-seven groups achieved a 5-year an overall survival rate of 71.2%. Following this study, several other studies demonstrated that the up-to-seven criteria could be useful as a model for evaluating potential candidates for liver transplantation to treat HCC<sup>[12-15]</sup>. Although the up-to-seven criteria have been analyzed all over the world, they have not been as widely accepted as the Milan criteria, even 4 years after their conception. Meanwhile, there is still no research on these criteria in China, where most HBC infections and nearly 55% of worldwide HCC occurs<sup>[16]</sup>. Therefore, in our study, we compared the outcomes of Milan criteria patients with those of up-to-seven criteria patients, and then we evaluated the effectiveness of the up-to-seven criteria as inclusion criteria for HCC LT.

## MATERIALS AND METHODS

From April 2002 to July 2008, 220 HCC patients underwent LT in our liver transplantation center and were included in

our study. All of these patients were diagnosed with HCC based on pre-operative imaging studies, and the diagnoses were confirmed by pathology. Patients with cholangio-hepatocellular cancer or other liver diseases were excluded from this study. All of the tumor characteristics were evaluated by histological examination. Of these 220 cases, 58 patients met the Milan criteria (Group 1), 90 patients met the up-to-seven criteria (Group 2) and 130 patients did not meet either the Milan criteria or up-to-seven criteria (Group 3). We retrospectively collected the data of these three groups and then compared their baseline characteristics, intraoperative data, post-operative recovery and long-term survival, including the overall survival, tumor-free survival and recurrence rate. All of the data were collected from the Chinese Liver Transplant Registry (<http://www.cltr.org>).

In our study, the grafts for liver transplantation were from living right lobe donors and deceased donors. No prisoners were included as donors, and all of the whole liver grafts were donations after cardiac death. All of these donations were volunteered by the donor or the family. For grafts that came from living donors, the donor was required to be within three degrees of consanguinity with the recipient, as verified by a DNA test, and all of the living donor liver transplantations were performed after obtaining approval from the Ethics Committee of the West China Hospital and local authorities. All of the donations were voluntary and altruistic. We informed the donors and their families of the possible risks of donor hepatectomy. Written consent was provided by the donors for the storage of their information in the hospital database and its use for research.

The surgical procedures performed on the donor and the recipients are described in our previous reports<sup>[17-19]</sup>. Routine post-LT triple-immunosuppressive treatment in our center includes tacrolimus or cyclosporin, mycophenolate mofetil, and steroids. For patients with HBV infection, the anti-HBV protocol after LT included lamivudine combined with low-dose hepatitis B immunoglobulin therapy<sup>[20]</sup>. The doses of tacrolimus and cyclosporine were adjusted based on the measured serum level.

### Statistical analysis

All of the data were managed and analyzed using SPSS 17.0 statistical software. Descriptive variables such as age, MELD score, and tumor diameter were expressed as the mean  $\pm$  SE. Categorical data such as gender and graft type were computed using the Pearson  $\chi^2$  test or Fisher's exact test. The overall survival and tumor-free survival rates were calculated and compared using Kaplan-Meier analysis. Only tumor-related deaths were included in the recurrence-free survival analysis. The log-rank test was performed to compare survival curves. Two-sided *P* values were computed and a difference of *P* < 0.05 was adopted as the threshold for statistical significance.

## RESULTS

### Baseline characteristics

Over six years, 220 HCC patients underwent LT at our

**Table 1** Baseline, tumor characteristics, and overall and tumor-free survival rates of the liver transplantation recipients

	Milan criteria (Group 1), <i>n</i> = 58	In up-to-seven criteria (Group 2), <i>n</i> = 90	Out up-to-seven criteria (Group 3) <i>n</i> = 120	<i>P</i> value 1 vs 2	<i>P</i> value 2 vs 3	<i>P</i> value 1 vs 3
Baseline characteristics						
Gender (M/F)	51/7	81/9	109/11	0.859	0.648	0.552
Age (yr)	48.4 ± 10.9	46.8 ± 10.8	45.4 ± 10.0	0.390	0.315	0.067
BMI (kg/m <sup>2</sup> )	23.3 ± 2.4	23.5 ± 2.3	23.3 ± 2.0	0.715	0.739	0.963
Underlying LD				0.775	0.452	0.312
HBV	54	83	78			
HCV	0	1	1			
No hepatic virus	4	6	16			
HBV-DNA(-/+)	29/39	45/45	82/38	0.838	0.070	0.174
DDLT/LDLT	36/22	62/28	98/23	0.393	0.022	0.003
Child score (A/B/C)	29/16/13	49/23/18	66/37/17	0.492	0.671	0.259
Meld score	12.6 ± 6.3	11.8 ± 6.3	10.8 ± 5.2	0.430	0.242	0.051
Donor Characteristics						
Donor age (yr)	37.2 ± 10.2	37.4 ± 11.4	36.9 ± 9.8	0.892	0.558	0.782
Donor BMI (kg/m <sup>2</sup> )	22.6 ± 3.1	22.7 ± 3.5	23.5 ± 3.6	0.921	0.672	0.691
Donor risk index	1.44	1.41	1.49	0.721	0.322	0.675
Tumor characteristics						
Total diameter (cm)	4.1 ± 1.5	4.4 ± 1.8	11.7 ± 4.4	0.307	0.000	0.000
Number (1/2/3/4-5/diffuse)	43/13/2/0/0	54/18/3/15/0	49/17/11/9/34	0.024	0.000	0.000
AFP level (ng/mL)	1361.7 ± 4633.1	1122.4 ± 3764.5	2320.6 ± 10672.4	0.735	0.316	0.520
Overall survival rate				0.036	0.001	0.000
1 yr	94.80%	87.80%	75%			
3 yr	91.40%	77.80%	53.30%			
5 yr	89.70%	76.60%	50%			
Tumor-free survival rate				0.046	0.000	0.000
1 yr	91.40%	85.60%	65.80%			
3 yr	86.20%	75.60%	42.50%			
5 yr	86.20%	75.60%	41.70%			

BMI: Body mass index; LD: Liver disease; HBV-DNA: Hepatitis B virus DNA; DDLT: Deceased donor liver transplantation; LDLT: Living donor liver transplantation; AFP:  $\alpha$ -fetoprotein; HCV: Hepatitis C virus.

transplantation center, and all of them were followed up for at least 5 years. The baseline characteristics of the donors and recipients are summarized in Table 1. There were no significant differences among three groups with respect to recipient gender, age, or body mass index (BMI). The most common etiology of cirrhosis was hepatitis B infection. There were only 2 cases of hepatitis C infection. No differences were observed in either underlying liver disease (hepatitis virus) or HBV-DNA level. However, fewer patients underwent LDLT in the out up-to-seven group: 19.2% (23 cases) of patients in the out up-to-seven group, 37.9% (22 cases) patients in the Milan group, and 31.3% (28 cases) patients in the in up-to-seven criteria group ( $P < 0.05$ ) underwent LDLT. The pre-LT liver function, determined by the Meld score and Child score, were also not different among the three groups. There were also no differences among the three groups with respect to donor characteristics, including donor age, BMI and donor risk index.

### Tumor characteristics

There was no difference in the total diameter of the tumors between the Milan criteria and the up-to-seven criteria groups ( $P = 0.307$ ). However, the diameter in the Out up-to-seven criteria group was much larger than that in the other two groups ( $P = 0.000$ ). The out up-to-seven criteria group had the highest tumor number, followed

by the up-to-seven criteria group. There were no diffused targets in either the Milan group or the up-to-seven criteria group. However, there were 34 cases with diffused targets in the out up-to-seven criteria group. Seventy-on cases were diagnosed with macrovascular invasion by pre-LT imaging scans, and the diagnoses were confirmed by histological examination. However, there was no significant difference in the AFP level among the three groups ( $P > 0.05$ , shown in Table 1). One new target was found in the explanted liver of a patient in the Milan group, and 3 new targets were found in the up-to-seven group. The diameters of these new targets ranged from 0.8 to 3.0 cm.

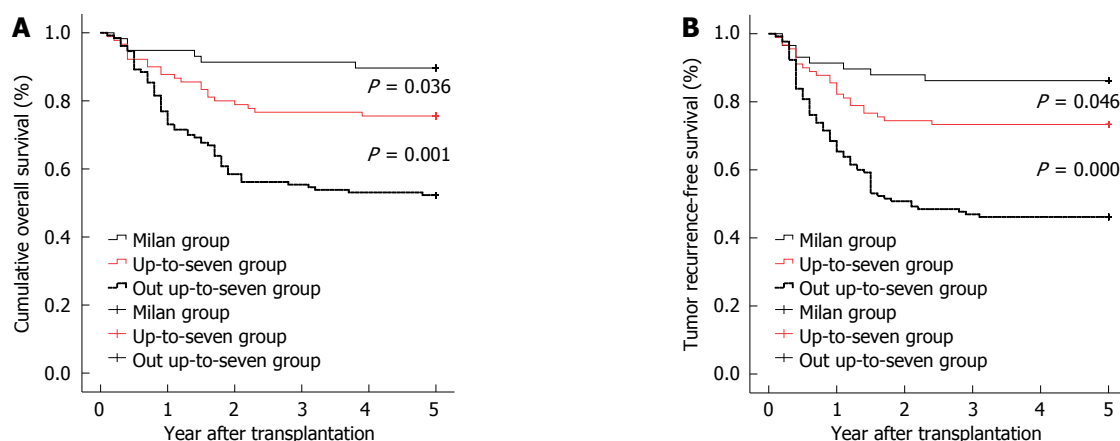
### Survival and tumor recurrence

The length of follow-up for all the patients in our study was at least 5 years, and no significant differences were observed among the groups. The 1-, 3-, and 5-year overall and tumor-free survival rates of Milan criteria group were superior to those of the up-to-seven patients [94.8% vs 87.8%, 91.4% vs 77.8%, and 89.7% vs 76.6%, respectively ( $P = 0.036$ ) and 91.4% vs 85.6%, 86.2% vs 75.6%, and 86.2% vs 75.6%, respectively ( $P = 0.046$ )]. The 1-, 3-, and 5-year overall survival rates (75%, 53.3%, and 50%, respectively) and tumor-free survival rates (65.8%, 42.5%, and 41.7%, respectively) in the patients whose HCCs did not meet the up-to-seven criteria were much

**Table 2** Site of hepatocellular carcinoma recurrence or metastasis after liver transplantation

	Liver	Lung	Bone	Liver + lung	Lung + bone	Intra-abdominal	Other
Milan group	3	1	0	1	0	0	0
In up-to-seven group	8	3	1	4	0	0	0
Out up-to-seven group	16	21	1	9	10	4	3

Other: Lung and brain (1 case), lung and spine liver, lung and bone.



**Figure 1** Survival and tumor recurrence. A: Overall survival rates of two groups ( $P = 0.498$ ); B: Tumor recurrence-free rates of two groups ( $P = 0.838$ ).

lower than those of the other patients ( $P < 0.01$ , Table 1). The most common reason for mortality within 1 year was complications, and not tumor recurrence, for the Milan criteria group and up-to-seven criteria group (none of the patients in the Milan criteria group and 2 patients (18.2%) in the up-to-seven group died from tumor recurrence within 1 year). However, most of the 26 (86.7%) deaths within 1 year in the out up-to-seven criteria group were due to tumor recurrence. However, 1 year after LT, the most common cause of mortality for all three groups was tumor recurrence.

The most common site of recurrence was the liver graft for all three groups, and lung metastasis was the second common site of recurrence. Additionally, some patients were diagnosed with combined organ recurrence or metastasis to the liver, lung or bone (Table 2). Although more patients were diagnosed with recurrence or metastasis in the out up-to-seven group than in the other groups, the site of recurrence or metastasis was not significantly different among the three groups. In the 71 cases who were diagnosed with macrovascular invasion, 54 (71.6%) tumors recurred or metastasized after LT (Figure 1).

## DISCUSSION

All of the baseline characteristics were comparable among the three groups, except for the source of the liver graft, as there were many fewer living donor liver transplantations in the up-to-seven group compared with the Milan criteria group. The main reason for this selective bias was the absence of a national organ allocation

system such as the United Network for Organ Sharing in China; the lack of such a system means that the criteria for HCC living donor liver transplantation are much stricter than deceased donor liver transplantation because living donor liver graft harvest involves potential risks to donors, including death<sup>[18,21]</sup>. However, this bias was assumed to have no impact on our analyses, as the results of another of our studies indicated that there were no significant differences in postoperative complications, tumor recurrence rate, survival rate, and HBV recurrence between deceased donor liver transplant (DDLT) and live donor liver transplantation (LDLT) patients<sup>[22]</sup>. Many other reports<sup>[23,24]</sup> have also indicated that there is no difference in long-term outcomes between DDLT and LDLT. Some published papers<sup>[25]</sup> have even indicated that early graft regeneration and features specific to living-donor liver transplantation (LDLT) may adversely influence the recurrence of HCC. Our data indicated that LDLT was performed more frequently in the Milan criteria group, so this selective bias did not affect the long-term survival rate.

Since the Milan criteria for HCC LT were proposed in 1996, dozens of models from all over the world have been developed to expand the indications for LT for patients with HCC without compromising overall or tumor-free survival compared with patients who underwent LT based on the Milan criteria. The main aim of expanding the Milan criteria was to include more HCC patients but maintain comparable outcomes. Although few reports have suggested that tumor involvement in the portal branches is a contraindication for LT<sup>[26,27]</sup>, there is general agreement among various researchers

that patients presenting macrovascular invasion or extrahepatic spread should be excluded from LT given the unacceptable rate of recurrence<sup>[10]</sup>; this presumption was confirmed by our analysis, which showed a very high recurrence rate (71.6%) in these cases. However, the proposed expanded criteria appear to be vague: the upper diameter of a single tumor ranges from 5 to 9 cm<sup>[6,28-30]</sup>, and the highest number of tumors ranges from 3 to unlimited<sup>[6,28,29,31]</sup>. Some published studies did not even impose upper limits on the tumor number or diameter<sup>[32,33]</sup>. Thirteen years after the Milan criteria were developed, the Mazzaferro group proposed an expanded set of criteria called the up-to-seven criteria (new Milan criteria). In their study, the 5-year overall survival rate for Milan group patients was 73.3%; this finding is comparable to our results, which showed a 5-year overall survival of 75%. However, for the up-to-seven criteria patients, the overall survival rate in our study was 53.3%, which was much lower than the 71.2% reported in the Mazzaferro *et al.*<sup>[11]</sup>. Several studies have evaluated the effectiveness of using the up-to-seven criteria as inclusion criteria for HCC LT<sup>[14,15]</sup>. de Ataide *et al.*<sup>[12]</sup> directly compared the long-term outcomes of a Milan criteria group and an up-to-seven criteria group. Their results showed that the post liver transplantation survival rates were 87.7%, 74.5% and 65.3% at 1, 3, and 5 years among patients who met the up-to-seven criteria, and these rates were similar to those in patients meeting the Milan criteria. However, there is still some disagreement regarding the up-to-seven criteria. In a letter to Mazzaferro and his colleagues, Sotiropoulos *et al.*<sup>[13]</sup> stated that although the up-to-seven criteria are based on objective tumor characteristics such as tumor size, tumor number, and microvascular invasion, these characteristics represent pathology findings and not preoperative objective tumor characteristics, and therefore, the up-to-seven criteria are illusive and not applicable in clinical practice. In the present study, 71 patients (59.1%) in the out up-to-seven criteria group showed macrovascular invasion, which was an independent risk factor for HCC recurrence after LT. Our data on the tumor characteristics for this analysis all come from pre-operative imaging data and were confirmed by the histological examination. Only a few targets (4 cases) were found in the explanted liver. We did not evaluate the new targets in the out up-to-seven group because there were some cases with diffused tumors, so finding and calculating new tumor targets would have been very difficult in these patients.

Our Milan criteria patients exhibited a 89.7% 5-year overall survival rate, and this rate is higher than that in some reports<sup>[10]</sup> but comparable with those in many other reports<sup>[29,34,35]</sup>. Although the up-to-seven criteria group included 90 patients, which was much higher than the number of patients in the Milan criteria group (53 cases), the main aim of expanding the Milan criteria was to include more HCC patients without compromising outcomes; this, in our study, long-term (5-year) survival was much lower in the up-to-seven group. The concept of the

“metro ticket” has been used to demonstrate this point, that is, expanding the criteria to allow both increased size and increased number of nodules resulted in an increased risk of recurrence. The further the criteria are expanded, the higher the risk in terms of survival<sup>[4]</sup>. However, although the survival rate in the up-to-seven criteria group was lower than that in the Milan criteria group, the 5-year overall survival rate was still considerable at 76.6%, which was comparable with the Milan criteria 5-year survival rate in many other reports<sup>[10]</sup>. Meanwhile, the overall survival rate of patients who met the up-to-seven criteria was much higher than those who did not meet up-to-seven criteria (5-year survival rate: 76.6% *vs* 50%). These comparisons suggest that the up-to-seven criteria may be accepted.

The limitations of this study include the fact that these data were retrospectively collected and analyzed. A future randomized study would be the best way to evaluate the effectiveness of the up-to-seven criteria as inclusion criteria for HCC LT. However, this ideal design would be very difficult to implement due to logistical challenges. In addition, a large multicenter study comparing a larger number of patients with HCC LT would be ideal for future analyses.

In conclusion, considering the differences in long-term outcome, care should be taken when using the up-to-seven criteria rather than the Milan criteria to include HCC patients in LT.

## ACKNOWLEDGMENTS

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## COMMENTS

### Background

Liver transplantation remains the best treatment for small hepatocellular carcinoma (HCC) resulting from chronic liver disease. However, post-operative recurrence is still a major problem related to HCC liver transplantation (LT). Stringent inclusion criteria have been adopted to ensure tumor free survival after LT. The first criteria for HCC LT were introduced in 1996 and were named the Milan criteria. Several years later, based on greater experience, some groups argued that the Milan criteria should be expanded. Therefore, the Milan group attempted to expand the Milan criteria and create a new set called the up-to-seven criteria (new Milan criteria): HCCs with seven as the sum of the size of the largest tumor and the number of tumors.

### Research frontiers

Although the up-to-seven criteria have been analyzed all over the world, they have not been as widely accepted as the Milan criteria, even 4 years after their conception. Meanwhile, there is still no research on these criteria in China, where most hepatitis B virus and hepatitis C virus infections and nearly 55% of worldwide HCC occurs.

### Innovations and breakthroughs

The up-to-seven criteria were introduced several years ago, but there is still no consensus about their effectiveness. Two hundred and twenty patients were divided into three groups according to the characteristics of their tumors in the authors' center. Considering that patients in the up-to-seven criteria group exhibited a considerable but lower survival rate compared with the Milan criteria group, the up-to-seven criteria should be used carefully and selectively.

### Applications

Considering the differences in long-term outcome, care should be taken when

using the up-to-seven criteria rather than the Milan criteria to include HCC patients in LT.

# Peer review

This is an interesting study comparing liver transplant outcomes in 3 groups of patients with different stage of HCC.

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