Liver Transplantation

OPEN

Milan-out Criteria and Worse Intention-to-Treat Outcome Postliver Transplantation

Julia Herreras, MD,1 Tommaso Di Maira, MD, PhD,1,2 Carmen Vinaixa, MD,1,2 Fernando San Juan, MD,3 Angel Rubín, MD,1,2 and Marina Berenguer, MD, PhD1,2,4

Background. Milan criteria are widely used for liver transplantation selection in hepatocellular carcinoma but have been recognized to be too restrictive. Milan-out criteria are increasingly being adopted. Our aim was to analyze if liver transplantation waitlisted Milan-out hepatocellular carcinoma patients have different outcome than Milan patients. Methods. Retrospective study including all consecutive patients with hepatocellular carcinoma admitted in the waiting list for liver transplantation between January 2012 and January 2015. We included 177 patients, 146 of which eventually transplanted. Downstaging was achieved in the Milan-out cases (n = 29) before waitlisting. Results. From diagnosis to last follow-up, 29% patients died. Survival at 1 and 5 years from diagnosis was 93% and 75%, respectively in the within Milan group compared with 91% and 61% in the Milan-out group (P=0.03). Treatment failure occurred in 20% of cases due to tumor progression in the waiting list (44%), death on the waiting list (20%), and hepatocellular carcinoma recurrence postliver transplantation (9%). Milan-out criteria was the only variable predictive of treatment failure remaining in the multivariate analysis with a hazard ratio (HR) of 1.7 (HR, 1.7; 95% confidence interval, 1.34-4.55; P=0.010) and HR of 1.43 (1.23-6.5) in the hepatocellular carcinoma recurrence. Conclusions. Milan-out criteria are associated with a higher intention-to-treat liver transplantation failure from time of inclusion in the waiting list. However, survival rates are still >50% at 5 years of follow-up.

Received 25 June 2019. Revision received 19 July 2019. Accepted 23 July 2019.
1 Hepatology and Liver Transplantation Unit and IS La Fe, Hospital Universitario y Politécnico La Fe, Valencia, Spain.
2 CIBEREhd, Instituto de Salud Carlos III, Madrid, Spain.
3 Hepatobiliary-pancreatic surgery and transplantation, Hospital Universitario y Politécnico La Fe, Valencia, Spain.
4 Faculty of Medicine, University of Valencia, Valencia Spain.
Correspondence: Marina Berenguer, MD, PhD, Hospital Universitario y Politécnico La Fe, Avda. Fernando Abril Martorell 106, 46026 Valencia Spain. (marina.berenguer@uv.es).
The authors declare no conflicts of interest.
Copyright © 2019 The Author(s). Transplantation Direct. Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.
ISSN: 2373-8731
DOI: 10.1097/TXD.0000000000000934
addition, most studies refer to transplant outcome in Milan-out patients from the time of LT and not from the time of HCC diagnosis.11-13

One of the very few studies confirming good results following downstaging with LRT comes from the United States. The authors analyzed the survival and failure of HCC therapy in Milan-in and Milan-out patients from time of HCC diagnosis.14 Waiting times in the United States are typically much longer than those reported in Spanish groups. We thus decided to conduct a similar study at a large Spanish reference center (Hospital La Fe in Valencia) aimed at confirming whether HCC downstaging outcomes by an intention-to-treat analysis from time of LT waiting list (WL) entry compare to standard of care (Milan-in criteria) HCC group.

MATERIAL AND METHODS

This is a retrospective cohort study, carried out at La Fe University Hospital (Valencia) including all consecutive patients with HCC admitted in the WL for LT between January 2012 and January 2015. This study was reviewed and approved by the local ethics committee. All patients were followed until January 2017 or death. Patients diagnosed with HCC but never included in the WL for LT were not analyzed in this series. The diagnosis of HCC for a lesion ≥1 cm was based on either quadruple-phase computed tomography (CT) or MRI with gadolinium contrast showing arterial phase enhancement and washout during the delayed images. Hepatic nodules <1 cm were not counted as HCC unless proven on a 3 months follow-up, according to the American Association for the Study of the Liver criteria.15 All HCC cases were evaluated for WL inclusion in a multidisciplinary committee according to the following protocol: patients fulfilling Milan Criteria and without other contraindication for LT were included and Model for End-stage Liver Disease (MELD) extra points assigned. The Milan criteria are defined as single HCC ≤5 cm or up to 3 HCCs ≤3 cm, without vascular invasion. Patients beyond Milan Criteria, with no limit in terms of size or number were enrolled in a downstaging protocol and listed once Milan criteria was achieved with persistence for at least 3 months. Downstaging was not performed in case of vascular invasion, extrahepatic disease, or alpha-fetoprotein (AFP) higher than 1000 g/dL at diagnosis.

The specific type of LRT was chosen based on the patient clinical status and HCC location. Treated patients underwent radiological evaluation (CT scan or MRI) 1 month after therapy to assess response after each LRT. Treatment response was assessed by measuring the diameter of the lesion without considering the areas of necrosis, as mRECIST16 criteria were not universally applied. In case of tumor stability or progression, a new LRT was performed. Patients with AFP values >400 mg/dL after downstaging procedure were excluded for LT. In addition, Milan-outpatients without radiological response are not waitlisted.

Once waitlisted, patients undergo an imaging test (CT or MRI) and AFP every 3 months. Patients with initial radiological response but evidence of tumoral progression (new tumors or growth of treated tumor) beyond Milan once waitlisted are dropped out from the WL; in case LRT cannot be applied, other therapies (Sorafenib) might be considered depending on the patient’s situation.

De novo development of one or more nodules after LT with typical features of HCC defined HCC recurrence. In case of doubts, histology was required.

Baseline characteristics namely age, gender, etiology of cirrhosis, date of HCC diagnosis, number of nodules, diameter of the major lesion, AFP levels, and MELD score at diagnosis were collected at time of WL inclusion. On-treatment variables including type and number of LRT, MELD, and Child-Pugh scores before and after each LRT, time from diagnosis to LT, and pretransplant AFP were collected for descriptive analysis. Donor and explant related factors were also collected including donor age, number of lesions, diameter of the largest lesion, tumor differentiation, necrosis, and presence of vascular and lymphatic dissemination.

The primary endpoint was the probability of treatment failure defined as any of the following events: (1) liver-related death on the WL and after LT; (2) dropout from the WL due to tumor progression despite LRT; and (3) HCC recurrence post-LT. Patients who developed a nonliver disease contraindicating LT or causing death and noncompliant patients were censored at the time of delisting or the development of the event. The principle of the present study was to demonstrate the intention-to-treat benefit of HCC downstaging in patients listed for LT.

Statistical Analysis

Data were expressed as median or mean according to their distribution, while and interquartile range (Q1-Q3) or range as measures of their dispersion, respectively. The categorical variables were presented by percentages. Distribution was assessed graphically and differences between categorical or continuous variables were analyzed by Chi-square, Student t, or Mann-Whitney U tests according to their distribution. The primary end-point was analyzed by an intention-to-treat analysis in a time-to-event fashion using a multivariable Cox regression adjusted for baseline characteristics. Independent variables associated with the outcome were selected by a forward stepwise model. A multivariable logistic regression analysis was applied to predict factors for treatment failure and HCC recurrence. Survival plots were obtained by Kaplan-Meier curves and differences analyzed by log-rank test. The level of statistical significance has been considered P<0.05. Statistical analysis was performed by PASW Statistic 18, release 18.0.0 (July 30, 2009).

RESULTS

Baseline Characteristics

A total of 177 patients diagnosed with HCC waitlisted for LT were included. Of these, 154 were men (87 %), 99.5% Caucasian, with a median age at HCC diagnosis of 58.5 years (range, 40-69 y). Most cases were related to chronic hepatitis C virus infection (45%) and/or excessive alcohol consumption (27%). At the time of HCC diagnosis, most patients had a compensated cirrhosis (73% child A) with a median MELD score of 9 (range, 6-27). Most HCC cases (n = 148, 84%) were within Milan at diagnosis. There were 29 (16%) out-of-Milan HCC cases waitlisted following successful downstaging therapy (Table 1). Although baseline characteristics of these 2 groups were not significantly different, there was a trend
for Milan-out cases to have worse prognostic features (higher AFP levels at diagnosis, higher median diameter of the largest lesion, higher number of lesions, and higher number of LRT) than the Milan-in cases (Table 2). Duration of follow-up did not differ between Milan-in and Milan-out patients (2.8 y [2-5 y] versus 2.6 y [2-4.6 y]) since HCC diagnosis.

Regarding LRT, most patients received 1 (n = 77) or 2 (n = 58) treatments during their waiting time. A total of 153 patients received LRT before being placed on the WL; additional LRT while on the WL were applied to 70 patients. Transarterial chemoembolization was the most commonly used procedure (57%) followed by radiofrequency ablation in 35% of cases, and others (radioembolization) in 8%. In 127 Milan-in patients (86%), LRT were performed as a bridge to transplantation. Milan-out patients, the duration for downstaging therapy was 8 months (range, 6-31 mo). Biological response, measured as the difference between pre-LRT and postprocedure (before transplantation) was positive (with a reduction of diameter) in 41 of the patients (23%), stable in 117 patients (66%) and negative (increased diameter) in 41 of the patients (23%).

Explant findings in those undergoing LT did not differ significantly between Milan-in and Milan-out cases (Table 3), but overall there was a trend for worse findings among the Milan-out patients, including the diameter of the largest lesion (22 mm IQ25-IQ75 15-30 mm) versus 32 mm (IQ25-IQ75 15-40 mm), number of lesions (2 versus 3), degree of differentiation (moderately and well differentiated in 52% and 42% of Milan-in cases versus moderately and poorly differentiated in 35% and 45% of Milan-out cases), degree of necrosis (total necrosis in 70% of Milan-in patients versus partial necrosis in 55% of Milan-out patients), or vascular invasion (9% versus 30%).

### Outcome

Out of the 177 patients, 146 patients were transplanted, 126 of which corresponding to the Milan-in group at diagnosis. Time on the WL did not differ significantly between the Milan-in and Milan-out cases (160 days [range, 3-528 days] versus 143 days [range, 60-364 days]). Out of the 146 LT cases, tumor recurrence occurred in 13 patients (8.9%) at a median of 570 days (60-970 days) post-LT. Overall, from the diagnosis of HCC until the last follow-up, 52 patients died. Survival rates at 1 and 5 years from diagnosis were 93% and 75%, respectively among the Milan-in patients. Lower survival rates, particularly at 5 years were achieved by the Milan-out patients (91% and 61%, respectively; \( P = 0.03 \)). From waitinglist to last follow-up, 29% patients died. Survival at 1 and 5 years since waitinglist was 88% and 77% in Milan-in patients and 86% and 61 % in Milan-out patients (\( P = 0.042 \)) (Figure 1). Survival since LT was also lower in the Milan-out patients compared with the Milan-in (85% and 64% versus 96% and 84%, respectively at 1 and 5 y; \( P = 0.041 \)) (Figure 2).

In the univariate analysis, variables associated with survival since diagnosis included the Milan-out criteria at diagnosis, the number of LRT received before transplantation, and the Child-Pugh score and AFP levels at diagnosis. In the multivariate analysis, both Milan-out criteria at diagnosis and AFP levels at diagnosis were independently associated with worse survival (hazard ratio [HR] of 1.7 [95% CI, 1.34-4.55; \( P = 0.01 \)) and 1.53; 95% confidence interval [CI], 3.8-6.1; \( P = 0.02 \))].

### Treatment Failure

Treatment failure occurred in 36 cases (20%), 16 (44%) due to tumor progression in the WL, 7 (20%) due to death on the WL secondary to decompensated liver disease, and 13 cases due to HCC recurrence (9% of the 146 LT patients). Treatment failure according to Milan criteria occurred significantly more in the group of Milan-out patients. Of those within Milan (n = 148), treatment failure occurred in 23 (15%) cases, due to HCC recurrence (n = 9, 7% of 126 LT patients), death secondary to liver disease (n = 4, 17%), and dropout secondary to tumor progression (n = 10, 43%). In turn, among Milan-out patients (n = 29), treatment failure occurred in 13 (45%) (4 due to HCC recurrence [20% of 20 LT cases], 3 deaths (10%) on the WL due to liver disease, and 6 [21%] dropout for tumor progression in the WL) (Figure 3).

### Tumor Progression or Death in WL

Besides the Milan criteria, other factors significantly associated with treatment failure in the univariate analysis were the number of LRT received before WL and AFP levels at diagnosis. In the multivariate analysis, only the variable Milan-in/Milan-out at time of HCC diagnosis remained in the model (HR, 1.7; 95% CI, 1.34-4.55; \( P = 0.010 \)) (Table 4).

### HCC Recurrence

Thirteen patients were diagnosed with HCC recurrence at a median of 18 months (range, 6-24 mo) since LT.
In the univariate analysis, factors associated with recurrence were Milan-out criteria and AFP levels at diagnosis, female gender ($P = 0.04$), and high MELD score ($P = 0.045$) and AFP levels ($P = 0.034$) at time of LT. In the multivariate analysis, out-of-Milan criteria (HR, 1.43; 95% CI, 1.23-6.5; $P = 0.048$), MELD score at LT (HR, 1.23; 95% CI, 1.03-4.5; $P = 0.046$), and female gender (HR, 1.32; 95% CI, 1.4-3.7; $P = 0.03$) remained significant in the model (Table 5).
DISCUSSION

Although Milan criteria have been used for years as the criteria to include patients in the WL for LT, many authors consider these criteria to be too restrictive. Indeed, patients with intermediate stages, after the application of LRT, can achieve substantial tumor volume reduction and be successfully transplanted.17,18 In fact, in recent years, several centers have endorsed these new expanded criteria and equate the survival of these patients with that of patients with tumors in the initial stages.19,20 Data on downstaging results though are controversial, due to a variety of reasons, particularly the differences in LRT, the wide variability in WL duration and particularly, the lack of intention-to-treat analyses since HCC diagnosis but rather survival analyses from transplantation.

We aimed to analyze our results in a large transplant center where WL times are typically shorter than those reported by
Transplantation DIRECT ■ 2019

Other United States or European centers, a factor that could result in different outcomes, as well as focusing on an intention-to-treat analysis from time of HCC diagnosis. Major findings from this study can be summarized as follows: (1) treatment failure, including death in the WL from liver disease, dropout due to tumor progression or post-LT HCC recurrence in those transplanted, occurred at a significantly higher rate in those who exceeded Milan criteria and who underwent a downstaging protocol. In fact, the Milan in/out variable was the only variable that remained significant in the multivariate analysis and (2) despite lower rates of treatment efficacy on intention-to-treat analysis, survival in the short term was good and similar to that achieved by patients fulfilling the Milan criteria. In the longer term, however, after a 5 years follow-up, survival rates dropped to be significantly worse than those achieved by patients with HCC Milan-in criteria but can still be considered extremely favorable when compared with other local therapies.

Two studies published in the United States in the last 2 years report treatment failure rates of about 30% assuming the same study design as ours that is, using the same definition of treatment failure and analyzing the data on an intention-to-treat basis. In these studies, the criteria used to select the Milan-out patients was the UCSF (California) criteria; in addition, and as mentioned previously, waiting times are significantly longer, and as a result, patients undergo a significantly higher number of LRT and have more advanced liver disease (higher MELD ad Child scores) at LT.14,21 These differences might explain, in part, the higher rate of treatment failure reported in the US studies. As in our study, tumor progression and death on the WL were also greater in the Milan-out patients.

More specifically, Yao et al14 analyzed survival since diagnosis in patients with beyond UCSF criteria, UCSF and Milan criteria obtaining good results in all groups. Patients exceeding UCSF criteria but successfully downstaged to Milan also managed to obtain survival rates comparable to Milan-in patients, both from time of inclusion in the WL and from time of LT, supporting LT as a therapeutic option for these expanded criteria tumors. In the downstaging group, variables related to the worst prognosis were advanced Child (as in our sample) and AFP levels higher than 1000 mg/dL. This last parameter is not comparable with our study since we did not include patients with AFP higher than 400 ng/dL on the WL. Reasons that may explain differences in results, particularly the worse long-term results (at 5 y) in the Milan-out versus Milan-in patients both on intention-to-treat but particularly after LT.

![FIGURE 3. Treatment failure: death on the waiting list due to liver failure and/or portal hypertension complications and/or tumor progression despite locoregional therapies; and hepatocellular carcinoma recurrence postliver transplantation.](image)

### TABLE 4.

| Variables associated with treatment failurea |
|------------------------------------------------|
| **Univariate analysis (n = 177)** | **Treatment failure (n = 23)** | **No treatment failure (n = 154)** | **P** |

| Gender at diagnosis (% men) | 18 (78) | 130 (84.4) | 0.313 |
| Age at diagnosis, y, median (IQR) | 57 (45-69) | 59 (40-68) | 0.316 |
| Etiology of liver disease at diagnosis (%) | | | |
| Alcohol | 7 (34.7) | 40 (26) | 0.149 |
| NASH | 1 (4.3) | 5 (2.2) | |
| HCV | 12 (52.1) | 69 (44.9) | |
| OH + HCV | 1 (4.3) | 26 (16.8) | |
| OH + NASH | 1 (4.3) | 4 (2.5) | |
| Other | 1 (4.3) | 10 (6.4) | |
| Child score at diagnosis (%) | | | |
| A | 15 (65.2) | 120 (72.3) | 0.910 |
| B | 7 (30.4) | 28 (2.4) | |
| C | 1 (4.3) | 6 (4.3) | |
| MELD score at diagnosis, median (IQR) | 6 (5-9) | 6 (5-10) | 0.123 |
| MELD score at LT, median (IQR) | 9 (6-18) | 9 (6-20) | 0.125 |
| Milan-out criteria (%) | 9 (40) | 16 (11.3) | 0.001 |
| AFP levels, mg/dL, median (IQR) | | | |
| At diagnosis | 11.50 (2-250) | 5.5 (2-321) | 0.003 |
| At LT | 22.9 (1.5-250) | 10.6 (1.3-329) | 0.056 |
| Total number of LRT, median (IQR) | 1 (0-3) | 2 (0-4) | 0.109 |
| LRT before waitlisting, median (IQR) | 1 (0-3) | 2 (0-4) | 0.003 |
| **Multivariate analysis** | | | |
| Milan-out criteria | 1.7 (1.34-4.55) | 0.010 |

*Treatment failure was defined as death on the WL due to liver failure and/or portal hypertension complications and/or tumor progression despite LRT.

AFP, alpha-fetoprotein levels; CI, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; IQR, interquartile range; LRT, locoregional therapies; LT, liver transplantation; MELD, Model for End-stage Liver Disease; NASH, nonalcoholic steatohepatitis; OH, alcohol; WL, waiting list.*
may relate to differences in patient population, donor rate, and time in the WL. Indeed, longer waiting times in the United States may result in better patient selection so that tumors with more biological stability eventually undergo LT while those with a more aggressive biology are typically excluded from the WL for tumor progression.\(^\text{22}\) Interestingly, the rate of dropout for tumor progression was higher in the study by Yao et al (32%) compared with ours (20%), indirectly supporting this concept. In fact, several authors have proposed that at least 3 months of tumor stability should be required after downstaging before including a patient on the WL. This “ablate and wait” criterion is a tool to determine the biology of the tumor trying to select the least aggressive ones. The “United Network for Organ Sharing” has more recently expanded this time to 6 months,\(^\text{23,24}\) and based on the results obtained in our and the study by Yao et al, we are considering to also apply the 6 months rule in our center.

AFP levels play an important role when selecting candidates for downstaging and both static as well as dynamic levels are predictors of treatment response. Indeed, many studies have shown that patients with high AFP values have typically a lower treatment response in terms of reduction in tumor volume.\(^\text{25,26}\) In our case, although there were no statistical differences, there was a trend for greater treatment failure among patients with high AFP levels at diagnosis once included in the WL. It is important to highlight that although eventually these patients achieved adequate downstaging and were thus allowed to be included in the WL, our sample is highly selected since patients with AFP higher than 400 ng/dL were excluded.

Our study has limitations. It is a retrospective study, carried out in a single referral center for LT with few Milan-out patients recruited. We have few patients with downstaging protocol. Indeed, patients evaluated both in our center as well as elsewhere who were treated with LRT but never reached the Milan-in criteria were not referred and/or included in the WL for LT, and so the results apply to the subgroup of HCC cases with initial adequate response to LRT. In addition, the criteria for downstaging were not completely standardized in a protocol and this may have generated a selection bias. Despite these limitations, we included a relatively selected cohort of patients that adequately represents the Spanish transplant population.

In conclusion, downstaging is a valid and increasingly used tool for selecting tumors with a presumably favorable biology and greater tumor stability. Although patients successfully downstaged have worse overall intention-to-treat outcomes compared with Milan-in patients, they achieve satisfactory post-LT survival rates, greater than the “minimum” of 50% at 5 years, and thus should not be denied this therapeutic option. Whether the LT criteria following successful downstaging should be the Milan criteria as opposed to an expanded one\(^\text{27}\) requires further investigation.

**ACKNOWLEDGMENTS**

We would like to thank G. Sapisochin for his helpful comments.

**REFERENCES**

1. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet*. 2012;379:1245–1255.
2. Bosetti C, Turati F, La Vecchia C. Hepatocellular carcinoma epidemiology. *Best Pract Res Clin Gastroenterol*. 2014;28:753–770.
3. Clavien PA, Lesurtel M, Bossuyt PM, et al. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol*. 2012;13:e11–e22.
4. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatology*. 2002;35:519–524.

5. Mazzaferrro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334:603–609.

6. Duffy JP, Vardanian A, Benjamin E, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. *Ann Surg*. 2007;246:502–509; discussion 509–511.

7. Lo C. Downstaging of hepatocellular carcinoma before transplantation: an advance in therapy or just another selection criterion. *Am J Transplant*. 2008;8:2485–2488.

8. Mazzaferrro V, Llovet JM, Miceli R, et al; Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol*. 2009;10:35–43.

9. Kumar Y, Sharma P, Bhatt N, et al. Transarterial therapies for hepatocellular carcinoma: a comprehensive review with current updates and future directions. *Asian Pac J Cancer Prev*. 2016;17:473–478.

10. Ste WH, Cheung TT. Bridging and downstaging therapy in patients suffering from hepatocellular carcinoma waiting on the list of liver transplantation. *Transl Gastroenterol Hepatol*. 2016;1:34.

11. Gunsar F. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria. *Exp Clin Transplant*. 2017;15(Suppl 2):59–64.

12. Chapman WC, Garcia-Aroz S, Vachharajani N, et al. Liver transplantation for advanced hepatocellular carcinoma after downstaging without up-front stage restrictions. *J Am Coll Surg*. 2017;224:610–621.

13. Xu DW, Wan P, Xia Q. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria: a review. *World J Gastroenterol*. 2016;22:3325–3334.

14. Yao FY, Mehta N, Flemming J, et al. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. *Hepatology*. 2015;61:1968–1977.

15. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53:1020–1022.

16. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*. 2010;30:52–60.

17. Xu X, Lu D, Ling Q, et al. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria. *Gut*. 2016;65:1035–1041.

18. Yao FY, Ferrelli L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology*. 2001;33:1394–1403.

19. Yao FY, Breitenstein S, Broelsch CE, et al. Does a patient qualify for liver transplantation after the down-staging of hepatocellular carcinoma? *Liver Transpl*. 2011;17(Suppl 2):S109–S116.

20. Yao FY, Kerlan RK Jr, Hirose R, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. *Hepatology*. 2008;48:819–827.

21. Yao FY, Hirose R, LaBerge JM, et al. A prospective study on down-staging of hepatocellular carcinoma prior to liver transplantation. *Liver Transpl*. 2005;11:1505–1514.

22. Cillo U, Giuliani T, Polacco M, et al. Prediction of hepatocellular carcinoma biological behavior in patient selection for liver transplantation. *World J Gastroenterol*. 2016;22:232–252.

23. Agopian VG, Morshedi MM, McWilliams J, et al. Complete pathologic response to pretransplant locoregional therapy for hepatocellular carcinoma defines cancer cure after liver transplantation: analysis of 501 consecutively treated patients. *Ann Surg*. 2015;262:536–545; discussion 543–545.

24. Beal EW, Dittmar KM, Hanje AJ, et al. Pretransplant locoregional therapy for hepatocellular carcinomas: evaluation of explant pathology and overall survival. *Front Oncol*. 2016;6:143.

25. Toro A, Ardiz A, Mannino M, et al. Effect of pre- and post-treatment α-fetoprotein levels and tumor size on survival of patients with hepatocellular carcinoma treated by resection, transarterial chemoembolization or radiofrequency ablation: a retrospective study. *BMC Surg*. 2014;14:40.

26. Lai Q, Iesari S, Melandro F, et al. The growing impact of alpha-fetoprotein in the field of liver transplantation for hepatocellular cancer: time for a revolution. *Transl Gastroenterol Hepatol*. 2017;2:72.

27. Toso C, Meeberg G, Andres A, et al. Downstaging prior to liver transplantation for hepatocellular carcinoma: advisable but at the price of an increased risk of cancer recurrence - a retrospective study. *Transpl Int*. 2019;32:163–172.