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World J Gastroenterol 2018 August 28; 24(32): 3567-3676



REVIEW

- 3567 Positioning of old and new biologicals and small molecules in the treatment of inflammatory bowel diseases
Reinglas J, Gonczi L, Kurt Z, Bessissow T, Lakatos PL
- 3583 Prognostic significance of tumor immune microenvironment and immunotherapy: Novel insights and future perspectives in gastric cancer
Lazăr DC, Avram MF, Romoșan I, Cornianu M, Tăban S, Goldiș A
- 3617 *Helicobacter pylori* infection and liver diseases: Epidemiology and insights into pathogenesis
Okushin K, Tsutsumi T, Ikeuchi K, Kado A, Enooku K, Fujinaga H, Moriya K, Yotsuyanagi H, Koike K

MINIREVIEWS

- 3626 Expansion of the hepatocellular carcinoma Milan criteria in liver transplantation: Future directions
Pavel MC, Fuster J
- 3637 Diagnosis and management of fibromuscular dysplasia and segmental arterial mediolysis in gastroenterology field: A mini-review
Ko M, Kamimura K, Ogawa K, Tominaga K, Sakamaki A, Kamimura H, Abe S, Mizuno K, Terai S

ORIGINAL ARTICLE

Basic Study

- 3650 Abnormal expression of HMGB-3 is significantly associated with malignant transformation of hepatocytes
Zheng WJ, Yao M, Fang M, Wang L, Dong ZZ, Yao DF

Retrospective Cohort Study

- 3663 C-peptide as a key risk factor for non-alcoholic fatty liver disease in the United States population
Atsawarungruangkit A, Chenbhanich J, Dickstein G

Clinical Trials Study

- 3671 Vascular anatomy of inferior mesenteric artery in laparoscopic radical resection with the preservation of left colic artery for rectal cancer
Wang KX, Cheng ZQ, Liu Z, Wang XY, Bi DS

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Expansion of the hepatocellular carcinoma Milan criteria in liver transplantation: Future directions

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Abstract

Milan criteria are currently the benchmark related to liver transplantation (LT) for hepatocellular carcinoma. However, several groups have proposed different expanded criteria with acceptable results. In this article, we review the current status of LT beyond the Milan criteria in three different scenarios-expanded criteria with cadaveric LT, downstaging to Milan criteria before LT, and expansion in the context of adult living donor LT. The review focuses on three main questions: what would the impact of the expansion beyond Milan criteria be on the patients on the waiting list; whether the dichotomous criteria (yes/no) currently used are appropriate for LT or continuous survival estimations, such as the one of "Metroticket" and whether it should enter into the clinical practice; and, whether the use of living donor LT in the context of expansion beyond Milan criteria is justified.

Key words: Hepatocellular carcinoma; Milan criteria; Liver transplantation; Living donor liver transplantation; Expanded criteria; Downstaging

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Core tip: After more than 20 years since their first description, the Milan criteria still represent the benchmark in liver transplantation for hepatocellular carcinoma. This review focuses on three unresolved issues, those being: the impact of expansion beyond Milan criteria for patients on the liver transplant waiting list; whether the dichotomous criteria (yes/no) currently used are appropriate for liver transplantation or continuous survival estimations, such as the one of "Metroticket" and whether

it should enter into the clinical practice; and, whether the use of living donor liver transplantation in the context of expansion beyond Milan criteria is justified.

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INTRODUCTION

Nowadays, hepatocellular carcinoma (HCC) represents the second cause of cancer-related death in the world^[1]. Liver transplantation (LT) is an attractive option for treatment of HCC, giving that it simultaneously addresses the HCC and the cirrhotic liver, which is at risk for development of new tumors.

Since the introduction of the so-called Milan criteria (MC; single lesion \leq 5 cm or up to three separate lesions, none larger than 3 cm)^[2] into clinical use, survival rates after LT for HCC have improved significantly. Today, the 5-year overall survival (OS) of patients within the MC reaches similar rates as those of nontumoral indications (65%-70% for HCC patients)^[3,4]. As a result, the MC have been included in the Barcelona-Clinic Liver Cancer (BCLC) pretransplant staging, and the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver-European Organisation for Research and Treatment of Cancer (EASL-EORTC) practice guidelines^[5-8].

However, the MC may seem too restrictive. Several groups have proposed different expansions of these classic criteria, with reasonable life expectancy after LT^[9-14]. The rationale behind the expansion is that approximately 25% of the patients classified as Milan-in before LT present a Milan-out HCC in the explant histology^[2,15,16]. The 5-year OS of these patients are better than the minimum acceptable rate of 50% proposed by some authors^[17,18]. Despite this, the majority of the transplant centers are still using the MC. Currently, the EASL-EORTC guidelines on management of the HCC do not recommend the expansion of criteria outside of prospective research studies^[8].

The International Consensus Conference regarding LT for HCC that was held in Zurich in 2010 states that the MC represent the benchmark for selection of patients for transplantation and the basis for comparison with other suggested criteria. However, according to the same group, modest expansion may be considered giving the favorable results of several studies^[19]. Theoretically speaking, at least three different scenarios may be planned for the expansion of the HCC criteria - transplantation with deceased donor grafts in Milan-out HCC patients, living donor (LD)LT for patients beyond MC, and successful downstaging to MC before LT in

patients initially Milan-out. Regarding the first of these three scenarios, the definition of a "time 0" (the moment when the patients with expanded criteria are included on the waiting list) will be very important, allowing for study of the expansion from an "intention-to-treat" point of view^[20].

Several important issues should be discussed in order to evaluate the impact of the expansion beyond MC.

The first issue to be considered is what the effect of transplanting Milan-out patients on the waiting list for LT will be^[21], by balancing the survival benefit for the patients beyond MC against the harm caused by delaying the LT for the other patients on the waiting list. According to the data published by United Network for Organ Sharing (known as UNOS) and the European Liver Transplant Registry (known as ELTR), the most important problem facing LT remains the scarcity of donors^[3,4]. Theoretically, the expansion of criteria could lead to an overload of an already-large waiting list by adding patients that, until this moment, were deemed to not benefit from this treatment. The decision on whether to expand the criteria depends on what number would be considered as acceptable lowest survival after LT by each transplant community^[22].

The second issue to be considered is if the decision to transplant an HCC patient should only depend on rigid criteria, like "size and number" or should be a dynamic decision in which expansion beyond the MC could be an option, depending on other characteristics such as the waiting list times and donor availability in each geographic region that performs LT.

The third issue to be considered is the strategy of using LDLT in patients with HCC, which is still questioned by some authors. Despite the advantage of transplanting patients beyond MC without affecting the conventional waiting list, at least two important problems have to be analyzed. One of them is the risk to the donor, especially in the context of expanding the criteria. The second one is that there are reports that describe significantly worse results with LDLT, as compared with conventional LT^[23].

The objectives of this article are to review the current literature related to the expansion beyond MC in the three described scenarios and to evaluate the relevant data linked to the issues presented above. We believe that the transplant with deceased donor grafts and the LDLT are marked by different characteristics, therefore we will discuss each one separately.

LT with deceased donor grafts in patients with HCC beyond MC

In the last years, it has become evident that the conventional LT (with cadaveric donors) for HCC beyond MC is not necessarily associated with worse results. Several authors have described modest expansions of the MC with acceptable OS and recurrence rates (see Tables 1 and 2). Giving all these results, Mazzaferro^[24] suggests that the tumor size and number used as criteria for transplantation should be defined at a regional

Table 1 Expanded criteria used for liver transplantation

Criteria	Type of donor	Detailed criteria
UCSF ^[9,27]	Cadaveric	Solitary tumor ≤ 6.5 cm or ≤ 3 tumors with the largest ≤ 4.5 cm
Up-to-seven ^[10]	Cadaveric/LDLT	Seven: sum of tumor number and size of the largest tumor without microvascular invasion
Clinica Universidad de Navarra (CUN) ^[12]	Cadaveric	1 tumor ≤ 6 cm or ≤ 3 tumors with the largest ≤ 5 cm
Toso ^[29]	Cadaveric	Total tumor volume ≤ 115 cm ³ and AFP ≤ 400 ng/mL
Hangzhou University ^[13]	Cadaveric	One of the following: Total tumor diameter ≤ 8 cm
Onaca (ITR) ^[32]	Cadaveric	Total tumor diameter > 8 cm with histological grade I or II and AFP ≤ 400 ng/mL Solitary tumor, ≤ 6 cm 2-4 tumors, ≤ 5 cm
Tokyo (5-5 rule) ^[53]	LDLT	Maximum 5 tumors ≤ 5 cm
Kyoto ^[55]	LDLT	≤ 10 tumors, ≤ 5 cm, DCP§ ≤ 400 mAU/mL
Kyushu University ^[57]	LDLT	Any number of tumors with diameter ≤ 5 cm or DCP§ ≤ 300 mAU/mL
Asan ^[58]	LDLT	≤ 6 tumors, diameter ≤ 5 cm
Samsung ^[59]	LDLT/cadaveric	≤ 7 tumors, diameter ≤ 6 cm, AFP ≤ 1000 ng/mL
BCLC ^[14]	LDLT	1 tumor, ≤ 7 cm 3 tumors, ≤ 5 cm 5 tumors, ≤ 3 cm
Maintained response within Milan criteria during 6 mo after downstaging		

AFP: Alpha-fetoprotein; BCLC: Barcelona-Clinic Liver Cancer; DCP: Des-gamma-carboxy prothrombin; LDLT: Living donor liver transplantation; LT: Liver transplantation.

Table 2 Results after liver transplantation with expanded criteria

Ref.	Type	Patients, n (type)	Criteria (findings)	Survival, time (%)	Recurrence, time (%)	Factors for survival	Factors for recurrence
Yao <i>et al</i> ^[9] , 2001	R	14 (MO)	UCSF (Histol)	5 yr (84.6)	-	pT4, total tumor diameter	-
Yao <i>et al</i> ^[27] , 2007	P	38 (MO)	UCSF (Radiol)	5 yr I-to-T (68)	5 yr DFS (93.6)	-	UCSF Vascular invasion AFP > 1000 ng/mL
Onaca <i>et al</i> ^[32] , 2007	R	129 (MO)	Onaca	5 yr I-to-T (68)	5 yr DFS (63.9)	-	Tumor > 6 cm AFP > 200 ng/mL Tumors > 4 Vascular invasion
Herrero <i>et al</i> ^[28] , 2008	P	26 (MO)	CUN (Radiol)	5 yr (73)	5 yr I-to-T (68)	-	-
Zheng <i>et al</i> ^[13] , 2008	R	99 (MI and MO), 26 (MO)	Hangzhou (Histol)	5 yr (70.7)	5 yr DFS (62.4)	Macrovascular invasion Tumor size > 8 cm AFP > 400 ng/mL	Macrovascular invasion Tumor size > 8 cm AFP > 400 ng/mL
Mazzaferro <i>et al</i> ^[10] , 2009	R	283 (MI and MO)	Up-to-seven (Histol)	5 yr (71.2)	-	Histological grading (III) Microvascular invasion	Histological grading (III)
Toso <i>et al</i> ^[29] , 2015	P	38 (MO)	Toso (Radiol)	4 yr (74.6) 4 yr I-to-T (53.8)	4 yr DFS (68)	-	-
Togashi <i>et al</i> ^[54] , 2016	R	14 (MO)	Tokyo	-	5 yr (8)	-	Tokyo criteria AFP ≥ 400 ng/mL DCP ≥ 200 mAU/mL
Kaido <i>et al</i> ^[56] , 2013	R	42 (MO)	Kyoto	5 yr (80)	5 yr (7)	-	Kyoto criteria Pretreatment of the HCC
Shirabe <i>et al</i> ^[57] , 2011	R	48 (MI and MO)	Kyushu (Histol)	5 yr (81.6)	5 yr DFS (80)	-	Kyushu criteria
Lee <i>et al</i> ^[58] , 2008	R	174 (MI and MO)	Asan (Histol)	5 yr (81.6)	5 yr (15)	Largest tumor > 5 cm Number > 6 Gross vascular invasion	Largest tumor > 5 cm Number > 6 Gross vascular invasion
Kim <i>et al</i> ^[59] , 2014	R	180 (in the whole study, including Samsung-out)	Samsung (Histol)	5 yr (81.6)	5 yr DFS -89.6	-	Tumors ≤ 7 Diameter ≤ 6 cm AFP ≤ 1000 ng/mL
Llovet <i>et al</i> ^[14] , 2018	P	22	BCLC (Radiol)	5 yr (80.2)	5 yr (23.8)	MI after locoregional therapies	-

AFP: Alpha-fetoprotein; BCLC: Barcelona-Clinic Liver Cancer; DFS: Disease-free survival; Histol: Histology; I-to-T: Intention-to-treat; LT: Liver transplantation; MI: Milan-in; MO: Milan-out; P: Prospective; R: Retrospective; Radiol: Radiology; UCSF: University of California San Francisco.

level depending on the dynamics of the waiting list, the proportion of patients with and without HCC on the waiting list, the harm to the patients remaining on the waiting list, and the donor availability.

The San Francisco group published, in 2001, an expansion based on explant histological characteristics (solitary tumor ≤ 6.5 cm or up to three tumors ≤ 4.5 cm)^[9]. The reported 5-year OS was 75.2% for all the patients meeting the University of California San Francisco (UCSF) criteria (including Milan-in) and was 84.6% for the 14 patients classified as Milan-out UCSF-in. However, it is expected that the pretransplantation radiological evaluation underestimates, with up to 25%-30% for the HCC stage, when it is compared to posttransplant histology findings^[25,26]. For this reason, the same group published, 6 years later, the results of a prospective study using the same criteria applied to the pretransplant radiology exam. The 5-year disease-free survival (DFS) was of 91.1% for Milan-in patients vs 93.6% for Milan-out UCSF-in patients^[27]. However, the application of these criteria was questioned by other authors. Decaens *et al.*^[20] analyzed the results of the UCSF criteria according to the intention-to-treat principle in a group with a relatively reduced waiting list time, of only 4 mo. When the UCSF criteria were applied at the "time 0" of inclusion on the waiting list, the 5-year OS of the Milan-out UCSF-in patients was 45.6% and of the Milan-in patients was 60.1%.

In 2009, Mazzaferro *et al.*^[10] published the results of a large, multicentric, retrospective study and identified a combination of tumor maximum size and number of nodules as a predictive factor for survival. The "up-to-seven" criteria (see Table 1) in patients without microvascular invasion was found to be associated with 5-year OS rate of 71.2%, which was comparable with that of the Milan-in patients. However, when the up-to-seven criteria was associated with microvascular invasion, the survival was significantly worse (48.1%). It is important to mention that the presence of microvascular invasion represents a variable not possible to identify before LT and that expansion beyond the MC is usually associated with higher rates of microvascular invasion^[20].

The group of Pamplona, Spain reported the results of LT with the Clinic of Universidad of Navarra (CUN) criteria^[12,28]. The 5-year OS was 68% when the analysis was performed from an intention-to-treat point of view, being statistically comparable to that for the patients with Milan-in tumors. Although none of the patients with Milan-out CUN-in HCC developed tumor recurrence in the posttransplant follow-up period, 12 of the patients recruited for that study progressed beyond the CUN criteria on the waiting list and were deemed to not benefit from LT^[28].

Toso *et al.*^[29] published the results of a prospective study with criteria which included total tumor volume and alpha-fetoprotein (AFP). Survival and recurrence rates of the Milan-out patients meeting the criteria were acceptable, even though the "intention-to-treat

analysis" showed statistically inferior results due to the waiting list drop-out rates. The criteria of the University of Hangzhou, China also took AFP levels into account^[13]. Two conclusions could be drawn from that study: first, the application of this criteria did not yield worse results when compared with MC; second, even the patients exceeding the MC but fulfilling the Hangzhou criteria presented improved prognosis when compared with the Hangzhou-out patients. It has to be mentioned that, currently, the AFP level is included in the selection criteria in France and Canada, where patients with values ≥ 1000 ng/dL are excluded for LT^[30,31].

Onaca *et al.*^[32] analyzed the results of the International Registry of Hepatic Tumors in Liver Transplantation and concluded, similarly, that a modest expansion beyond MC could still offer favorable results (see Table 1). When patients presented in the explant analysis with one tumor of ≤ 6 cm or 2-4 tumors of ≤ 5 cm, the 5-year DFS was 64%.

Downstaging to Milan-in HCC before LT

In the context of HCC, there is a clear difference between the "bridge treatments" (referring to patients already on the waiting list for LT and submitted to locoregional therapies in order to diminish the drop-out rates) and the "downstaging" (defined as the treatment applied to patients initially outside of the established criteria). The latter is mainly used as a selection tool for the patients with better prognosis that could benefit from LT^[33]. The strategy of downstaging to MC before LT by using locoregional therapies has been the subject of debate. In this review we will only be referring to the prospective studies related to the subject.

Roayaie *et al.*^[11] describes the results of the protocol of Mount Sinai Medical Center, which consisted of arterial chemoembolization with mitomycin C, doxorubicin and cisplatin at the time of diagnosis, LT with single systemic intraoperative dose of doxorubicin before revascularization of the new liver, and systemic doxorubicin for a total of six cycles, beginning on the sixth postoperative week. This protocol was applied to patients with unresectable HCC larger than 5 cm. The 5-year DFS of a subgroup of patients with tumors of 5-7 cm was considered acceptable (55%).

Yao *et al.*^[34] published, in 2015, an intention-to-treat study for a group of patients transplanted after downstaging and compared their results with the ones of Milan-in patients from an intention-to-treat point of view. Even though the cumulative risk for drop-out was higher in the downstage group (34.2% vs 25.6% at 2 years), the 5-year OS and the 5-year intention-to-treat OS were not statistically different between the groups. The factors related to the probability of drop-out were AFP > 1000 ng/mL and cirrhosis of Child B grade.

The group of Bologna also compared the results of downstaging and LT in 48 patients with those of 129 Milan-in patients, and concluded that the rates of transplantation, DFS and intention-to-treat OS were

Table 3 Prospective studies of downstaging of hepatocellular carcinoma before liver transplantation

Ref.	Criteria	Downstaging success rate (%)	LT rate (%)	Survival, time and rate (%)	HCC recurrence (%)
Roayaie <i>et al</i> ^[11] , 2002	Mount Sinai protocol		53.75	5 yr OS (44) 5 yr DFS (48) 5 yr DFS, tumors < 7 cm (55)	
Yao <i>et al</i> ^[72] , 2015	Beyond Milan: single tumor ≤ 8 cm, 2–3 tumors (at least one > 3 and ≤ 5 cm, total diameter ≤ 8 cm), 4–5 tumors each ≤ 3 cm and total diameter ≤ 8 cm	To MC: 65.3	54.2	5 yr OS (77.8) 5 yr I-to-T (56.1)	7.8
Bologna criteria - Ravaioli <i>et al</i> ^[53] , 2008	Beyond Milan: 1 lesion ≤ 6 cm, 2 lesions ≤ 5 cm, 3–5 lesions ≤ 4 cm and total diameter ≤ 12 cm	To MC: 72.9	66.7	3 yr DFS (71) 3 yr I-to-T (56.3)	18.8
Millonig <i>et al</i> ^[73] , 2007	UCSF	RECIST	84.8	5 yr CR (66.6); PR (63.7); NR (25)	25
Graziadei <i>et al</i> ^[37] , 2003	Beyond Milan, no upper limit	Partial response (> 50% of tumor size)	66.6	4 yr OS (41); 5 yr I-to-T (31)	30

CR: Complete response; HCC: Hepatocellular carcinoma; I-to-T: Intention-to-treat; LT: Liver transplantation; NR: No response; PR: Partial response; UCSF: University of California San Francisco.

comparable between the two groups^[35]. On the other hand, Millonig *et al*^[36] studied the effect of transarterial chemoembolization (TACE) on Milan-in and Milan-out UCSF-in patients. The response-to-treatment was evaluated according to RECIST criteria. Better intention-to-treat OS and OS rates were observed for the Milan-in patients with complete or partial response to the treatment. Interestingly, the association of good response to TACE and good prognosis was not observed in the Milan-out patients, who were also more likely to drop-out or to present with recurrence after LT.

Graziadei *et al*^[37] published the results of a series of HCC patients without pretreatment criteria, with the only criteria for transplantability being a response of 50% or more of the total tumoral volume. With this type of protocol, the results were statistically inferior to those of Milan-in patients submitted to the same therapy (see Table 3).

Overall, the results of these studies and several other retrospective studies are positive and offer the possibility of identifying a group of patients that can obtain acceptable survival rates after LT, despite presenting with a tumoral stage beyond MC. The EASL-EORTC guidelines of 2012 did not recommend the downstaging outside of prospective trials^[8], but the AASLD guidelines of 2018 not only recommend locoregional therapies for the Milan-in patients on the waiting list but also suggest that the patients beyond the MC should be considered for LT after successful downstaging to Milan^[38] when this status is maintained at least 3 mo to 6 mo^[39]. However, the level of evidence and the strength of the recommendation are still very low, probably because of the lack of intention-to-treat studies related to downstaging in the literature^[39]. The same type of recommendation related to LT after successful downstaging has been included in the EASL Clinical Practice Guidelines of 2018^[40].

Effect of expanding beyond the MC on the LT waiting list

The main problem facing LT remains the difference between the availability of organs and the number of patients on the waiting list. The last Organ Procurement and Transplantation Network (commonly known as OPTN) report^[3], from 2012, describes an increase of the median pretransplant waiting time from 12.9 mo in 2009 to 18.5 mo in 2011. Similar data have been published by the European LT Registry^[4]. It seems clear that by expanding the HCC transplant criteria, the number of possible candidates on the waiting list will rise. The two main questions related to expanding beyond the MC are: what is the minimal acceptable OS after LT for HCC patients; and, whether the expansion beyond MC would have a positive or a negative effect on the posttransplant survival of all the patients on the waiting list.

Initial reports suggested 50% as the minimal acceptable survival after LT for HCC patients^[41], but the International Consensus Conference Report for LT for HCC from Zurich 2012 reported that the expansion beyond MC has to take into account the effect of delaying the LT for all potential liver recipients on the waiting list, including the ones with non-tumoral indications^[19]. Therefore, this report recommends to reserve LT for patients who have an expected survival comparable to that of non-HCC patients.

Using a theoretical Markov model, the group from Michigan, United States compared the survival benefit of transplanting a patient with an HCC beyond the MC and the harm caused to the other patients on the waiting list^[21]. The results of that study showed that the adoption of more liberal criteria would lead to an increase in risk of death (of 44%) among all patients on the waiting list. The adverse effect caused by expanding the criteria would outweigh its benefits when the expected 5-year OS of the transplanted Milan-out patients would be of

less than 61%. However, this result was very sensitive to the characteristics of donation and waiting list times of each geographical region, offering values between 25% and 72%.

Ten years after that publication, the analysis could be very different. Graft characteristics will have changed, with increased use of expanded criteria donors, such as aged donors, steatotic livers or donation after cardiac death (DCD) grafts^[42]. On the other hand, factors related with the recipient's prognosis, like administration of direct-acting antiviral (DAA) treatment with 90% rates of hepatitis C virus (HCV) negativization, could change the characteristics of the waiting list^[43]. In the last reports of the United States' transplant registry, the HCV was no longer the principal indication for LT, being overcome by HCC and alcohol intake^[44]. Furthermore, recent published data have shown continuous improvement of the post-transplantation survival rates^[44,45].

Related to the use of expanded criteria donors in LT for HCC, a theoretical model study from the University of Chicago, United States, from 2012, compared the effectiveness of DCD vs brain-dead donor LT in terms of costs, quality of life and beyond 1-year survival^[46]. In the context of HCC, the use of DCD livers for LT, when compared with the alternative of waiting for a brain-dead donor liver, resulted in a survival benefit for patients without model for end-stage liver disease (commonly known as MELD) prioritization points. However, that study only referred to Milan-in patients. The inclusion of patients beyond the MC onto the waiting list could change the results of this analysis.

As described above, modest expansion of the HCC LT indications may offer results comparable to those of Milan-in patients and of non-HCC recipients. Since several expansion studies reported 5-year survival rates of more than 70%, it seems that LT can be an option for carefully selected patients beyond MC.

A different approach to separate the patients with good or bad prognosis after LT, including those beyond MC, would be the use of combined scores which take into account tumor characteristics (total tumor volume, rather than size and number) and AFP cut-off values (see above)^[29,40,47]. In this way, both large HCC and small ones with potentially aggressive behavior as well as poor post-LT outcomes could be identified.

Regarding the effect of expanding criteria for the waiting list, the analysis is more complex, taking into account not only the recipient prognosis but also characteristics that depend of each geographic region that performs LT, like the number of patients on the waiting list, available donors, and their quality. Thus, the decision on whether to expand the HCC transplantation criteria should probably be made at a regional level after analyzing the impact of all these items.

Dichotomous vs continuous selection criteria

Despite the success of the MC in LT for HCC, one of the questions that has arisen is whether a dichotomous yes/

no criteria is the best strategy to decide which patients should benefit from the transplant. Even inside the MC, there is a 10%-15% risk of recurrence after LT^[48] and, as discussed above, several expanded criteria of LT are associated with OS and recurrence rates comparable to those of MC^[10,27,28,32]. So, it is clear that not all the patients accepted for LT have a good prognosis and not all the patients discarded for LT based on MC have a dismal one.

In 2009, Mazzaferro *et al.*^[10] proposed a prognostic model, based on posttransplant estimation of survival probabilities related to the histological stage. This model, known as the "Metroticket", was recently validated by Raj *et al.*^[49]. In that retrospective analysis of a group of patients with a known 5-year OS of 74%, the model estimated a survival of 70%, statistically not different from the real one. By offering individualized survival predictions, the Metroticket could play a role in the regional organ allocation process. As described, if the expected survival of an individual is similar to that offered to transplanted Milan-in patients, then the LT could be justified depending on the characteristics of each individual region.

However, there are authors who have criticized that both dichotomous and continuous selection models only predict the posttransplant outcome, without taking into account the patient's survival perspectives without transplantation, geographical differences in terms of donation or waiting list times, or the proportion of patients with and without HCC on the waiting list^[50,51].

LDLT for expansion beyond MC

The strategy of LDLT in the context of HCC is different from the LT with deceased donor grafts because of, at least, two reasons. First of all, LDLT does not affect the conventional waiting list, therefore an expansion of the MC could be planned in this context without the fear of affecting other patients waiting for an organ. Second of all, LDLT is a complex procedure that involves not only the recipient, but also a living donor who is a healthy person submitted to a major surgery without a direct benefit. For this reason, the benefit of the recipient should always be evaluated in the context of the risk to the donor, a concept known as "double equipoise"^[52].

The majority of LDLT studies regarding CHC expansion criteria have come from Asia, where, for cultural and religious reasons, the cadaveric donation is infrequent (see Tables 1 and 2).

The University of Tokyo published the "5-5 rule criteria" (see Table 1). Using these criteria, 5-year DFS was found to be 94%, while in the patients beyond Tokyo it was only 50%^[53]. Two years ago, that same group published the results of their series after a large follow-up. The 5-year recurrence rates were 8% for Milan-out Tokyo-in patients and 6% for Milan-in patients. The OS and DFS rates were comparable between the two groups^[54].

The group from Kyoto included dex-gamma-

carboxi prothrobine (DCP) in the criteria for LT (see Table 1)^[55]. Applying these criteria, the 5-year OS and recurrence rates were 80% and 7%, respectively, when all the patients (Milan-out Kyoto-in and Milan-in) were considered^[56]. The criteria of the University of Kyushu also took into account the DCP, but did not impose a limit on tumor number^[57]. By using the Kyushu criteria, the 3- and 5-year DFS was 80%. In a multivariate analysis that considered UCSF, up-to-seven, Tokyo and Kyoto criteria, the Kyushu criteria was the only one statistically related to the DFS.

Another LDLT expanded criteria is the one of Asan Medical Center. The survival and recurrence rates of patients within these criteria were comparable with MC and UCSF survival rates, with the advantage that the Asan criteria can select more patients that can benefit from the transplant^[58].

Kim *et al.*^[59] defined a set of expanded criteria based on reviewing the explant histology of 180 patients, the major portion of this population being submitted to LDLT. The results showed a DFS benefit when the number of tumors was lower than 7, the maximum diameter was smaller than 6 cm, and the AFP was less than or equal to 1000 ng/mL.

Our group also published, this year, the results of a prospective study of 22 patients with BCLC expanded criteria who had submitted to LDLT^[14]. The criteria were related to the size and number of the tumors but also to the successful downstaging after locoregional therapies. The results were remarkable, with a 5-year OS of more than 80%. One of the factors that influenced the OS was a "Milan-in" status before the transplant and after performing locoregional therapies as downstaging or bridging therapy (see Table 1). As remarked by other authors, the results of this study seem to favor downstaging over expansion in the context of LDLT, even though the sample size is small^[60].

All these studies demonstrate that the expansion of the MC in the context of LDLT does not necessarily associate with worse results. However, the majority of these articles are retrospective analyses of patients selected by the means of explant histological characteristics. Furthermore, some of them analyzed the survival and recurrence rates in Milan-in patients and with expanded criteria all together, which could have biased the results.

The report from the Vancouver Forum on the Care of the Living Donor from 2005 established that LDLT should be performed only if it offers an advantage to the recipient when compared to the alternative of waiting for a deceased donor graft and if the risk of the donor is justified by the expectation of an acceptable outcome of the recipient^[61].

One of the main issues in LDLT is the safety of the donor. Clavien's group^[62] analyzed the results of several important transplant centers throughout the world and published benchmark values related to acceptable complication rates for donors. That study described acceptable complication rates at discharge values below

26.9% for any complication and 6% for major complications (\geq IIIA of Clavien-Dindo classification)^[63]. Today, the reported donor mortality after LDLT is 0.15%-0.20%^[52]. In the particular scenario of LDLT for HCC beyond MC, the concept of double-equipoise should be taken into account, it being unacceptable that a donor should take any risk if the benefit to the recipient is expected to be very low^[52]. However, the living donor studies presented above report survival rates comparable to those of LT for MC and lead to optimism regarding the possibility of using LDLT for expanding HCC criteria.

The other important issue related to LDLT for HCC involves the reports of higher rates of recurrence than are related to the conventional LT^[23,64]. One possible explanation of these results could be related to the reduced waiting time before LDLT compared with the usual waiting list time for conventional LT. It is possible that this reduced time did not permit drop-out of patients with aggressive HCC^[64]. Theoretically, this concept can also apply to the expansion beyond MC. However, a meta-analysis published in 2012 by the group from Guangzhou, China showed no statistical differences between living and cadaveric LT in terms of 5-year OS or recurrence^[65]. Of note, in our experience with the application of BCLC expanded criteria for LDLT, the 5-year recurrence rate was approximately 20%, but the OS rate was comparable to that published for Milan-in patients with cadaveric donors^[3,4,14].

We believe that as long as the results in terms of survival of selected HCC patients beyond MC (*i.e.* up-to-seven, UCSF, extended criteria BCLC) submitted to LDLT are comparable to those obtained after conventional LT for HCC Milan-in, the utilization of LDLT in this context could be justified.

FUTURE DIRECTIONS

DAA treatment for HCV is one of the most important medical breakthroughs of the last decade. Its impact is already apparent on the United States' liver waiting list, where HCV is no longer the first indication for LT^[44]. The liver grafts that are no longer needed for HCV patients could be used to explore the expansion beyond MC. On the other hand, since the association between HCV and HCC is well documented, the DAA treatment is expected to have an impact on the incidence of HCC as well^[51]. However, further information is needed in order to explore these scenarios.

Some of the most intriguing future directions of research of HCC treatment are the molecular and genetic analyses and investigations into the relationship of tumor biology and recurrence (see Table 4). It is known today that complex genetic and epigenetic alterations, chromosomal mutations and changes in molecular pathways lead to HCC development^[66-71]. Even though these insights have shown much promise in improving HCC treatments, one of their main issues is the retrospective character of the results themselves. In fact, the vast majority of the related studies analyzed

Table 4 Impact of genetic and molecular factors in post-liver transplantation outcome

Ref.	Criteria	Survival, time and rate (%)	Recurrence, time and rate (%)
Schwartz <i>et al</i> ^[68] , 2008 Dvorchick <i>et al</i> ^[69] , 2008	FAI < 0.27 FAI and macrovascular invasion (Pittsburg criteria)	Stage I (FAI ≤ 20% and no macrovascular invasion) - 5 yr DFS (92.8)	5 yr (10)
Miltiados <i>et al</i> ^[67] , 2015 Sugimachi <i>et al</i> ^[70] , 2015	Progenitor cell markers (CK19 or S2 signature) miR-718 and his target gene HOXB8	5 yr (67) 5 yr (≈ 80)	5 yr (19)
Barry <i>et al</i> ^[71] , 2012 Liese <i>et al</i> ^[72] , 2016	67 miRNA miR-214, miR-3187 and MC	5 yr DFS (≈ 90)	

DFS: Disease-free survival; FAI: Fractional allelic imbalance; MC: Milan criteria; miRNA: MicroRNA.

the molecular and genetic characteristics in tumor samples of explanted tissues, which makes any kind of pretransplant selection of these patients based on the tumor biology virtually impossible. However, identification and measurement of genetic markers in serum before LT, like of microRNAs, could be a future direction of investigation^[69]. However, more studies are necessary in order to confirm these results.

CONCLUSION

The current medical literature seems to support that modest expansions of HCC LT criteria beyond Milan offer results comparable to those of MC. However, these proposals require further prospective validation using radiological findings collected before LT as a selection tool. As summary, the three important questions cited at the beginning of this article will be addressed in the concluding remarks.

First of all, the effect of possible MC expansion on the waiting list is a variable depending not only on the stage of the HCC patients but also on regional characteristics of the waiting list itself and donors. Thus, we believe that the expansion of MC is a decision that will have to be analyzed carefully in each transplant region and according to the principle of survival benefit for all of the patients on the waiting list.

Second of all, in the Metroticket era, the use of a threshold of acceptable survival, rather than strict dichotomous yes/no criteria, could offer a flexibility to the HCC criteria and may help to expand LT indications beyond the MC in regions where the waiting list pressure permits.

Finally, in the real-life context of cadaveric donor shortage, the use of LDLT is generally accepted. As long as the expansion beyond MC in the context of LDLT offers survival rates comparable to those of accepted indications for LT, its use seems justified.

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