REVIEW

Selection of patients with hepatocellular carcinoma for liver transplantation: Past and future

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Abstract

The aim of liver transplantation (LT) for hepatocellular carcinoma (HCC) is to ensure a rate of disease-free survival similar to that of patients transplanted due to benign disease. Therefore, we are forced to adopt strict criteria when selecting candidates for LT and prioritizing patients on the waiting list (WL), to have clarified indications for bridging therapy for groups at risk for progression or recurrence, and to establish certain limits for downstaging therapies. Although the Milan criteria (MC) remain the standard and most employed criteria for indication of HCC patients for LT by far, in the coming years, criteria will be consolidated that take into account not only data regarding the size/volume and number of tumors but also their biology. This criteria will mainly include the alpha fetoprotein (AFP) values and, in view of their wide variability, any of the published logarithmic models for the selection of candidates for LT. Bridging therapy is necessary for HCC patients on the WL who meet the MC and have the possibility of experiencing a delay for LT greater than 6 mo or any of the known risk factors for recurrence. It is difficult to define single AFP values that would indicate bridging therapy (200, 300 or 400 ng/mL); therefore, it is preferable to rely on the criteria of a French AFP model score > 2. Other single indications for bridging therapy include a tumor diameter greater than 3 cm, more than one tumor, and having an AFP slope greater than 15 ng/mL per month or > 50 ng/mL for three months during strict monitoring while on the WL. When considering the inclusion of patients on the WL who do not meet the MC, it is mandatory to determine their eligibility for downstaging therapy prior to inclusion. The upper limit for this therapy could be one lesion up to 8 cm, 2-3 lesions with a total tumor diameter up to 8 cm, or a total tumor volume of 115 cm^3. Lastly, liver allocation and the prioritization of patients with HCC on

the WL should take into account the recently described HCC model for end-stage liver disease, which considers hepatic function, HCC size and the number and the log of AFP values. This formula has been calibrated with the survival data of non-HCC patients and produces a dynamic and more accurate assessment model.

Core tip: This article aims to provide clinicians who treat patients with hepatocellular carcinoma, in whom liver transplantation may be indicated, with an actualized tool that considers a combination of morphological (size and number of tumors) and biological data (alpha fetoprotein value) and that facilitates the process of selecting candidates, predicts the indication of and response to neoadjuvant therapy prior to transplantation and also aids in the prioritization of patients once they are on the waiting list.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a major global health problem. It is the sixth most common cancer worldwide[1] and the third most common cause of cancer death[2]. Without treatment, the 5-year survival rate is 10%-12%[3,4]. In the early stages, curative treatment includes resection, radiofrequency ablation and liver transplantation (LT). The latter technique remains the most effective treatment method in cases of early HCC because it jointly eliminates the tumor and the underlying disease and shows 1- and 5-year survival rates of 85% and 70%, respectively[5]. However, LT does not completely eliminate the possibility of recurrence, which is still a serious problem; therefore, it is discussed in this review.

DIAGNOSIS

In the last decade, great improvements in HCC diagnosis[6] have occurred, which are mainly based on imaging tests. In recent years, HCC has been diagnosed earlier[7], and due to the improvements in imaging tests, a progressive decline in the use of alpha fetoprotein (AFP) levels for the surveillance of HCC in cirrhotic patients[6,8,9]

has occurred owing to their lack of appropriate sensitivity and specificity[8].

For lesions less than 1 cm, ultrasonography is repeated every three months, and for lesions larger than 1 cm, a typical image (arterial hypervascularity and venous delayed phase wash out) can be used to confirm the diagnosis[8] because this method is 100% specific, with a very high predictive value[10]. When a surveillance test is positive, a more definitive noninvasive imaging exam is recommended. Recent guidelines endorse multiphasic computerized tomography (CT) and magnetic resonance imaging (MRI) with hepatobiliary agents as first-line modalities for this purpose. Both modalities provide excellent sensitivity for nodular HCCs larger than 2 cm, modest sensitivity for 1-2-cm HCCs, and poor sensitivity for HCCs smaller than 1 cm. However, MRI is emerging worldwide as a leading method for the diagnosis and staging of HCC, and it is the most sensitive method for the detection of small HCCs[11]. However, the combination of dual-phase CT-angiography in the arterial and portal phase with positron emission tomography (PET) imaging using (18)F-fluorodeoxyglucose [(18)FDG] appears to be a sensitive method for the detection of HCC with the alternative presence of hypervascularity or hyperaccumulation of (18)FDG[12].

If the radiological pattern is not typical, the test should be repeated. If the result does not meet the criteria for HCC, a biopsy of the lesion can be performed while taking into account that a negative finding after a biopsy does not exclude HCC[1], and the possible complications of a biopsy such as hemorrhage and needle track tumoral implant should be considered[13]. Although in a recent, long retrospective series the incidence of HCC was only 0.2%[14], in a meta-analysis the incidence was 2.7% overall or 0.9% per year[15].

STAGING

The TNM classification, which is widely accepted for the staging of cancer, for HCC has a lower capacity to predict long-term survival[16]. For this reason, the Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy is most often used[9,17] because it includes information concerning the tumor, hepatic function and the general clinical status[18]. However, in spite of these facts, the TNM classification is used as the reference for pathological studies of surgical specimens.

SELECTION OF CANDIDATES WITH HCC FOR LT

The aim of LT for HCC is to obtain a level of disease-free survival (DFS) similar to that of patients who are transplanted for benign disease; therefore, we are obliged to adopt strict selection criteria for candidates, with the intention of obtaining the maximum survival with the minimum possible recurrence.

Table 1 Isolated biological criteria for the selection of candidates with hepatocellular carcinoma for liver transplantation		
Ref.	Pretrasplant AFP levels (ng/mL)	Importance
Figueras *et al*[19]	> 300	Factor for mortality
Yao *et al*[16]	> 1.000	Reduced survival
Bruix[20]	> 200	Significant worse outcomes
Xu *et al*[21]	> 400	Higher tumor recurrence
Mailey *et al*[22]	Low (≤ 20)	Mediun and high: Higher mortality
	Mediun (20-399)	
	High (≥ 400)	
Muscari *et al*[23]		DFS Recurrence
	Normal	71% 4%
	10-150	75% 10%
	150-500	57% 24%
	> 500	46% 62%
Chiao *et al*[24]	> 1.000	Reason for exclusion from the WL
Hameed *et al*[25]		
Menon *et al*[26]	> 10.000	Reason for exclusion from the WL

AFP: Alpha fetoprotein; DFS: Disease-free survival; WL: Waiting list.

Isolated biological criteria for the selection and prognosis of patients with HCC for LT

More than a decade ago, several authors noted the importance of the isolated AFP value in predicting mortality and/or posttransplant recurrence. High AFP values may be a marker for vascular invasion or extra hepatic disease that has escaped detection by conventional imaging techniques. It has been observed that a pretransplant AFP level higher than 300 ng/mL is the only factor independently associated with mortality after LT[19], and a level higher than 1000 ng/mL is a significant predictor of reduced survival[16]. In general, HCC patients on the waiting list (WL) with a baseline serum level of AFP > 200 ng/mL display significantly worse outcomes[20]; however, several detrimental cut-off values for AFP levels have been reported recently. Xu *et al*[21] found that pre-transplant AFP levels > 400 ng/mL were associated with higher tumor recurrence. Mailey *et al*[22] classified patients into low (≤ 20 ng/mL), medium (20-399 ng/mL), or high (≥ 400 ng/mL) AFP level groups. In a multivariate analysis, the medium and high AFP groups were associated with higher mortality. Another study[23] correlated the DFS and 5-year recurrence rate to the AFP level. Normal AFP values between 10-150 ng/mL, those from 150-500 ng/mL and those > 500 reduce DFS from 71% to 57%, 46% and 28%, respectively, and increase the recurrence rate from 4% to 10%, 24% and 62%, respectively. Recently, it was shown once again that an AFP level > 1000 ng/mL is a reason for exclusion from the WL[24,25], confirming data reported in 2001[16]. However these data have not been taken into account by programs using expanded criteria that only consider an AFP level greater than 10000 ng/mL as a reason for exclusion[26]. This matter will be further examined when discussing the indications for downstaging of HCC prior to LT (Table 1).

In Japan, des-gamma carboxy prothrombin (DCP) is well established as a biomarker and is reported to

Table 2 Selection criteria base on radiological/morphological tumor characteristics		
Ref.	Parameters	Importance
Bismuth *et al*[30]	Up to 3 nodules	Best results
	Each < 3 cm	
Mazzaferro *et al*[31]	Single lesion < 5 cm	DFS > 75%
	< 3 lesions, each < 3 cm	Recurrence < 15%
	No macrovascular invasion	
	No extrahepatic disease	
Löhe *et al*[34]	Single tumor with size > 5 cm	Reduction in DFS
Yao *et al*[16]	Single lesion ≤ 6 cm	DFS > 75%
	2-3 lesions each ≤ 4.5 cm	Recurrence < 15%
	Total tumor diameter ≤ 8 cm	
Mazzaferro[41]	Ordinates: *n* of tumors	Progressive reduction of 5 yr survival
	Abscissas: Tumor size	
Mazzaferro *et al*[42]	Up to 7, as the sum of:	71.2% 5 yr survival
	Largest tumor in centimeter	
	and *n* of tumors	
Jang *et al*[46]	10 as the sum of:	If >: Decreased DFS
	Largest tumor in cm and	
	n of tumors	

DFS: Disease-free survival.

correlate with post-LT recurrence of HCC[27,28]. We cannot predict whether new molecular markers of HCC such as PIVKA-II, a protein induced by the absence of Vit K, will have widespread use, but Japanese studies suggest that it is correlated with microvascular invasion[29].

Selection criteria based on radiological/morphologic tumor characteristics

Some criteria include the number and size of the tumors and the tumor volume.

Criteria based on number and size: In 1993, Bismuth *et al*[30] noted that patients transplanted for HCC with up to 3 nodules (each < 3 cm) exhibited the best results. In 1996, the Milan criteria (MC)[31] set clear limits on the selection of HCC patients for LT, consisting of a single lesion < 5 cm or fewer than three lesions, each < 3 cm and without macrovascular invasion or extrahepatic disease, which resulted in 5-year DFS > 75% and a recurrence rate < 15%[31]. Since that time, these standard selection criteria for LT due to HCC have been accepted worldwide[20,32,33]. Other authors have confirmed that a single tumor with a size > 5 cm causes a reduction in DFS[34]. The MC have received criticism because the radiological studies used for evaluations are not very accurate[35] and highly variable between centers. In addition, some authors have argued that these criteria are strict[20], with tumor size and tumor number cut-offs that are somewhat arbitrary and too restrictive, and that they deprive patients of the possible benefit of LT[36] and therefore should be extended[16,37,38] (Table 2).

Thus, in 2001 the so-called expanded criteria of the University of San Francisco, California (UCSF) were proposed by Yao *et al*[16], which set the limit for LT to a single lesion ≤ 6.5 cm in diameter or 2-3 lesions each ≤ 4.5 cm with a total maximum diameter ≤

Table 3 Selection criteria based on functional/radiological features of the tumor

Ref.	Parameters	Importance
Hiraoka *et al*[56]	Hyperintensity on gadoxetic acid-enhanced MRI	HCC with more malignant potential
Ferda *et al*[12]	Hipervascularity or hiperaccumulation of (18)FDG/PET/	Distinguishing between welland
	with Dual-phase CT angiography (arterial/portal phase)	Poorly differentiated HCC
Ochi *et al*[57]	High positivity in (18)FDG/PET/CT	Increase the risk of early recurrence
Kornberg *et al*[58]	mSUV	Reflects the existence of distant microsatellite
Kornberg[59]	Positivity in (18)FDG/PET/CT	Statistically significant lower survival post LT

CT: Computerized tomography; MRI: Magnetic resonance imaging; HCC: Hepatocellular carcinoma; PET: Positron emission tomography; LT: Liver transplantation; mSUV: Maximun standized uptake value; (18)FDG: (18)F-fluorodeoxyglucose.

8 cm, thus obtaining similar survival after LT to that obtained with the MC. These criteria were criticized because in this study, only 24% of the patients did not meet the MC[39], and because it was a retrospective study based on the histology of explants[40]. By that time, Mazzaferro[41] had introduced the concept of the Metroticket calculator, a system of orderly Cartesian ordinates (number of tumors) and abscissa (tumor size) in which the progressive reduction of 5-year survival is graphically represented as these parameters increase, leading to the expression "the longer the trip, the higher the price". In 2009, Mazzaferro *et al*[42] found that a total tumor diameter greater than 7 cm resulted in an increase in the percentage of recurrence and proposed a new MC (the so-called up-to-seven), using seven as the sum of the size of the largest tumor (in centimeter) and the number of tumors, which yielded 5-year overall survival of 71.2%. Many groups have validated these criteria[43,44], but after 5 years, they have not been accepted as widely as the MC. Other authors have made similar suggestions[45]; however, others have placed this limit at 10 cm, which results in a decrease in DFS[46]. This value should be universally accepted as the upper limit[26]. The expanded criteria require further validation because recurrence could be less often reported, increasing the risk of vascular invasion, microsatellites and poorly differentiated tumors[35,47,48].

Morphological criteria based on the total tumor volume: Toso *et al*[37] calculated the total tumor volume (TTV) as the sum of the volumes of all tumors using the formula $(4/3)\pi r^3$, where r is the maximum radius of each tumor. The radiological accuracy of this formula was greater, and based on the risk of recurrence, a threshold of 115 cm^3 was established, which allowed the selection of more patients for LT with results similar to those of the MC and UCSF criteria[37]. According to this mathematical formula, the largest tumor has the maximum importance. As a result, the possibility of correct staging increases because larger tumors are evaluated more accurately than smaller ones.

Expansion of the MC may be justified in regions with less organ shortage, but this will require demonstrating high survival rates for the newly eligible patients[49]. Regional variation in survival does not facilitate a national policy[50], but it is undeniable that in the USA, 97% of patients transplanted for HCC meet the MC[51],

and although this number has changed somewhat recently, the number of inclusions for patients for LT that do not meet the MC is still less than 5%[52]. It should be mentioned that until very recently, the criteria used in the United Kingdom for LT for HCC considered a maximum tumor diameter up to 15 cm (up to 5 tumors all ≤ 3 cm), which is well beyond the limit of the MC and UCSF criteria[26].

Selection criteria based on functional/radiological features of the tumor: Dynamic MRI may constitute a non-invasive and promising method to assess the biology of HCC due to its greater avidity of contrast uptake, which implies a higher degree of microscopic vascular invasion and greater aggressiveness[53,54]. Tumors that are heterogeneously hyperintense in the hepatobiliary phase on gadoxetic acid-enhanced MRI have more malignant potential than other types of HCC[55]. Other authors[56] have used 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) not only for detection[12] but also as a prognostic factor, which distinguishes between well and poorly differentiated HCC[12]. High positivity of HCC increases the risk of early recurrence after curative resection[56], and the maximum standardized uptake value (mSUV) of 18F-FDG PET/CT reflects the existence of distant microsatellites; therefore, it can be a useful tool in the treatment protocol of HCC[57]. In a comparison of two groups of transplanted patients who did not meet the MC, other authors[58] found that patients with positive PET findings had significantly lower survival than PET negative patients (Table 3).

Combined morphological and biological tumor parameters: Adequate patient selection should be based on tumor biology assessed *via* serum or pathological parameters rather than on the macro morphology of HCC[59]. In fact, the aggressiveness of a tumor can be determined by a higher histological grade and greater microscopic vascular invasion, and a biopsy can used to predict DFS. The Toronto criteria[60] select patients with HCC for LT who do not meet the MC by biopsy exclusion of poorly differentiated tumors, resulting in 5-year overall survival (OS) and DFS values of 70% and 66%, respectively, which are similar to those of the MC (72% and 70%, respectively). However, there is little correlation between the biopsy and

Table 4 Combined morphological/biological selection criteria

Ref.	Parameters	Importance
DuBay *et al*[60]	Liver tumor biopsy	Excluding poorly differentiated tumors
Toso *et al*[52]	TTV > 115 cm^3	Reduced survival at 3 yr (< 50%)
	AFP > 400 ng/mL	Limit for indication for LT
Lai *et al*[62]	AFP > 400 ng/mL	Strongest predictor for recurrence
	Total tumor diameter > 8 cm	
Duvoux *et al*[63]	Model combining log10 AFP, tumor size and *n* of tumors: Score > or < 2	Score greater that 2 predict a market increase in 5 yr risk of recurrence and decreased survival
Berry *et al*[66]	AFP < 15 or > 15 ng/mL	AFP levels predicts post-transplant survival independently of MC

TTV: Total tumor volume; AFP: Alpha fetoprotein; MC: Milan criteria; LT: Liver transplantation.

histology of an explant due to tumor heterogeneity and because, in multifocal disease, the dominant lesion is not always the most biologically representative. For these reasons, currently, the biopsy has a limited role in pre-LT staging[61] (Table 4).

In 2009, Toso *et al*[52] found that only the TTV and AFP levels predicted survival and established a composite score with a TTV > 115 cm^3 or AFP > 400 ng/mL as limits for indication for transplantation because patients with greater values for these parameters had 3-year survival rates < 50%.

Using a multivariate analysis, Lai *et al*[62] found that an AFP level > 400 ng/mL and a total tumor diameter > 8 cm were the strongest predictors for recurrence.

Recently, Duvoux *et al*[63] generated an improved prognostic model for predicting recurrence in LT candidates with HCC. A prognostic score was developed and validated prospectively. The AFP level independently predicted tumor recurrence and was correlated with vascular invasion and differentiation. A model combining the log10 value of the AFP, tumor size and number of tumors was highly predictive of tumor recurrence and death. Using a simplified version of the model with untransformed AFP values, a cut-off value of 2 was identified. In the validation cohort, a score greater than 2 predicted a marked increase in 5-year risk of recurrence and decreased survival. Among patients who exceeded the MC, a score of 2 or lower identified a subgroup of patients with AFP levels less than 100 ng/mL and a low 5-year risk of recurrence. In contrast, for patients who met the MC, a score greater than 2 identified a subgroup of patients with AFP levels greater than 1000 ng/mL and a high risk of recurrence. We will refer to this as the French model.

Our group[64], based on our previous experience with LT for patients with HCC and cirrhosis, has performed an analysis of the risk factors for HCC relapse and applied the French AFP model to LT for HCC and cirrhosis patients who met the MC[65]. We were able to confirm the predictive value for tumor relapse of the French AFP model both pre- and postoperatively.

Berry *et al*[66] established that the AFP level, rather than the tumor burden, was most strongly associated with posttransplant survival. Thus, patients with HCC and AFP levels < 15 ng/mL at the time of transplantation

did not exhibit excess posttransplant mortality; increases in AFP (16-65 ng/mL; 66-320 ng/mL and > 320 ng/mL) result in progressively worse posttransplant mortality than similar increases in recipients without HCC. Patients who did not meet the MC showed excellent survival if their AFP level was < 15 ng/mL. In contrast, patients who met the MC exhibited poor survival if their serum AFP level was substantially elevated (serum AFP ⩾ 66 ng/mL). AFP changes while on the WL closely corresponded to changes in posttransplant mortality. Not only the absolute serum AFP level but also changes in this level strongly predicted posttransplant survival independently of tumor burden.

These models, combining data related to the tumor (size and number of tumors) with preoperative levels of AFP, had previously been studied by Japanese authors[67] in living-donor liver transplant (LDLT) patients (Table 5). In these models, a value of 1 to 4 points (p) was assigned to each of the following parameters: tumor size: ⩽ 3 cm (1 p), 3.1-5 cm (2 p), 5.1-6.5 cm (3 p), > 6.5 cm (4 p); number of tumors: 1 (1 p), 2-3 (2 p), 4-5 (3 p), > 5-6 nodules (4 p); AFP: ⩽ 20 ng/mL (1 p), 20.1-200 ng/mL (2 p), 200.1-1000 ng/mL (3 p), and > 1000 ng/mL (4 p). Candidates with 3-6 total points were "transplantable" and those with 7-12 points were "non-transplantable". In Japan and other Asian countries, due to the severe organ shortage, LDLT comprises the majority of LT[68]. Each center has developed and proposed expanded selection criteria based on institutional and regional experience, which vary from the model of Tokyo University[68], which only considers morphological tumor parameters, *i.e.*, up to 5 nodules with a maximum diameter ⩽ 5 cm, without taking into account any biological markers. The Kyoto group[69] considers patients with less than 10 nodules, all less than 5 cm, with a DCP level < 400 mAU/mL, and the Kyushu group[70] also use extended criteria without limiting the number of nodules but require a maximum tumor diameter less than 5 cm and DCP levels under 300 mAU/mL.

ORGAN ALLOCATION FOR LT

The allocation of organs for LT follows criteria of prioritization that have varied throughout the history

Table 5 Japanese combined morphological/biological selection criteria for living-donor liver transplant

Ref.	Parameters					Importance: Limits for LDLT
	Value	1p	2p	3p	4p	
Yang *et al*[67]	T size (cm)	⩽ 3	3.1-5	5.1-6.5	> 6.5	Patients with 3-6 points are transplantable
	n of tumors	1	2-3	4-5	> 5 or 6	Those with 7-12 points are not transplantable
	AFP (ng/mL)	< 20	20-200	200.1-1.000	< 1.000	
Akamatsu *et al*[68]	Up to 5 nodules					Upper limit for LDLT
	Maximum diameter ⩽ 5					
Kaido *et al*[69]	Less that 10 nodules, all < 5 cm					Upper limit for LDLT
	DCP < 400 mAu/mL					
Shirabe *et al*[70]	*n* of nodules: No limit					Upper limit for LDLT
	Maximun diameter: < 5 cm					
	DCP < 300 mAu/mL					

AFP: Alpha fetoprotein; DCP: Des-gamma carboxy prothrombin; LDLT: Living-donor liver transplant.

of LT, from prioritization of the more serious patients based on the Child-Turcotte-Pugh score and the time of inclusion on the WL to the more recent model for end-stage liver disease (MELD) score. However, because this method does not consider the risk of neoplastic growth while on the WL, HCC patients are prioritized based on their exception points and the MELD exception, with the goal of obtaining similar WL mortality for neoplastic and non-neoplastic patients. Exception points are assigned every 3 mo[36] because progression of HCC can produce a 15% increase in mortality[71]. Paradoxically, several years later, it was found that the likelihood of undergoing transplantation was higher for HCC candidates than for other patients[72], which produced a clear disadvantage for non-HCC patients[73]. For this reason, the "HCC-MELD" equation (1.27/MELD - 0.51/logAFP + 4.59) has been proposed[74], which takes into account hepatic function and the log of the AFP value, and has been calibrated to the survival of non-HCC patients. This formula gives additional points to patients with HCC, not arbitrarily, but based on a calculation of the benefits of transplantation, in a manner similar to that for patients without HCC. Other authors[73], with a similar aim, have studied and validated a new and promising model for allocation of patients using a large cohort in the United States and United Kingdom that includes: HCC size, HCC number, AFP value, and the classic MELD score calculated according to the following formula: New MELD = -37.8 + 1.9 × MELD + 5.9 (if HCC number ⩾ 2) + 5.9 (if AFP level > 400 ng/mL) + 21.2 (if HCC size > 1 cm). This new model provides a dynamic and more accurate assessment of dropout than the use of the MELD exception, showing a distribution similar to that of the MELD for non-HCC patients. Both scores could be used in parallel for the management of WL patients with and without HCC.

NEOADJUVANT TREATMENT OF PATIENTS ON THE WL (BRIDGING AND DOWNSTAGING TREATMENTS)

HCC patients who meet the MC and are included on the WL should be monitored every 3 mo by CT/MRI and AFP level evaluation for the identification of those at high risk of dropout[75]. AFP progression while on the WL[66], and more specifically an AFP increase of > 15 ng/mL per month, is the most relevant preoperative prognostic factor for low OS and DFS[76]. For patients with changes in tumor size and/or an increase of in the AFP level > 50 ng/mL, locoregional therapy (LRT) or removal of the patient from the WL should be performed, if necessary[77].

Bridging therapy
Bridging therapy is used for patients with HCC who meet the MC and are included on the WL but have the possibility of a delay in LT > 6 mo. Its purpose[78] is to prevent tumor progression[79], reduce the recurrence of HCC after LT and increase posttransplant survival. As the waiting time for LT has progressively increased[79], treatment of HCC in patients awaiting LT has become routine[80]. Bridging is not indicated for tumors that meet the current MC, except for those with a diameter greater than 3 cm or patients with more than 1 tumor, because these patients are more likely to have recurrence after LT[81].

The most employed method of LRT for bridging therapy is percutaneous ablation[1], which is frequently performed by radiofrequency (RF) and less often performed by ethanolization (ET) or surgery. ET and RF have similar effectiveness for tumors less than 2 cm, but with increased tumor size, RF is more effective and shows similar results to surgery. In lesions > 3 cm, ET failures increase; therefore, it is rarely used as bridging therapy[82,83].

Patients with small solitary tumors and very well preserved liver function are the best candidates for surgical resection[1], but tumor recurrence complicates 70% of cases at 5 years[6]. Certain favorable locations, such as peripheral tumors and left hepatic lobe location, may allow laparoscopic resection, which avoids the greater complexity of transplantation after laparotomic surgery. Resection may offer improved local tumor control and allows full microscopic analysis, with subsequent study of its biological aggressiveness, which

could lead to subsequent elective LT. Subsequent tumor recurrence after resection is an absolute indication for LT; this so-called salvage transplantation was first described by Majno *et al*[84] in 2000. This procedure requires fewer donors and allows better management of the WL.

Downstaging
Downstaging[78,79] is used to convert tumors that initially do not meet the transplant criteria, usually intermediate multinodular asymptomatic tumors (stage B of the BCLC)[6], into tumors that meet the MC (the most frequent endpoint), UCSF criteria or the up-to-seven criteria, with the aim of including the patients on the WL once the tumor has decreased in size. Tumors with more favorable histology are more likely to respond to treatment and exhibit a good outcome after LT[85]. The eligibility criteria for downstaging should have an upper limit, which can be set as follows[85]: (1) one lesion > 5 cm and up to 8 cm; (2) two to three lesions with at least one lesion > 3 cm and not exceeding 5 cm, with a total tumor diameter up to 8 cm; or (3) four to five lesions with none > 3 cm, and a total tumor diameter up to 8 cm.

The LRT technique depends on each center, and the response is evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) or the modified RECIST (mRECIST)[86], which we will further discuss later. Once the treatment is completed, it is mandatory to follow the "ablate and wait policy"[81], with close monitoring for at least 3 mo before inclusion on the WL[50,85] to evaluate the tumor's behavior and exclude aggressive tumors from LT; therefore, a total of six months will elapse until transplantation[81].

Some authors[87] have attempted to perform a meta-analysis of HCC downstaging, which has been impossible due to many factors such as the great variability of the inclusion criteria protocols[79], variability of post-treatment response assessment and absence of histological information on tumor biology[87]. At the moment, there is no evidence that patients submitted to downstaging followed by LT have a worse prognosis than those who initially meet the MC. Therefore, we must assume that those patients should be eligible for LT, as if they had been from the start[87], and will show an excellent posttransplantation outcome[85], reaching 5-year survival rates comparable to those of patients who meet the MC or UCSF criteria and do not require downstaging[75,88].

Trans-arterial chemoembolization (TACE) is the form of LRT most often used for downstaging[75], followed by RF ablation[89]. Chemoembolization improves the survival of stringently selected patients with unresectable HCC[90]. Posttransplant survival has shown a marked benefit in response to TACE, but this benefit was only seen in patients whose disease meets, but does not exceed, the MC[91]. TACE can reduce the percentage of posttransplant recurrence (17% with treatment *vs* 36% without treatment)[92], and it is possible to verify its effectiveness using (18)FDG PET/CT to compare the SUV before and after treatment[93].

At the present time, there is no evidence demonstrating the superiority of one form of LRT over another, but merging the techniques of drug eluting beads-TACE and trans-arterial radio-embolization with Yttrium-90 and external bean conformal radiotherapy[78] is generally better tolerated than conventional techniques.

Response criteria following downstaging with LRT
The efficacy of neo-adjuvant treatments should be evaluated[79] by the rate of dropout from the WL and, methodologically, with a 3-mo interval mRECIST[86] reassessment that considers not only the reduction in size, but the amount of tumor necrosis and the disappearance of any intratumoral arterial enhancement in conjunction with the initial and post-treatment AFP levels.

Patients presenting with an AFP level > 1000 ng/mL submitted to downstaging are a special problem because such high levels predict a greater risk of tumor recurrence and are considered the only factor in treatment failure[85].

In these cases, a stable decrease in the AFP level to < 500 ng/mL is necessary in subsequent determinations until LT to consider the downstaging effective[50,94]. However, other authors[48] state that the level should be < 400 ng/mL because levels > 400 ng/mL in the immediate pretransplant period are a unique risk factor for recurrence after LRT[36]. This is because patients who did not show a reduction of the AFP level to ⩽ 400 after downstaging had less intent-to-treat survival, and only the last pretransplant AFP value, not the original value (even if it was originally > 1000 ng/mL) or changes in the AFP level, independently predicted posttransplant survival[95]. Others have set the level to 100 ng/mL[96], but in general, the mean AFP levels are higher in patients who do not achieve successful downstaging[97]. AFP levels are considered to play an important role in monitoring the response and/or tumor progression after LRT[25,98].

Combined radiological and biological modifications permit documentation of the response to LRT in patients waiting for LT and are essential elements for further refining the selection criteria for potential liver recipients with HCC[94]. An AFP level ⩾ 100 ng/mL, a maximum tumor size ⩾ 7 cm and a lack of complete necrosis at LT after TACE were found to be independent predictors of HCC recurrence[46]. However, patients with maximum tumor size < 7 cm who achieve complete necrosis together with AFP levels < 100 ng/mL at LT may be the best candidates for LT following downstaging[46].

In addition, an AFP slope > 15 ng/mL per month and mRECIST progression are unique independent risk factors for HCC recurrence and patient death regardless of whether the patient meets the MC[94].

CONCLUSION
Although the MC remain by far the standard and the most employed inclusion criteria for LT for HCC, in the

coming years, criteria will be consolidated that take into account not only data regarding the size/volume and number of tumors but also their biology, including AFP value and some of its published logarithmic models. Additionally, the AFP value will be considered in the allocation and prioritization of patients in the WL with the aforementioned new reform of the MELD-HCC system. Furthermore, the number of tumors, their volume and AFP levels will be important determinants for bridging and downstaging therapy and to evaluate the patient response. AFP values > 1000 ng/mL must be considered a sign of a bad prognosis and a questionable indication for LT unless the value can be reduced to < 400 ng/mL. Organ scarcity and the probability of recurrence following LT for HCC necessitate that all of these facts should be taken into account.

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