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MINIREVIEWS

Liver transplantation for hepatocellular carcinoma beyond the Milan criteria: A review

Dong-Wei Xu, Ping Wan, Qiang Xia

Dong-Wei Xu, Ping Wan, Qiang Xia, Department of Liver Surgery, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China

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Correspondence to: Dr. Qiang Xia, Department of Liver Surgery, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Dongfang Road, NO. 1630, Shanghai 200127, China. xiaqiang@shsmu.edu.cn
Telephone: +86-21-68383775
Fax: +86-21-58737232

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Abstract

Liver transplantation (LT) has been accepted as an effective therapy for hepatocellular carcinoma (HCC). The Milan criteria (MC) are widely used across the world to select LT candidates in HCC patients. However, the MC may be too strict because a substantial subset of patients who have HCC exceed the MC and who would benefit from LT may be unnecessarily excluded from the waiting list. In recent years, many extended criteria beyond the MC were raised, which were proved to be able to yield similar outcomes compared with those patients meeting the MC. Because the simple use of tumor size and number was insufficient to indicate HCC biological features and to predict the risk of tumor recurrence, some biological markers such as Alpha-fetoprotein, Des-Gamma-carboxy prothrombin and the neutrophil-to-lymphocyte ratio were useful in selecting LT candidates in HCC patients beyond the MC. For patients with advanced HCC, downstaging therapy is an effective way to reduce the tumor stage to fulfill the MC by using liver-directed therapy such as transarterial chemoembolization, radiofrequency ablation and percutaneous ethanol injection. This article reviews the recent advances in LT for HCC beyond the MC.

Key words: Liver transplantation; Biological marker; Milan criteria; Hepatocellular carcinoma; Downstaging therapy; Adjuvant treatment

Core tip: The Milan criteria (MC) were widely used in selecting liver transplantation (LT) candidates in hepatocellular carcinoma (HCC) patients. Because a substantial subset of HCC patients exceeding the MC and who would benefit from LT may be unnecessarily excluded from the waiting list, many extended criteria beyond the MC were raised. To predict the risk of tumor recurrence, some biological markers were also useful in HCC patients beyond the MC. Downstaging and adjuvant therapies are effective ways to reduce the tumor stage and the risk of recurrence. This article reviews the recent advances in LT for HCC

beyond the MC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second cause of cancer-related death all over the world. Liver transplantation (LT) has been accepted as an effective therapy for HCC with decompensated liver cirrhosis. In the early stage of HCC treatment, however, the high tumor recurrence rate and poor survival outcomes after LT aroused attention[1-4]. Mazzaferro *et al*[5] in 1996 reported that patients with a single tumor ⩽ 5 cm in diameter, or no more than three tumors ⩽ 3 cm, displayed a favorable long-term prognosis. The 4-year overall and recurrence-free survival rates were 85% and 92%, respectively, which were comparable to LT recipients with benign diseases. The MC have been verified by several centers around the world since then and adopted by the United Network for Organ Sharing as the main basis for selecting patients with early-stage HCC for LT. However, many extended criteria beyond the MC were proposed recently because only a fraction of HCC patients are suitable for LT according to the MC. Because the simple use of tumor size and number were insufficient to precisely represent HCC biological features, some biological markers were used in many studies to evaluate the risk of tumor recurrence after LT for patients with HCC beyond the MC. Moreover, downstaging therapy to bring tumors to fulfill the MC has also become an alternative to treatment for patients with advanced HCC.

EXTENDED CRITERIA OF LT FOR HCC

Because the use of MC unnecessarily exclude a substantial subset of patients with HCC exceeding the MC who might benefit from LT from the transplant waiting list, several extended criteria beyond the MC have been reported recently, such as the Pittsburgh criteria, the University of California at San Francisco (UCSF) criteria, the up-to-7 criteria, among other criteria. Although these criteria greatly expanded the indication of LT for HCC, most studies showed that the newly added patients using extended criteria could achieve similar outcomes compared with patients within the MC[6-16].

The Pittsburgh criteria

To establish a more precise system to predict the prognosis of HCC patients undergoing LT, Marsh *et al*[15] investigated 307 transplant recipients with HCC and found that the depth of vascular invasion, tumor size, lobar distribution and lymph node status were independent predictors of tumor free survival, while tumor number did not affect the prognosis. On the basis of these results, they proposed the modified TNM criteria (also known as the Pittsburgh criteria), which significantly expanded the indication of LT for HCC. Chen's study[17] showed that the Pittsburgh Modified TNM Criteria were more reliable for prognostic prediction in HCC patients undergoing LT than the International Union Against Cancer (UICC) pTNM staging system. However, lymph node metastasis and tumor vascular invasion is difficult to diagnose before surgery in many cases, which limited its application.

The UCSF criteria

Yao *et al*[7] retrospectively analyzed 70 consecutive transplant recipients and proposed the UCSF criteria: solitary tumor ⩽ 6.5 cm or ⩽ 3 nodules with the largest lesion ⩽ 4.5 cm and a total tumor diameter ⩽ 8 cm (Table 1). The 1- and 5-year survival rates of the patients meeting the UCSF criteria were 90% and 75.2%, respectively, which is similar to the patients fulfilling the MC. Patients meeting UCSF criteria but exceeding the MC had a 2-year survival rate of 86%, and the UCSF criteria added the LT candidates by 51.5% without compromising the survival.

In recent years, many centers have testified to the value of the UCSF criteria. The University of California at Los Angeles Transplant Center[18] in 2007 reported 467 cases of transplant recipients and 5-year survival rates of patients meeting the MC and UCSF criteria were 79% and 64%, respectively, with no significant difference found between the use of the MC and UCSF criteria. However, in this series, the 5-year survival rate of patients exceeding UCSF criteria was less than 50%.

The up-to-7 criteria

In another attempt to expand the MC, Mazzaferro *et al*[8] proposed the up-to-7 criteria [the sum of the tumor number and the size of the largest tumor (in cm) was not larger than 7] on the basis of 1556 patients from 36 centers (Table 1). In this study, 283 patients without microvascular invasion but met the up-to-7 criteria achieved a 5-year overall survival of 71.2%. The model established in this study firstly stratified HCC patients in a continuum of outcome probabilities, and offered consistent data to estimate the outcome of LT recipients for HCC. However, the up-to-7 criteria did not apply tumor grading, etiology of cirrhosis, cause of death, response to pretransplant treatments or some genomic markers that may predict the outcomes of HCC patients. Moreover, the size and the number of tumors may be inaccurate when using imaging techniques, which may cause understaging or

Table 1 Selection criteria in different centers for hepatocellular carcinoma beyond the Milan criteria

Criteria	Year	Country	Sample size		Contents of criteria	Survival (5-yr)	
			DDLT	LDLT		OS	RFS
UCSF[7]	2001	America	70	0	Tumor ≤ 6.5 cm, or ≤ 3 nodules with the largest ≤ 4.5 cm and a total tumor ≤ 8 cm	75.2%	None
Up-to-7[8]	2009	Italy	1404	121	The sum of the tumor number and the size of the largest tumor no larger than 7 cm	71.2%	None
Tokyo[9]	2007	Japan	0	78	Tumors no larger than 5 cm and no more than 5 nodules	75.0%	94% (3-yr)
Hangzhou[12]	2008	China	195	0	Tumor ≤ 8 cm, or tumor > 8 cm, histopathologic grade I or II and preoperative AFP ≤ 400 ng/mL	78.3%	62.4%
Kyoto[6]	2007	Japan	0	125	Tumor ≤ 10 nodules, all ≤ 5 cm and a serum DCP level ≤ 400 mAU/mL	86.7%	None
Shanghai[14]	2009	China	1074	4	Tumor ≤ 9 cm, or ≤ 3 lesions with the largest ≤ 5 cm, tumor ≤ 9 cm without macrovascular and lymph node invasion and extrahepatic metastasis	78.1%	52.6%
Asan[11]	2008	South Korea	0	221	Tumor ≤ 5 cm in diameter, ≤ 6 in nodule number, and free of gross vascular invasion	81.6%	None

UCSF: University Of California San Francisco; LDLT: Living donor liver transplantation; DDLT: Deceased donor liver transplantation; OS: Overall survival; RFS: Relapse free survival.

overstaging.

The Tokyo criteria

The 5-5 rule (tumors no larger than 5 cm and no more than 5 nodules), the first well-defined criteria for potential candidates for living donor liver transplantation (LDLT), was proposed by University of Tokyo in 2007[9] (Table 1). In the study, 78 adult patients underwent LDLT were investigated, and the 3-year recurrence-free survival rate of patients fulfilling and exceeding the criteria was 94% and 50%, respectively. Compared with patients fulfilling the MC, patients within the 5-5 rule showed equivalent recurrence-free survival rates. Due to the short median follow-up period and the small patient number, however, a further large-scale study is necessary to verify the general application of the 5-5 rule.

The Hangzhou criteria

Nearly half of HCC cases in the world are from China. Data from the China Liver Transplant Registry (CLTR) showed that more than 23000 patients with HCC underwent LT before 2012[19]. The Hangzhou center, established by Chinese researchers, adopted the histopathologic grade and biological marker alpha fetoprotein (AFP) for selection of LT candidates. The Hangzhou criteria included a total tumor diameter less than or equal to 8 cm or a total tumor diameter more than 8 cm, with a histopathologic grade Ⅰ or Ⅱ and a preoperative AFP level less than or equal to 400 ng/mL (Table 1). Notably, a 5-year survival rate of 72.3% was achieved in HCC patients within the Hangzhou criteria. A recent study that reviewed 6012 HCC patients based on the CLTR data reported that the Hangzhou criteria added to the LT candidates by 51.5% compared with the use of the MC[19].

Other criteria from Asian countries

Kyushu University reported that patients with an HCC ≤ 5 cm and a serum Des-Gamma-carboxy prothrombin (DCP) level ≤ 300 mAU/mL could achieve a 5-year survival rate of 82.7%[13] (Table 2). At Kyoto University, a 5-year survival rate of 86.7% was achieved in patients with an HCC ≤ 10 nodules; all nodules were ≤ 5 cm in diameter and had a serum DCP level lower than 400 mAU/mL[6] (Table 2). The study from the Asan Medical Center in South Korea showed that the 5-year survival rate of patients with an HCC ≤ 5 cm in diameter, ≤ 6 in nodule number, and free of gross vascular invasion was 81.6%[11].

Furthermore, the Shanghai criteria include a solitary lesion ≤ 9 cm in diameter or no more than three lesions with the largest being ≤ 5 cm with a total tumor diameter ≤ 9 cm without macrovascular invasion, lymph node invasion and extrahepatic metastasis, and this criteria achieved a 5-year overall survival of 78.1%[14]. In another study conducted in Shanghai, a new promising grading system for HCC exceeding the MC was established by Wan *et al*[20]. Patients with grade I (maximum tumor size ≤ 10 cm, preoperative AFP ≤ 400 ng/mL and no vascular and extrahepatic invasions) could achieve similar survival outcomes compared with patients fulfilling the MC (Table 2).

BIOMARKERS USED TO PREDICT HCC RECURRENCE AFTER LT

Most of the extended criteria above are established based on tumor size and number, which are more objective and convenient for clinical application, but insufficient to precisely indicate HCC biological features and to predict the risk of tumor recurrence. Many

Table 2 Tumor markers and the cut-off of different selection criteria

Markers	Authors	Cut-off	Other content	Survival (5-yr)	
				OS	RFS
AFP	Zheng *et al*[12]	AFP ≤ 400	Hangzhou criteria	78.3%	62.4%
	Toso *et al*[27]	AFP ≤ 400	Total tumor volume ≤ 115 cm^3	None	None
	Wan *et al*[20]	AFP ≤ 400	Tumor ≤ 10 cm, no vascular and extrahepatic invasions	73.7%	74.4%
DCP	Ito *et al*[6]	DCP ≤ 400	Tumor size ≤ 10 cm	86.7%	None
	Soejima *et al*[13]	DCP ≤ 300	Tumor size ≤ 5 cm	None	93.8% (3-yr)
NLR	Xiao *et al*[43]	NLR < 4	None	61.5%	60.7%
AFP/CA199	Wan *et al*[30]	AFP ≤ 400, CA199 ≤ 400	None	74.6%	78.5%
NLR/CRP	Na *et al*[47]	NLR < 6.0 or CRP < 1.0	None	None	None
DCP/AFP	Todo *et al*[35]	DCP ≤ 100, AFP ≤ 200	Milan criteria	None	96.4%
	Shindoh *et al*[36]	AFP ≤ 250, DCP ≤ 450	Tokyo criteria	84.0%	96.8%

AFP: Alpha fetoprotein; DCP: Des-Gamma-carboxy prothrombin; NLR: Neutrophil-to-lymphocyte ratio; OS: Overall survival; RFS: Relapse free survival.

centers have demonstrated that vascular invasion and poor tumor differentiation are the most important factors affecting HCC recurrence[18,21,22]. Large or multiple HCCs were not always associated with poor biological behavior, indicating that tumor size and number could not completely predict vascular invasion and tumor grade. Although some studies have added the histopathologic characteristics of the tumor when evaluating the risk of tumor recurrence[7,12,14,15], the histopathologic results are usually difficult to obtain before LT. However, many biomarkers and their dynamic changes were demonstrated to be promising predictors for the prognosis of HCC patients after LT.

AFP

AFP is the most common prognostic maker that has been studied extensively in HCC. Several centers have identified the value of preoperative AFP concentrations in predicting prognosis after LT for HCC patients[10,12,23-25]. A recent study by Berry *et al*[26] also showed that preoperative AFP level could independently predict the prognosis of HCC patients after LT. In 2009, Toso *et al*[27] investigated 6478 recipients of the Scientific Registry of Transplant Recipients (SRTR) and proposed that the total tumor volume (TTV) and preoperative AFP level could independently predict patient survival. Recently, they reconfirmed the previously proposed viewpoint and expanded the criteria to HCC patients with TTV (≤ 115 cm^3)/AFP (≤ 400 ng/mL)[28]. A systematic review conducted by Hakeem *et al*[29] has shown that a preoperative AFP level > 1000 ng/mL was associated with poorer outcomes of recipients with HCC. A study by Wan *et al*[30] showed that the use of serum AFP and carbohydrate antigen 19-9 (CA19-9) level will greatly improve the prognostic prediction of HCC patients after LT. Xu *et al*[31] investigated the AFP data before and after LT in 97 patients and reported that post-transplant AFP levels that did not decrease to ≤ 20 ng/mL within 2 mo were indicative of higher risk of recurrence. Another study conducted by Hanouneh *et al*[32] confirmed patients beyond the MC with tumor growth < 1.61 cm^3/mo experienced less recurrence than those beyond the MC with tumor growth > 1.61 cm^3/mo.

DCP

DCP, also known as protein induced by vitamin K absence or antagonist Ⅱ (PIVKA-Ⅱ), has also been used as an important HCC biological marker. Correlations between DCP levels and HCC microvascular invasion and metastasis have been reported in several studies[33,34]. In the transplantation field, centers from Japan first used the DCP levels in LT candidate selection[6,13]. Todo *et al*[35] conducted a study involving 49 centers of 653 patients and reported that recipients beyond the MC but with serum AFP levels ≤ 200 ng/mL and serum PIVKA-Ⅱ levels ≤ 100 mAU/mL had a 5-year disease-free survival rate of 84.3%. Recently, Shindoh *et al*[36] also confirmed the predictive value of pre-transplant AFP and DCP levels for post-transplant HCC recurrence. After investigating 124 patients who underwent LDLT for HCC, they proposed a new scoring system that was composed of AFP (≤ 250 ng/mL), DCP (≤ 450 mAU/mL) and the Tokyo criteria (≤ 5 tumors with each tumor ≤ 5 cm). Patients fulfilling all or two of the three factors (AFP, DCP and the Tokyo criteria) had better 5-year disease-free survival rates than patients fulfilling only one, or none of the three factors.

Neutrophil-to-lymphocyte ratio

Neutrophil-to-lymphocyte ratio (NLR), also known as an index of systemic inflammation, has been reported to be associated with the prognosis of HCC patients[37]. Several studies have highlighted the value of preoperative NLR in predicting outcome after LT for HCC[38-41]. A study conducted by Harimoto *et al*[42] showed that the 3-year survival rate after recurrence in patients with NLR < 4 (43.6%) was higher than patients with NLR ≥ 4 (0%). Xiao *et al*[43] determined that NLR ≥ 4 was the main predictor of tumor

recurrence in HCC patients after LT. A recent study, however, reported that NLR was not significantly associated with post-LT HCC recurrence. Another study also showed that increased NLR was associated with worse overall survival and recurrence-free survival[44].

C-reactive protein

Serum C-reactive protein (CRP), another inflammation maker, has also been shown to be related to the prognosis of HCC patients. Both An *et al*[45] and Kim *et al*[46] determined that, the high CRP level was an independent factor in predicting poor outcomes in HCC patients beyond the MC, but not in patients within the criteria. Na *et al*[47] investigated 224 patients and reported that the disease-free survival and overall survival in patients with NLR levels $\geqslant$ 6.0 or CRP levels $\geqslant$ 1.0 were significantly worse than those of patients with NLR levels < 6.0 or CRP levels < 1.0. Chung *et al*[48] also confirmed that the intra-operative decline of CRP was related to the occurrence of gross post-transplant outcomes. However, another study reported that the pre-transplant CRP level was not significantly associated with disease-free survival[36]. The clinical relevance and prognostic value of these inflammatory markers are still being debated, and further studies are needed to confirm their role in LT.

Fluorine-18-fluorodeoxyglucose

Fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) has been verified to be effective in predicting the outcome of HCC patients after liver resection and detecting extrahepatic metastases and recurrent HCC[49-52]. In the transplantation field, Yang *et al*[53] first reported that the recurrence-free survival rate of PET (-) recipients was significantly higher than that of PET (+) recipients. Several centers successively highlighted the value of preoperative FDG-PET in the assessment of tumor aggressiveness and in the prediction of tumor recurrence after LT[54-57]. A recent study conducted by Kornberg *et al*[58] showed the 5-year recurrence-free survival rate of recipients exceeding the MC with PET (-) was comparable to that of recipients within MC (81% *vs* 86.2%), but it was significantly higher than that of recipients exceeding MC with PET (+) (n = 14, 21%, P = 0.002).

HCC DOWNSTAGING ADJUVANT THERAPY BEFORE LT

Downstaging has been proved to be an effective way for patients with advanced HCC to reduce the tumor stage to fulfill the MC and achieve a complete pathologic response (cPR) by undergoing neoadjuvant therapies such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA) and percutaneous ethanol injection. A recent systemic review including 950 patients reported that more than 40% of patients successfully reduced HCC to within the MC[59]. Lei *et al*[60] investigated 72 patients with advanced HCC and reported that recipients fulfilling the MC or UCSF criteria after accepting successful preoperative downstaging therapy in LDLT can achieve similar outcomes. Yao *et al*[61] also confirmed that after successfully downstaging to within the MC, HCC recipients could achieve low HCC recurrence rates and excellent post-transplant survival which was comparable to those fulfilling the MC without downstaging therapy. Agopian *et al*[62] performed a retrospective review of 501 patients who received neoadjuvant therapies and found that compared with recipients without cPR, patients with cPR had significantly lower MELD scores and significantly superior 1-, 3-, and 5-year recurrence-free and disease-specific survival.

TACE has been widely used as an optional treatment for patients with unresectable HCC. The initial experience showed conflicting outcomes in treating HCC patients awaiting LT with TACE[63,64]. Recently more studies highlighted the importance of TACE in downstaging therapy and cPR[65-69]. In a retrospective report by Chapman *et al*[65], patients successfully downstaged by TACE alone achieved excellent midterm disease-free rates and overall survival. In another study, 77% T3N0M0 HCC patients successfully reduced their tumor stage to fulfill the MC by TACE[67]. Several studies regarded that TACE mediates its effect by inducing complete histological necrosis, with reported rates of cPR in 27% to 57% of patients with TACE[68,69].

RFA has also been verified as an effective treatment for HCC by many studies[70]. In the transplantation field, RFA was used as a bridge treatment to LT in many centers[71-73]. Yao *et al*[71] reported HCC patients exceeding the conventional criteria achieved an excellent survival rate after LT when combining RFA with other loco-regional therapies. Tsuchiya *et al*[74] recently reported that recurrence within 1 year after initial locally curative RFA therapy and AFP levels > 100 ng/mL were independently associated with earlier recurrence in patients exceeding the MC.

Although more and more centers have highlighted the value of various downstaging therapies, the post-transplant HCC recurrence rates are higher than patients fulfilling MC without pre-transplant therapies[59]. To further study the role of these downstaging therapies in patients with advanced HCC, more randomized data comparing these therapies are also necessary.

LDLT *VS* DDLT FOR HCC BEYOND THE MC

Currently, approximately 70% of LDLT recipients are from Asian countries due to the shortage of deceased donation, which was caused by many social and cultural reasons. There are several advantages

including reducing the pretransplantation waiting time of patients with HCC, alleviating the ischemia-reperfusion injury because of shortened ischemic time**,** providing a an optimal donor graft for those with end-stage liver disease and even a timely graft for patients with fulminant hepatic failure promote the development of the approach. Although LDLT is criticized for its higher rate of surgical complications post-transplantation(biliary complications, vascular complications) than DDLT[75,76], it has been generally recognized by most studies that LDLT could achieve a comparable long-term survival rate in adult patients compared with DDLT[77-79].

The criteria from western countries were mainly based on a single-center experience with DDLT. Centers from Japan[6,9,13] and South Korea[11], however, proposed appropriate criteria for patients undergoing LDLT. Shirabe *et al*[80] recently investigated 109 consecutive HCC recipients undergoing LDLT and reported that compared with the other expanded criteria (UCSF, Tokyo, Kyoto University and Up-to-seven criteria), the Kyushu University criteria were the most powerful predictive criteria for HCC recurrence after LT.

For patients with HCC exceeding the MC, whether recurrence and survival rate in LDLT are different from those in DDLT remains controversial. Woo *et al*[81] reviewed 37 patients exceeding the MC and reported that a tumor size > 6 cm, progressive disease after pre-transplant treatment and a tumor exposed to the liver surface may be useful for identifying those with high HCC recurrence potential after LDLT. A study from Bhangui *et al*[82] confirmed the advantage of shorter waiting time in LDLT; they also verified that patients exceeding the MC and UCSF criteria showed a trend toward worse outcomes with LDLT compared with those of DDLT. Recently, a study conducted in Hangzhou, however, showed that outcomes after LDLT are better than those after DDLT for HCC patients who did not meet the Hangzhou criteria[83].

For patients within the MC, the long-term survival rate was comparable between DDLT and LDLT. However, to further verify the value of LDLT in HCC recipients exceeding the MC, further case-controlled research with larger patient number needs to be conducted to propose more appropriate selection criteria.

POSTTRANSPLANT ADJUVANT TREATMENT FOR HCC

Sorafenib (SFN), an oral multi kinase inhibitor, has been approved for the treatment of unresectable HCC for years. Recently, many studies verified its value in reducing the risk of recurrence and treatment for recurrent HCC after LT. Huang *et al*[84] conducted a prospective randomized study for recipients with HCC exceeding the MC and reported that compared with capecitabine, SFN could reduce or delay tumor recurrence after LT and improve patient survival. In a case-control study designed in Taiwan, HCC patients exceeding the MC after OLT treated with adjuvant sorafenib had better disease-free and overall survival rate than those in the control group[85]. Other studies[86-88] also confirmed the role of SFN in the treatment of HCC recurrence.

Calcineurin inhibitors (CNIs) were widely used in LT. However, the short and long term adverse effects including renal dysfunction and a dose-dependent increase in the post-transplant risk of HCC recurrence drew attention[89-91]. The mammalian target of rapamycin inhibitors (mTORi), such as everolimus or sirolimus, might represent an alternative immunosuppressive agent; the antineoplastic effect of mTORi has also been confirmed by several studies[92]. Two meta-analyses have reported that compared with CNIs or SRL-free regimens, sirolimus is associated with significantly lower HCC recurrence rates after LT[93,94]. A more recent meta-analysis including 42 studies of 3666 patients confirmed that compared with CNIs, mTORi was associated with lower rates of HCC recurrence after LT[95]. Moreover, the rates of HCC recurrence in HCC patients within the MC were lower in mTORi (3.8% *vs* 9.2%, $P = 0.03$), but no difference was observed among patients who had HCC exceeding the MC (29.5% *vs* 29.2%, $P = 1.0$)[95].

CONCLUSION

As various therapies mature, the treatment of HCC has progressed greatly. Because a large number of patients who exceeded the MC were unnecessarily excluded according to the MC, several extended criteria beyond the MC were proposed to benefit these recipients. Moreover, many biological markers such as AFP, DCP, NLR and CRP have been verified to be closely associated with HCC patients' prognosis and the risk of post-transplant recurrence. Although downstaging tumors to fulfill the MC allows patients with advanced HCC to potentially have an opportunity for LT, the high tumor recurrence rate after LT reported in some studies has raised attention. Moreover, SFN and mTORi may be useful to reduce the risk of HCC recurrence and to treat recurrent HCC after LT. As for the selection of graft type, the outcomes of LDLT for patients beyond the MC remains controversial.

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