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Hepatocellular carcinoma beyond Milan criteria: Management and transplant selection criteria

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Abstract

Liver transplantation (LT) for hepatocellular carcinoma (HCC) has been established as a standard treatment in selected patients for the last two and a half decades. After initially dismal outcomes, the Milan criteria (MC) (single HCC $\leqslant$ 5 cm or up to 3 HCCs $\leqslant$ 3 cm) have been adopted worldwide to select HCC patients for LT, however cumulative experience has shown that MC can be too strict. This has led to the development of numerous expanded criteria worldwide. Morphometric expansions on MC as well as various criteria which incorporate biomarkers as surrogates of tumor biology have been described. HCC that presents beyond MC initially can be downstaged with locoregional therapy (LRT). Post-LRT monitoring aims to identify candidates with favorable tumor behavior. Similarly, tumor marker levels as response to LRT has been utilized as surrogate of tumor biology. Molecular signatures of HCC have also been correlated to outcomes; these have yet to be incorporated into HCC-LT selection criteria formally. The ongoing discrepancy between organ demand and supply makes patient selection the most challenging element of organ allocation. Further validation of extended HCC-LT criteria models and pre-LT treatment strategies are required.

Key words: Hepatocellular carcinoma; Milan criteria; Liver transplantation; Expanded criteria; Locoregional therapy; Down staging

Core tip: Numerous expanded selection criteria for hepatocellular carcinoma (HCC)-liver transplantation (LT) have been proposed worldwide. Surrogates of favorable tumor biology such as Post-locoregional therapy strategies which observe tumor behavior, and the addition of HCC biomarkers to selection criteria have been explored. Further investigation is encouraged to identify patients beyond MC with the most favorable tumor biology for LT.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, with over 700000 new cases diagnosed yearly worldwide[1]. HCC continues to be a global health problem due to insufficient screening and surveillance and poorly controlled risk factors[2]. HCC arises most frequently in patients with chronic liver disease from diverse etiologies, and liver transplantation (LT) has been established as a standard treatment in selected patients for the last two and a half decades[3]. However, an ongoing conundrum is the discrepancy between organ demand and supply, making patient selection the most challenging piece of the puzzle to prevent organ misutilization[4].

Poor patient selection (excessive tumor burden, unknown tumor biology) made initial results of LT for HCC quite dismal[5]. It wasn't until 1996, when Mazzaferro *et al*[6] defined tumor criteria for patient selection (single lesion $\leqslant$ 5 cm, or up to 3 lesions $\leqslant$ 3 cm each in the absence of tumor vascular invasion or evidence of extra-hepatic metastases) associated with comparable outcome to patients undergoing LT without HCC. The study revealed 4 year post-LT survival > 75% and post-LT recurrence rate in the order of 8%. These criteria have since been known as the Milan criteria (MC), and have been adopted worldwide to select HCC patients for LT[7].

Patients who present with HCC beyond MC can be down-staged *via* loco-regional therapy (LRT). LRT are trans-catheter, needle based or radiation treatments which target the tumor and induce selective tumor necrosis[8]. The efficacy of these treatments is gauged radiologically by the modified Response Evaluation Criteria in Solid Tumors[9]. Tumor response to LRT, post LRT observation before LT, and HCC biomarkers have been described for selecting the most favorable tumor biology in patients presenting with HCC beyond MC[9-11].

Although strict adherence to MC can produce outcomes comparable to LT for non-HCC, cumulative experience over the last two decades have shown that MC can be too strict, and that select patients beyond MC may benefit from LT with adequate survival[12]. This has led to the development of numerous HCC expanded criteria worldwide, applied for both cadaveric and live donor liver transplantation.

Herein, we review various expanded HCC criteria and outcomes, impact of tumor response to LRT in post-LT outcome and emerging HCC molecular signatures that may be incorporated into patient selection criteria in the near future.

EXTENDED LT-HCC CRITERIA

In 2001, Yao *et al*[13] published one of the most popular expanded LT-HCC criteria. The University of California, San Francisco (UCSF) criteria considered a single lesion $\leqslant$ 6.5 cm, or 2-3 lesions $\leqslant$ 4.5 cm each, with total tumor diameter $\leqslant$ 8 cm.

Tumor recurrence was 11.4% and 5 years post-LT survival was in the order of 72.4%[13]. The original UCSF criteria were developed based on explant histopathological analysis, but subsequently have been validated utilizing pre-LT imaging. In 2007, Yao *et al*[14] published a prospective study utilizing the UCSF criteria revealing 80% 5 years post-LT recurrence free survival (RFS). Alongside MC, UCSF criteria have been the most widely recognized transplant criteria for HCC, and can expand 5%-20% the indication of LT for HCC patients[14]. Currently, some worldwide transplant centers utilize UCSF as the standard selection LT criteria for HCC[15].

The Navarro extended criteria described by Herrero *et al*[16] in 2001 can expand the MC by considering LT for a single lesion $\leqslant$ 6 cm, or 2-3 lesions $\leqslant$ 5 cm each. In their analysis, 12.7% of the cohort experienced tumor recurrence. Post-LT 5 years overall survival and RFS was 79% and 70% respectively.

Silva *et al*[17] published the Valencia criteria in 2008. These would consider LT in HCC patients with 1-3 lesions $\leqslant$ 5 cm each, and total tumor $\leqslant$ 10 cm. Two hundred and fifty-seven patients undergoing LT for HCC were analyzed, however only 10% were beyond MC based on pre-LT imaging. Patients who fell within the Valencia criteria demonstrated post-LT 5 year survival comparable to patients within MC. The Valencia criteria expands LT to a higher maximum tumor burden compared to both MC and UCSF criteria, without detriment to patient survival, however similar to the Navarro criteria, due to the small number of patients in this cohort, these criteria require further validation.

Correlation of tumor size and number according to explant pathology and post-LT survival in 1206 patients from the International Registry of Hepatic Tumors, led to the recommendation of LT for a single lesion $\leqslant$ 6 cm, or 2-4 lesions $\leqslant$ 5 cm each by Onaca *et al*[18] in 2007. Survival in patients exceeding MC but meeting these criteria were not significantly lower than for patients meeting MC. Five years post-LT RFS with a single lesion 5.1-6.0 cm in diameter, or with 2-4 lesions (largest 3.1-5.0 cm) were 63.9%, and 64.6% respectively, compared to 5 years post-LT RFS of 61.8% if MC were met[18].

Other proposed extended criteria do not put a limit to number of tumors recommended for LT. Roayaie *et al*[19] in 2002, demonstrated 55% 5 years post- LT RFS for patients with lesions 5-7 cm in diameter. In 2004, Kneteman *et al*[20] reported the outcomes of LT utilizing extended criteria described as a singles lesion < 7.5 cm, or multiple lesions < 5 cm each. Four year post-LT survival was 82.9% *vs* 87.4% in the MC group.

One of the more recently proposed extended criteria is the Up-to-7 criteria proposed by Mazzaferro *et al*[21] in 2009. A cohort of 1556 patients undergoing cadaveric LT and LDLT for HCC from 36 transplant centers was analyzed, 71.5% of the cohort had HCC exceeding MC. The Up-to-7 criteria are defined as the sum of the

size of the largest tumor in cm and the total number of tumors in the absence of tumor microvascular invasion. Five years post-LT survival for patients within the Up-to-7 criteria compared to MC were 71.2% *vs* 73.3%[21]. The major limitation of these criteria is the lack of pre-LT information about microvascular invasion. Currently, this can only be partially projected *via* assessment of alpha-fetoprotein (AFP) level.

Extended LT-HCC criteria using living donors

Outcomes in HCC patients undergoing living donor liver transplantation (LDLT) were shown to be equivalent to cadaveric liver transplantation[22]. Soejima *et al*[23] reported that tumor diameter > 5 cm was associated with worse prognosis; however the number of tumors was not. In the cohort of 60 patients who underwent LDLT for HCC, 67% were beyond MC based on pre-LT imaging. Three years post-LT survival of 68.6% was reported for patients beyond MC[23].

Jonas *et al*[24] also described their extended criteria based on a cohort of 21 patients undergoing LDLT for HCC. Three year survival rates for patients not meeting MC or USCF criteria were 62% and 53% respectively. Sugawara *et al*[25] proposed an expansion of selection criteria to include up to 5 HCC lesions, ⩽ 5 cm each. In their cohort of 78 patients, post-LT RFS at 3 years was 94%.

Table 1 demonstrates an overview of proposed morphometric based expanded selection criteria.

INCORPORATION OF SURROGATES OF TUMOR BIOLOGY TO SELECTION CRITERIA

Tumor markers

Post-LT outcomes in patients with HCC are in part a consequence of tumor biology. As a result of the impossibility to unveil this feature solely through morphometric imaging characteristics, multiple studies have attempted to include other indicators of tumor behavior as selection criteria. AFP and des-γ-carboxyprothrombin (DCP) both have established correlations with post treatment prognosis[26,27]. A pre-LT AFP level > 1000 ng/mL has been demonstrated as a significant predictor of HCC recurrence post-LT[26]. A large scale analysis of United Network for Organ Sharing (UNOS) data has demonstrated that patients transplanted beyond MC with an AFP level of 0 to 15 ng/mL (normal range) had improved survival[28].

One of the most popular HCC-LT extended criteria including biomarkers as surrogates of tumor biology are the Hangzhou criteria (absence of macrovascular invasion and total tumor diameter ⩽ 8 cm. If the tumor burden is > 8 cm, histopathology *via* tumor biopsy should be non-poorly differentiated HCC and AFP level should be ⩽ 400 ng/mL[29].

In the original cohort of 195 patients, fulfilling Hangzhou criteria led to a 5 year survival of 70.7% and DFS: 62.4%. On the other hand, patients beyond Hangzhou criteria had a 5 year survival of 18.9% and DFS: 4.7%[29]. A large scale comparative study of multiple extended criteria confirmed post LT survival associated with LT beyond MC but meeting Hangzhou at 1-, 3-, 5- and 10-years was 89.5%, 70.8%, 62.4% and 52.9% respectively. Additionally, 1-, 3-, 5- and 10-year RFS was 81.6%, 64.3%, 56.5%, and 37.2% respectively. Compared to MC, expanded criteria expanded transplantable patients by 12.4% for Valencia, 16.3% for UCSF, 19.6% for Navarro, and 51.5% for Hangzhou. RFS rates were comparable to MC[30].

In 2012, Lai *et al*[31] also suggested that the combination of total tumor diameter > 8 cm and an AFP level ⩽ 400 ng/mL would result in favorable survival outcomes. The 5 year DFS rate was 74.4%. It was also noted that patients with increased AFP values in response to LRT had higher recurrence rates[31]. Duvoux *et al*[32] have suggested a predictive scoring model that combines the AFP level at listing with MC. In their model, an AFP level ⩽ 100 ng/mL in the setting of patients beyond MC (1-3 lesions with a maximum tumor diameter of 6 cm) demonstrated 5- year survival near 70%[32].

Similar criteria have been applied to LDLT as well. In a multicenter study from Japan, Todo *et al*[33] suggested that the combination of an AFP cut of level ⩾ 200 ng/mL and protein induced by vitamin K absence or antagonism factor Ⅱ (PIVKA Ⅱ) ⩾ 100 mAU/mL are significant predictors for poor post LT survival. These combined were described as the A-P level. Five year DFS for beyond MC HCC patients and within the A-P cutoff level was similar to those within MC at 78.7% and 90.4% respectively.

Kwon *et al*[34] demonstrated their outcomes incorporating an AFP level ⩽ 400 ng/mL as a selection criteria along with any number of lesions ⩽ 5 cm each. In a cohort of 139 patients, 5 year survival was noted at 79.9%, without a significant difference between patients within or beyond MC[34]. More recently in 2015, Toso *et al*[35] in a prospective study suggested extended LT criteria described as a combination of a total tumor volume ⩽ 115 cm^3 and an AFP level ⩽ 400 ng/mL. Four year post LT survival was similar between the extended criteria group and the MC group at 78.7% and 74.6% respectively[35].

A lower AFP cut off rate of < 100 ng/mL as a critera for HCC-LT was recommended by Grąt *et al*[36]. A retrospective analysis of a 121 patients demonstrated significant prediction of recurrence in patients transplanted within UCSF and Up-to-7 criteria who surpassed this limit. Five year RFS for patients meeting UCSF and within the AFP cut off was superior to those meeting USCF but beyond the cut off limit at 100% *vs* 69% respectively. Similarly, when applied to the Up-to-7 criteria, 5 year RFS for those meeting both the criteria and cut off limit was noted at 100% *vs* 71.9% for beyond the cut off limit[36].

DCP, often utilized as a tumor marker for HCC in Japan, has been incorporated into the Kyoto criteria published by Fujiki *et al*[37] in 2009: A DCP level of ⩽ 400 mAU/mL in addition to morphometric criteria of up

Table 1 Expanded morphometric criteria for hepatocellular carcinoma-liver transplantation

Ref.	Year	Description	Donor type	*n*	Survival
Yao *et al*[13]	2001	1 lesion ≤ 6.5 cm, or 2-3 lesions ≤ 4.5 cm each. Total tumor diameter ≤ 8 cm	Cadaveric	70	5 yr OS: 72.4%
Herrero *et al*[16]	2001	1 lesion ≤ 6 cm, or 2-3 lesions ≤ 5 cm each	Cadaveric	47	5 yr OS: 79%
Roayaie *et al*[19]	2002	Any number of lesions, 5-7 cm each	Cadaveric	43	5 yr RFS: 55%
Keneteman *et al*[20]	2004	1 lesion < 7.5 cm, or multiple lesions < 5 cm each	Cadaveric	40	4 yr OS: 82.9% 4 yr RFS: 76.8%
Onaca *et al*[18]	2007	1 lesion ≤ 6 cm, or 2-4 lesions ≤ 5 cm each	Cadaveric	1206	5 yr RFS: 1 lesion ≤ 6 cm: 63.9%/or 2-4 lesions 3.1 cm-5 cm each: 64.6%
Soejima *et al*[23]	2007	Any number lesions ≤ 5 cm each	Living	67	3 yr OS: 68.6%
Jonas *et al*[24]	2007	Single lesion and diameter, or any number of lesions ≤ 6 cm each. Total tumor diameter ≤ 15 cm	Living	21	3 yr OS: 53%
Sugawara *et al*[25]	2007	Up to 5 lesions ≤ 5 cm each	Living	78	3 yr RFS: 94%
Silva *et al*[17]	2008	1-3 lesions ≤ 5 cm each. Total tumor diameter ≤ 10 cm	Cadaveric	257	5 yr OS: 67%
Mazzaferro *et al*[21]	2009	The sum of the size and number of tumors not exceeding 7 in the absence of microvascular invasion	Both	1556	5 yr OS: 71.2%

RFS: Recurrence free survival; OS: Overall survival.

to 10 nodules ≤ 5 cm each. Five year recurrence was similar for patients within MC, and patients beyond MC but meeting Kyoto criteria at 7% and 4% respectively. Five year survival for patients meeting Kyoto criteria was 89%[37]. Takada *et al*[38] also propose similar selection criteria. In their cohort of 136 patients, those who met the proposed selection criteria demonstrated a 5 year survival rate of 87%.

Lee *et al*[39] proposes the incorporation of 18F-Fluoro-deoxyglucose positron emission tomography (PET) to HCC-LT selection criteria. Retrospective analysis of 2806 patients demonstrated that patients with PET negative scans preoperatively in combination with a total tumor diameter ≤ 10 cm demonstrated 5 year overall survival and DFS rates of 73.4% and 80.4% respectively, which was not significantly different from those within MC[39].

Table 2 demonstrates an overview of proposed expanded selection criteria which incorporate biomarkers to morphometric tumor measurements.

Downstaging and response to LRT

LRT in HCC-LT candidates is considered an element of two approaches: For patients listed/to be listed within MC, LRT is applied neo-adjuvently as bridging therapy to halt tumor progression[40]. Patients who present initially beyond MC are downstaged to reduce tumor size to meet MC[41]. Both strategies provide the opportunity to evaluate radiological and laboratory surrogates of tumor response, which could unveil more aggressive tumors with less favorable biology in order to be excluded from LT.

Since tumor behavior over time is a surrogate of tumor biology, LRT followed by a required waiting time before LT can help to unveil tumor biology and has been coined as the "ablate and wait" strategy[10].

A systematic review and pooled analysis of 13 studies revealed the success rate of downstaging raging between 11%-77%. There was no significant difference in utilizing Transarterial Chemoembolization or Transarterial Radioemobilzation. Post LT recurrence rates were noted to be as high as 16%, however survival outcomes could not be calculated due to heterogeneity of the data which prevented adequate analysis. Further investigation is required to determine the effect of heterogeneous downstaging protocols in term of LRT modality, frequency, and waiting period pre- LT[42].

The correlation between the AFP expression in response to LRT and post LT survival has also been investigated. A multicentric study which included 422 patients who underwent LRT before LT for HCC (306 within MC, 116 beyond MC) demonstrated an increased risk for HCC recurrence and death with an AFP slope > 15 ng/mL per month[43].

Future directions: Molecular signatures

Genetic molecular signatures have been explored for their potential as biomarkers for HCC[44]. Dvorchik *et al*[45] assessed fractional allelic imbalance rates in a panel of 9 tumor suppressor genes. A higher rate of tumor suppressor gene mutation correlated with worse post-LT outcome independently of tumor vascular invasion or tumor burden[45].

MicroRNA (miRNA) signatures detected in serum exosomes have also been described as potential biomarkers for HCC. In a cohort of 6 HCC patients miR-718 was described as significantly linked to HCC; and this was further validated in a cohort of 59 LDLT HCC cases. In the validation cohort, miR-718 expression levels were significantly lower in patients beyond MC, and with poorer histological differentiation. However, due to the small incidence of recurrence in this cohort, no direct association could be linked to miR-718[46].

Another study analyzed paraffin embedded tissue from 69 HCC LT patients (which included 40 post LT recurrences) for miRNA expression. The biomarker proposed by this study consisted of 67 miRNAs, this biomarker had significantly identified the HCC recurrent cases, and it also displayed significance when applied to patients within and beyond MC[47].

A predictive scoring system was recently published combining MC with miRNA markers to identify the risk of

Table 2 Expanded criteria that incorporate tumor biomarkers for hepatocellular carcinoma-liver transplantation

Ref.	Year	Morphometric criteria	Biomarker criteria	Donor type	*n*	Survival
Kwon *et al*[34]	2007	Any number of lesions ≤ 5 cm each	AFP ≤ 400 ng/mL	Living	139	5 yr OS: 79.9%
Takada *et al*[38]	2007	Up to 10 lesions ≤ 5 cm each	PIVKA-II ≤ 400 mAU/mL	Living	136	5 yr OS: 87%
Zheng *et al*[29]	2008	Total tumor diameter ≤ 8 cm or total tumor diameter > 8 cm with histopathologic grade Ⅰ or Ⅱ	If total tumor diameter > 8 cm: AFP ≤ 400 ng/mL	Cadaveric	195	5 yr OS: 70.7%, 5 yr DFS: 62.4%
Fujiki *et al*[37]	2009	Up to 10 lesions ≤ 5 cm each	DCP ≤ 400 mAU/mL	Living	144	5 yr OS: 89%
Lai *et al*[31]	2012	Total tumor diameter ≤ 8 cm	AFP ≤ 400 ng/mL	Cadaveric	158	5 yr DFS: 74.4%
Grąt *et al*[36]	2014	UCSF or Up-to-7 criteria	AFP < 100 ng/mL	Cadaveric	121	5 yr OS: 100%
Toso *et al*[35]	2015	Total tumor volume ≤ 115 cm^3	AFP ≤ 400 ng/mL	Cadaveric	166	4 yr OS: 74.6%
Lee *et al*[39]	2015	Total tumor diameter ≤ 10 cm	PET/CT negative uptake	Living	280	5 yr OS: 73.4%, 5 yr DFS: 80.4%

AFP: Alpha fetal protein; UCSF: University of California, San Francisco; DFS: Disease free survival; PIVKA-Ⅱ: Protein induced by vitamin K absence or antagonism factor Ⅱ; OS: Overall survival.

HCC recurrence post- LT. Two miRNA markers significant of tumor recurrence (miR-214, miR-3187) were identified *via* microarray analysis of paraffin explant samples of 40 patients. In another validation cohort of 22 patients, high expression of miR-214 and low expression of miR-3187 were significantly associated with HCC recurrence. A predictive score including levels of these miRNAs and MC status was successful in identifying patients with a lower risk for tumor recurrence and death[48].

CONCLUSION

Although there remains a large discrepancy between cadaveric organ availability and demand, numerous selection criteria for HCC exceeding the well-established MC have been proposed worldwide. Only a few of these criteria have been validated by multiple independent studies. The current direction of incorporating biomarkers and other surrogates of tumor biology to morphometric criteria is highly encouraged, however this is not without challenge. The most commonly used HCC biomarker AFP, is not a reliable indicator for HCC. AFP levels are not elevated in up to 40% of cases [49,50], furthermore AFP is challenged by its poor sensitivity and specificity[51]. Pre-LT tumor biopsy is somehow discouraged, due in part to tumor heterogeneity when multifocal HCC is present, as well as the risk of needle-tract seeding[52].

In light of the current organ shortage, hepatic resection followed by salvage LT has also been suggested as a treatment strategy for HCC. A systematic review by Chan *et al*[53] demonstrated median overall survival at 1-, 3- and 5-years post LT was 89%, 80%, and 62% respectively. Additionally, tissue specimens obtained from a pre-LT resection can assist in selection of tumors with a favorable histopathological profile for LT[53].

Monitoring radiologic and laboratory (tumor markers) tumor response post-LRT has been utilized to identify tumors with favorable biology; and in line with this current UNOS guidelines for organ allocation in the United States require listing HCC patients for 6 mo before qualification for HCC exception points[54].

miRNAs are stable in blood and resistant to RNAases, which makes them promising HCC biomarkers[46]. Further validation of extended HCC-LT criteria models that incorporate predictors of tumor biology are needed to optimize organ utilization in an ongoing era of organ shortage.

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