Liver transplantation for intermediate hepatocellular carcinoma: An adaptive approach

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Abstract
Hepatocellular carcinoma is becoming an increasing indication for liver transplantation, but selection and allocation of patients are challenging because of organ shortages. Conventional Milan criteria are the reference for the selection of patients worldwide, but many expanded criteria, like University of California San Francisco criteria and up-to-7 criteria, have demonstrated that survival and recurrence results are lower than those for restricted indications. Correct staging is crucial and should include surrogate markers of biological aggressiveness (α-fetoprotein, response to loco-regional treatments). Successful down-staging can select between patients with tumor burden initially beyond transplantation criteria those with a more favorable biology, provided a 3-mo stability in meeting the transplantation criteria. Allocation rules are constantly adjusted to minimize the imbalance between the priorities of candidates with and without hepatocellular carcinoma, and take into account local donor rate and waitlist dynamics. Recently, Mazzaferro et al proposed a benefit-oriented "adaptive approach", in which the selection and allocation of patients are based on their response to non-transplantation treatments: low priority for transplantation in case of complete response, high priority in case of partial response or recurrence, and no listing in case of progression beyond transplantation criteria.

Key words: Milan criteria; α-fetoprotein; Down-staging; Allocation; Adaptive approach

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Core tip: Hepatocellular carcinoma is an increasing indication for liver transplantation, but the selection of patients is challenging because of organ shortages. Conventional Milan criteria is the reference for the selection of patients worldwide, but many expanded criteria, like University of California San Francisco criteria and up-to-7 criteria, have demonstrated that survival and recurrence results are lower than those for restricted indications. Correct staging is crucial and should include surrogate markers of biological aggressiveness (α-fetoprotein, response to loco-regional treatments). Successful down-staging can select between patients with tumor burden initially beyond transplantation criteria those with a more favorable biology, provided a 3-mo stability in meeting the transplantation criteria. Allocation rules are constantly adjusted to minimize the imbalance between the priorities of candidates with and without hepatocellular carcinoma, and take into account local donor rate and waitlist dynamics. Recently, Mazzaferro et al proposed a benefit-oriented "adaptive approach", in which the selection and allocation of patients are based on their response to non-transplantation treatments: low priority for transplantation in case of complete response, high priority in case of partial response or recurrence, and no listing in case of progression beyond transplantation criteria.
criteria have also demonstrated satisfactory results. Correct staging should include surrogate markers of biological aggressiveness. Additionally, successful down-staging can help select patients with a more favorable biology. Allocation rules are adjusted to minimize the imbalance between the priorities of candidates with and without hepatocellular carcinoma. Recently, a benefit-oriented "adaptive approach" was proposed, in which the selection and allocation of patients are based on their response to treatments.

Biolato M, Marrone G, Miele L, Gasbarrini A, Grieco A. Liver transplantation for intermediate hepatocellular carcinoma: An adaptive approach. World J Gastroenterol 2017; 23(18): 3195-3204 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i18/3195.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i18.3195

INTRODUCTION

In the United States, about 6500 liver transplantations (LT) are performed every year, hepatocellular carcinoma (HCC)[1] the main indication in nearly 1500 of these. Both incidence and mortality for HCC are increasing in the United States due to progressive ageing of the main cohort with chronic hepatitis C, immigration from areas where hepatitis B is endemic, and epidemic of nonalcoholic fatty liver disease[2,3]. Consequently, there is growing pressure on the waiting list for LT owing to a rise in the number of patients with HCC: the estimated number of potential candidates with HCC who could benefit from LT is more than 20000 per year in the United States[4]. The overall incidence of HCC in Europe is much higher, approaching 65000 cases every year[5]; disappointingly, as per the report by the European Liver Transplant Registry[6], only 6000 LT were performed in 2011, of which 1000 were for HCC. The shortage of available organs and the needs of patients with non-HCC indications for the LT are making the inclusion of patients with HCC on the waiting list challenging.

CONVENTIONAL AND EXPANDED

SELECTION CRITERIA FOR LT FOR HCC

Selection of patients with HCC for LT is based on the Milan criteria (single HCC ≤ 5 cm or ≤ 3 nodules each ≤ 3 cm and no macrovascular invasion on imaging)[7]. In the original study published in 1996, patients transplanted within the Milan criteria have a 5-year post-transplant survival of 70% and a 5-year tumor recurrence rate of less than 10%[8]. A meta-analysis of 19 studies including 3949 patients confirmed better post-transplant survival in patients meeting the Milan criteria at the time of the explant pathology examination[9]. In 2002, the Milan criteria were incorporated in the Tumor Node Metastasis staging system[10], and adopted as a prioritization tool in the United Network of Organ Sharing (UNOS)[11]. Today, clinical practice guidelines and consensus conference recommend the Milan criteria as a reference for the selection of patients with HCC for LT worldwide (Table 1)[12-19]. According to American and European guidelines, the Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely-accepted system to assess the prognosis of patients with HCC and to suggest treatment allocation[12,14]. In the BCLC system, the Milan criteria are represented by simplification of the watershed between the early and intermediate stage[7]. An exception to this simplification is patients with large solitary HCCs (≥5 cm) without vascular invasion that are assigned to the early stage and should be considered for resection[20]. According to the BCLC system, LT should be offered only to patients with early HCC, while patients in the intermediate stage should be treated in first line by transarterial chemoembolization (TACE)[7]. Nevertheless, the Milan criteria are often considered restrictive, and some patients with HCC in the intermediate stage can benefit from LT[21].

In 2001, the University of California San Francisco (UCSF) criteria (single HCC ≤ 6.5 cm or ≤ 3 nodules at most with the largest ≤ 4.5 cm and total tumor diameter ≤ 8 cm) demonstrated a 5-year post-transplant survival of 75% and a 5-year tumor recurrence rate of 11%[22]. UCSF criteria have been validated by the proponent group with preoperative radiological staging[23], and the outcomes have been confirmed by other retrospective studies[24,25]. The limitation of the UCSF criteria is that it has much overlap with the Milan criteria, and at best, would increase the proportion of patients available for LT by approximately 20%[26]; despite this, it was estimated that the adoption of the UCSF criteria within the Organ Procurement and Transplantation Network (OPTN) would increase on-list mortality by 44% for both HCC and non-HCC patients[27].

In 2009, Mazzaferro et al[28] presented a retrospective analysis of data based on post-explant pathology among 1556 patients with HCC (70% exceeding Milan criteria) who underwent transplantation at 36 centers. Survival was correlated with the size of the largest nodule, the number of nodules, and the presence of microvascular invasion in explants. The authors developed a predictive model, called the Metroticket calculator, to estimate the 5-year overall survival of patients undergoing LT according to the number and size of the nodules, incorporating nodules with a diameter greater than 10 mm and no more than 10 nodules. In conclusion, they showed that 283 patients exceeding the Milan criteria, who fell within a new selection criteria called the "up-to-7 criteria" (the sum of the largest tumor diameter in centimeters and
the number of nodules is ≤ 7, without microvascular invasion), have a 5-year post-transplant survival of 71% and a 5-year tumor recurrence rate of 9%. The main drawback of the up-to-7 criteria is that it includes a histological parameter that is not available before LT in the prognostic model.

D’Amico et al. evaluated the up-to-7 criteria (defined without considering microvascular invasion) in a retrospective pathological study of 479 explanted livers from two centers and reported a 5-year recurrence rate of 14%; interestingly, patients beyond the up-to-7 criteria but without macrovascular invasion and poorly differentiated grade had a 5-year recurrence rate of only 24%. Raj et al. externally validated the Metroticket calculator (calculated on pre-transplant radiological data) in a retrospective cohort of 97 patients listed for HCC, showing a 5-year predicted and observed post-transplant survival of 69.7% and 74% respectively. A prospective validation of the up-to-7 criteria using pre-transplant radiological reports is still lacking. In 2012, the BCLC B subclassification proposal selected the up-to-7 criteria to distinguish major from minor tumor burden within intermediate HCC, and considered these patients for transplantation, either according to the extended criteria or downstaging policy.

Some expansions of the up-to-7 criteria have been reported in the literature. For example, the current United Kingdom listing criteria consider a single nodule ≤ 5 cm, ≤ 3 cm up to 5 nodules, or single nodule > 5 cm and ≤ 7 cm, where there has been no evidence of tumor progression (volume increase by < 20%), no extrahepatic spread, and no new nodule formation over a 6-mo period in which loco-regional treatments may be given.

### MAIN ISSUES IN THE STAGING OF HCC BEFORE LT

In most studies, a discrepancy between the radiological staging at listing and the pathological staging conducted on explanted liver was observed; the overall accuracy was less than 50% in a retrospective analysis of 789 liver transplant recipients of the UNOS/OPTN database. Both understaging and overstaging were reported, mainly because of 25% inaccuracy in the predicted number of nodules, while the largest nodule size is relatively reproducible. Although adverse histopathological factors (poor differentiation and/or microvascular invasion) generally correlate with nodule number and size, about 20% of patients within the Milan criteria have these characteristics, increasing the risk of recurrence in this subgroup. Correct staging is crucial in selecting patients with HCC for inclusion on the waiting list for LT.

The gold standard of imaging is dynamic computed tomography (CT) or magnetic resonance imaging (MRI), including unenhanced, arterial, portal venous, and delayed phases. Typical imaging patterns rely on the presence of arterial enhancement, followed by washout on portal venous or delayed imaging, and is specific for HCC in nodules > 10 mm in cirrhotic livers. CT and MRI are also standard tests to characterize number, size and location of nodules, and exclude macrovascular invasion and extrahepatic spread. CT and MRI examinations should follow established protocols, which define the amount and rate of contrast given, the precise individualized timing of image acquisition and image reconstruction with minimum slice thickness. According to a recent study, MRI seems slightly superior to CT in recognizing the typical vascular pattern for HCC (sensitivity 82% vs 67%, specificity 95% vs 90%). Further added value of MRI with respect to CT is made up of diffusion-weighted MRI and MRI hepatobiliary contrast agents. According to AASLD and EASL guidelines, chest CT and bone scan should be performed to exclude metastatic spread, but the incidence of bone metastases in patients with HCC at an early stage is very low, and the cost-effectiveness of bone scintigraphy debated.

Pre-transplant evaluation of patients with HCC is one of the few areas in which the measurement of serum alpha-fetoprotein (AFP) is still of clinical significance, representing a surrogate marker of biological aggressiveness and an independent predictor of post-transplant survival. Many studies demonstrated that AFP is a surrogate marker of adverse pathological findings (tumor differentiation,
microvascular invasion and/or satellite nodules) which are established risk factors for post-transplant HCC recurrence.\textsuperscript{[41-43]} Duvoux et al.\textsuperscript{[41]} showed that AFP level improves the predictive ability of the Milan criteria, owing to its ability to identify subgroups of patients at high risk of recurrence (> 1000 ng/mL within Milan criteria and > 100 mg/mL beyond Milan criteria). Cut-off AFP levels of 300 ng/mL, 400 ng/mL, and 1000 ng/mL have been proposed for inclusion on the waiting list for LT and/or for drop-out\textsuperscript{[40,41,44]}. An alternative approach proposed as dropout criteria for dynamic measurement of AFP, called progression of AFP, is defined as a steady increase of AFP level > 15 ng/mL per month during the waiting list\textsuperscript{[42]}. In the last few years, new scores integrating AFP into preoperative radiology staging have been designed and validated. Duvoux et al.\textsuperscript{[41]} proposed a new predictive score for HCC recurrence, namely the AFP model, which assigns a score between 0-9 based on the number of nodules, maximum diameter of the largest nodule and AFP level at listing, where low-risk patients (score ≤ 2) had a 5-year survival of 68% and a recurrence rate of 9%. The AFP model was subsequently externally validated and officially adopted by the French organization Organ Sharing for HCC patients\textsuperscript{[45]}. Toso et al.\textsuperscript{[46,47]} proposed and validated a new composite criteria including total tumor volume (TTV; ≤ 115 cm\(^3\)) and AFP (≤ 400 ng/mL); patients transplanted within these criteria showed an overall 5-year survival of 75% and a recurrence rate of 9%, at the cost of higher risk of dropout in comparison to patients within the Milan criteria and patients transplanted beyond the Milan criteria; prospective validation of these markers could open a new indication for preoperative biopsy.

Increased uptake of fluorine-18-fludeoxyglucose ([18F]-FDG) at preoperative positron emission tomography (PET) is an independent risk factor for HCC recurrence post-transplant\textsuperscript{[54]}. At present, high costs, lack of external prospective validation on large western cohorts, and lack of cost-effective analysis limit widespread use of PET in LT candidates\textsuperscript{[55]}.

**DOWNSTAGING OF INTERMEDIATE HCC BEFORE LT**

Down-staging is defined as the reduction of the HCC burden with locoregional therapy to meet the eligibility criteria for LT. According to the International Consensus Conference, successful downstaging should achieve a 5-year post-transplant survival compared to HCC patients who meet the criteria for LT without requiring downstaging\textsuperscript{[19]}. This recommendation originates from a balance between the patient’s perspective, who otherwise had no other effective treatment option, and that of the transplant community, who should justify allocation of a scarce organ to these patients. Two prospective large single-center studies from Bologna and San Francisco compared successfully downstaged patients within the Milan criteria and patients who initially met the Milan criteria (most of whom underwent bridging treatments while awaiting LT). Eligibility criteria for downstaging in these studies are reported in Table 3. The downstaging success rate was around 70%, and the transplant rate of patients within and beyond the Milan criteria were similar. Both studies showed similar post-transplant survival, intention-to-treat survival and HCC recurrence for downstaged patients and the control group, but a higher rate of dropout from the waitlist for downstaged patients\textsuperscript{[56-58]}. Most employed locoregional treatments include...
TACE and percutaneous or laparoscopic radiofrequency ablation (RFA) or combination treatments, but percutaneous ethanol injection (PEI), resection, transarterial chemoembolization, radioembolization, and even sorafenib were used. The type of treatment is generally determined on a case-by-case basis, also accounting for the severity of the underlying liver disease; there is no evidence that one type of locoregional treatment is superior to another, as each carries some risk.[59]

According to EASL guidelines, response to downstaging treatment should be based on the radiographic measurements of the maximal diameter of viable nodules that enhanced CT or MRI, not including the area of necrosis (modified RECIST criteria).[60] It is unclear if inclusion on the waiting list for LT patients with HCC was successfully downstaged to meet transplant criteria, at the same time exhibiting tumor progression by mRECIST criteria, often as a result of the development of a new lesion.[58,61] Most reports have used the Milan criteria as the endpoint for successful downstaging, whereas upper limits in terms of tumor size and number for eligibility to downstaging are debated; generally, the presence of macrovascular invasion, extrahepatic spread and probable levels of AFP > 1000 ng/mL are considered absolute contraindications.[60,62,63]

According to most protocols, at least 3-6 mo of observation is required after successful downstaging. This biological selection criterion (the time acting as surrogate marker of tumor aggressiveness) is based on an original study by Otto et al.[63] who showed that patients with sustained complete response to TACE during the waiting time had 5-years recurrence-free survival after LT of 95%, vs 35% of patients with progression during waitlist after an initial response to TACE. It is likely that the waiting time, before or after listing, allows exclusion of the more biologically unfavorable HCCs, especially within the group beyond Milan, and that early transplantation could worsen post-transplant outcomes.[64] It is currently being debated whether the efficacy of downstaging depends on an effective neoadjuvant therapy or a selection tool of HCCs with a more favorable biology.[65] Since dropping out from the waiting list, poorer post-transplant survival and higher tumor recurrence rate are dependent on the long waiting time to balance the minimal observation period of disease stabilization and priority allocation for downstaged patients, which remains a challenge.

When downstaged patients are listed, they undergo CT or MRI scan and AFP determination at least every 3 mo. If HCC progresses after listing beyond the transplant criteria, patients are temporarily removed from the waiting list (delisting), and a new downstaging treatment may be considered. For patients who respond to the initial downstaging process, further treatment (bridge therapy) of residual tumors by TACE and/or RFA should be considered, where the waiting time is expected to be at least 6 mo, in order to reduce drop-out risk.[59,65] It must be remembered that in all studies that evaluated the applicability of expanded criteria against the Milan criteria, the majority of patients received downstaging treatments.

| Protocol          | Inclusion criteria                                                                 | Criteria for successful downstaging | Minimal observation period | Ref. |
|-------------------|------------------------------------------------------------------------------------|--------------------------------------|-----------------------------|------|
| Bologna “rule of six” | Single HCC ≤ 6 cm  
2 HCC ≤ 5 cm  
Less than 6 HCCs ≤ 4 cm and a total tumor diameter ≤ 12 cm  
Absence of vascular or biliary invasion on CT/MRI  
AFP < 400 ng/mL during waiting time | Milan criteria | 3 mo | 56 |
| San Francisco (UCSF) | Single HCC ≤ 8 cm  
2 or 3 HCC ≤ 5 cm (total tumor diameters ≤ 8 cm)  
4 or 5 HCC ≤ 3 cm (sum of maximal tumor diameters ≤ 8 cm)  
Absence of vascular invasion on CT/MRI | Milan criteria | 3 mo | 58 |

CT: Computed tomography; MRI: Magnetic resonance imaging; HCC: Hepatocellular carcinoma.

**ORGAN ALLOCATION POLICIES FOR LT CANDIDATES WITH AND WITHOUT HCC**

Allocation rules are constantly being adjusted to minimize the imbalance between the priorities of HCC and non-HCC candidates in terms of drop-out rate and post-transplant survival. The need to allocate the scarce resources ethically, and with equity and justice is generally addressed today by referring to the principles of urgency, utility and benefit (Table 4).[66]

Urgency refers to an allocation policy aimed at minimizing the risk of drop-out from the waiting list and prioritizing candidates with worse pre-LT prognosis (“sickest patient first”). In non-HCC patients, liver disease severity is ranked through the Model for End-stage Liver Disease (MELD) score, which is based on serum creatinine, serum total bilirubin, and INR, which can accurately predict 3-mo mortality.[67] Under the MELD allocation system, the priority for patients with HCC is assigned using arbitrary exception points based on the HCC stage and waiting time, corresponding to an estimation of a 10% waitlist drop-out. This MELD-based allocation system has been criticized because of...
Table 4  Liver graft allocation policies for candidates to liver transplantation with and without hepatocellular carcinoma

| Principle | Reference outcome | Tools for prioritization | Comments |
|-----------|------------------|--------------------------|----------|
| Urgency   | Risk of drop-out from the waiting list | MELD | MELD exception points, adjusted MELD, HCC-MELD equation, deMELD |
| Utility   | Post-LT patient (graft) survival | DRI, D-MELD | Milan criteria |
| Benefit   | Post-LT patient benefit | Minimum value of MELD score > 15 | HCC-MELD |

LT: Liver transplantation; HCC: Hepatocellular carcinoma; MELD: Model for end-stage liver disease; DRI: Donor risk index; D-MELD: MELD and donor age.

overestimation of drop-out risk for HCC patients, who consequently have easier access to transplantation than non-HCC ones, and failure to incorporate surrogate markers of biological aggressiveness of HCC (AFP, response to loco-regional treatments)\(^6\)\(^8\).

Utility refers to an allocation policy centered on liver graft and the duty of the transplant community to maximize a limited resource. The reference outcomes are post-transplant graft and patient survival, and patients with the lowest post-transplant mortality are prioritized. Since donor characteristics significantly affect liver transplantation outcomes, a proper allocation based on utility takes into account donor and recipient characteristics and donor-recipient matching. Donor Risk Index (DRI), which includes donor age, donation after cardiac death, split/partial grafts, race, height, cause of brain death, donor location, and cold ischemia time, has been proposed to inform the process of organ acceptance\(^6\)\(^9\). D-MELD is the arithmetic product of donor age and recipient MELD score, and has been proposed in order to predict the outcome after LT and optimize donor-recipient matching\(^7\)\(^0\). As previously reported, the Milan criteria identify HCC patients with the best post-transplant survival.

Benefit refers to the allocation policy aimed at maximizing the life-saving potential of procured livers by prioritizing patients based on their gained lifetime from the transplantation. It is expressed by a gain in life years and is estimated by the difference between the number of years gained by the transplant minus the number of years offered by alternative treatments or best supportive care\(^7\)\(^1\). In non-HCC patients, transplant benefit has been used to demonstrate that patients with a MELD < 15 may not improve their risk of death by receiving a transplant compared to remaining on the list\(^7\)\(^2\). By contrast, HCC candidates appear to have a positive 5-year survival benefit after transplantation for every stage, provided macrovascular invasion and extrahepatic spread have been excluded\(^7\)\(^3\). If benefit is applied to HCC without adjustments, it may prioritize patients at the highest risk or recurrence, therefore, it is crucial to account for the feasibility of alternative treatments and accurately evaluate transplant benefit for HCC patients\(^7\)\(^4\).

Many urgency-based scores (adjusted MELD, HCC-MELD equation, deMELD), based on parameters such as native MELD score, size and number of HCC nodules and AFP levels, have been proposed to refine the drop-out risk from the waiting list, but their impact on post-transplant survival and recurrence remains unclear\(^7\)\(^5\)\(^-7\)\(^7\). The most promising is represented by the HCC-MELD system, which allows the comparison of HCC patients to non-HCC patients in the same numerical MELD score, and considers 5-year transplant benefit as the endpoint\(^7\)\(^8\). The HCC-MELD score (equation 1.27*MELD -0.51/logAFP +4.59) gives considerable weight to the severity of liver function impairment as an indication of the inapplicability of alternative therapies, and reflects the negative impact of AFP on post-transplant prognosis, but this system still needs validation.

It should be underlined that allocation policies are influenced by the national/regional dynamics of the waiting list, including donor rate, median waiting time, proportion of patients with HCC in the waitlist, and median MELD of non-HCC patients on the waitlist. Lastly, the introduction of direct antiviral agents in daily practice has led to increased organ availability for patients with HCC, since this class of drugs were able to reverse liver dysfunction and favored the inactivation and delisting of about 1 patient out of 3, and 1 patient out of 5 in about one year, respectively\(^7\)\(^9\).

CONCLUSION

Recently, a benefit-oriented “adaptive approach” was proposed in order to reach an agreement between different positions on tumor stage, response to treatments and priority in allocation in a sustainable manner with respect to donors’ shortage\(^8\)\(^0\),\(^8\)\(^1\). In this approach, excluding patients with macrovascular invasion, extrahepatic spread, comorbidities, and age beyond limits, all referred patients with early and intermediate and even end-stage HCC are considered “transplantable”. With the exception of patients with end-stage HCC meeting transplant criteria and listed according to the MELD score, all other HCC patients should undergo a first-line non-transplantation treatment (resection, RFA, TACE, combination...) on a case-by-case basis. The subsequent transplant process would depend on the response to treatment:
low priority for LT in case of complete response, high priority in case of partial response or recurrence, no listing in case of progression or recurrence over transplantation criteria. Conventional or expanded transplantation criteria should be established according to the local donor rate and waitlist dynamics. Patients over transplantation criteria should be considered only after successful downstaging and 3-mo stability in meeting the transplantation criteria. AFP response should be evaluated in parallel with radiological response, and should inform eligibility, priority and drop-out of patients.

We believe that this approach, properly modulated in local realities in terms of transplantation criteria, eligibility for downstaging protocols and allocation priorities, can be a sustainable compromise to allow physicians to offer LT to most patients with transplantable HCC.

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P- Reviewer: Frankova S, Tchilikidi KY, Xu X S- Editor: Yu J L- Editor: A E- Editor: Wang CH
