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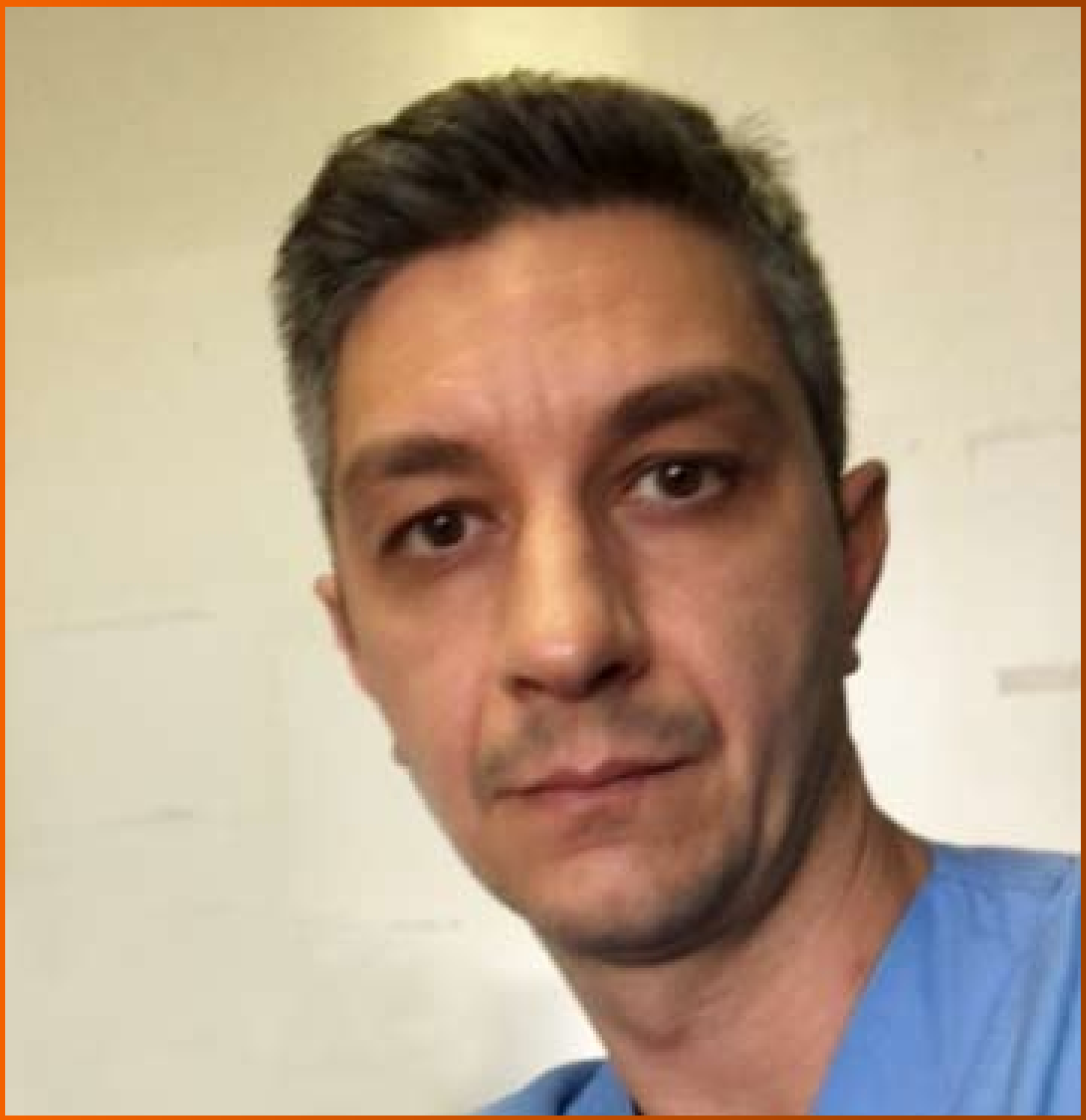

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EDITORIAL

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

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 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.

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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 $\leqslant$ 5 cm or $\leqslant$ 3 nodules each $\leqslant$ 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 $\leqslant$ 6.5 cm or $\leqslant$ 3 nodules at most with the largest $\leqslant$ 4.5 cm and total tumor diameter $\leqslant$ 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

Table 1 Indications for liver transplantation in patients with hepatocellular carcinoma according to current guidelines

International society	Year	Listing criteria	Downstaging	Ref.
American Association for the Study of Liver Diseases (AASLD) for hepatocellular carcinoma	2010	Milan criteria	No	[12]
American Association for the Study of Liver Diseases (AASLD) for liver transplant	2013	Milan criteria	Yes	[13]
European Association for the Study of the Liver (EASL), European Organisation For Research And Treatment Of Cancer (EORTC)	2011	Milan criteria	No	[14]
European Society for Medical Oncology (ESMO), European Society of Digestive Oncology (ESDO)	2012	Milan criteria	No	[15]
Asian Pacific Association for the Study of the Liver (APASL)	2010	Milan criteria	No	[16]
Japan Society of Hepatology (JSH)	2014	Milan criteria	No	[17]
American Hepato-Pancreato-Biliary Association (AHPBA)	2010	Milan criteria	Yes	[18]
International Consensus Conference	2010	Milan criteria	Yes	[19]

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*[29] 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*[30] 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[21].

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[31].

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[32]. 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[33,34]. 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[28,29]. Correct staging is crucial in selecting patients with HCC for inclusion on the waiting list for LT (Table 2).

The gold standard of imaging is dynamic computed tomography (CT) or magnetic resonance imaging (MRI), including unenhanced, arterial, portal venous, and delayed phases[19]. 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[7]. 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[35]. 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%)[36]. Further added value of MRI with respect to CT is made up of diffusion-weighted MRI and MRI hepatobiliary contrast agents[37,38]. According to AASLD and EASL guidelines[12-14], chest CT and bone scan should be performed to exclude metastatic spread; however, the incidence of bone metastases in patients with HCC at an early stage is very low, and the cost-effectiveness of bone scintigraphy debated[39].

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[40]. Many studies demonstrated that AFP is a surrogate marker of adverse pathological findings (tumor differentiation,

Table 2 Preoperative stadiation for patients with hepatocellular carcinoma evaluated for liver transplantation

Diagnostic test	Indications	Comments
Computed tomography (CT) with contrast medium of chest-abdomen-pelvis	Standard test to perform the diagnosis of hepatocellular carcinoma (HCC) in cirrhotic livers to characterize number, size and location of nodules, and exclude macrovascular invasion and extrahepatic spread	Require adherence to established protocols for optimization
Magnetic resonance imaging (MRI) with contrast medium of abdomen	Slightly superior to CT according to recent data	Consider in individual patients
Bone scan	Standard test to exclude bone spread	Cost-effectivity debated
Alpha-fetoprotein (AFP)	Center-specific cut-off for inclusion on the list and drop-out	Surrogate marker of biological aggressiveness
Preoperative biopsy	Proposed to assess tumor grading	Low accuracy
Positron emission tomography (PET)	Proposed predictor of HCC recurrence	Cost-effectivity unclear

microvascular invasion and/or satellite nodules) which are established risk factors for post-transplant HCC recurrence[41-43]. Duvoux *et al*[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[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[42]. In the last few years, new scores integrating AFP into preoperative radiology staging have been designed and validated. Duvoux *et al*[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 $\leqslant$ 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[45]. Toso *et al*[46,47] proposed and validated a new composite criteria including total tumor volume (TTV; $\leqslant$ 115 cm^3) and AFP ($\leqslant$ 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 (42% *vs* 25%). The Hangzhou criteria (total tumor diameter < 8 cm, or any tumor diameter but AFP $\leqslant$ 400 ng/mL and well-moderated differentiation simultaneously) provided an expansion of 51.5% compared to the Milan criteria, with comparable post-transplant survivals[48]. Finally, an update of pre-operative Metroticket calculator was developed including serum AFP levels[49].

Some centers proposed tumor grading, pre-operatively assessed by needle biopsy of liver nodules, as selection criteria, reserving only patients with well or moderately-differentiated HCC[50] for inclusion on the waiting list for LT. Despite low risk of tumor seeding and hemorrhage, the obtained results often did not correlate with grade or presence of microscopic vascular invasion on final pathology, maybe due to possible heterogeneity of differentiation in diverse areas of the tumor[51,52]. In 2015, Miltiadous *et al*[53] described two progenitor cell markers (Cytokeratin 19 and S2 signatures) in explant tumors that independently predict tumor recurrence in 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[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[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[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 down-staged 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 down-staged patients and the control group, but a higher rate of drop-out from the waitlist for downstaged patients[56-58].

Most employed locoregional treatments include

Table 3 Eligibility criteria for downstaging of hepatocellular carcinoma before liver transplantation

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.

TACE and percutaneous or laparoscopic radiofrequency ablation (RFA) or combination treatments, but percutaneous ethanol injection (PEI), resection, transarterial chemoinfusion, 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[19,58].

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*[62], 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[63]. 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[64]. 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.

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
		Non-HCC	HCC	
Urgency	Risk of drop-out from the waiting list	MELD	MELD exception points, adjusted MELD, HCC-MELD equation, deMELD	"Sickest patient first"
Utility	Post-LT patient (graft) survival	DRI, D-MELD	Milan criteria	Donor/recipient matching
Benefit	Post-LT patient benefit	Minimum value of MELD score ⩾ 15	HCC-MELD	Feasibility of alternative treatments

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)[68].

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[69]. 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[70]. 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[71]. 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[72]. 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[73]. 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[74].

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[75-77]. 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[78]. 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[79].

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[80,81]. 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.

REFERENCES

1 Accessed 2017-01-12. Available from: URL: https://srtr.transplant.hrsa.gov/annual_reports/2012/Default.aspx
2 **White DL**, Thrift AP, Kanwal F, Davila J, El-Serag HB. Incidence of Hepatocellular Carcinoma in All 50 United States, From 2000 Through 2012. *Gastroenterology* 2017; **152**: 812-820.e5 [PMID: 27889576 DOI: 10.1053/j.gastro.2016.11.020]
3 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]
4 **Prasad KR**, Young RS, Burra P, Zheng SS, Mazzaferro V, Moon DB, Freeman RB. Summary of candidate selection and expanded criteria for liver transplantation for hepatocellular carcinoma: a review and consensus statement. *Liver Transpl* 2011; **17** Suppl 2: S81-S89 [PMID: 21748847 DOI: 10.1002/lt.22380]
5 International Agency for Research on Cancer, 2011. Accessed 2017-02-03
6 European Liver Transplant Registry, 2011. Accessed 2017-02-03
7 **Bruix J**, Reig M, Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. *Gastroenterology* 2016; **150**: 835-853 [PMID: 26795574 DOI: 10.1053/j.gastro.2015.12.041]
8 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428 DOI: 10.1056/NEJM199603143341104]
9 **Mazzaferro V**, Bhoori S, Sposito C, Bongini M, Langer M, Miceli R, Mariani L. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. *Liver Transpl* 2011; **17** Suppl 2: S44-S57 [PMID: 21695773 DOI: 10.1002/lt.22365]
10 **American Joint Committee on cancer**. Cancer staging handbook. TNM liver classification. In: Greene FL, Page DL, Fleming ID. Editor American Joint Committee on cancer staging manual. 6th ed. New York: Springer-Verlag, 2002: 131-144
11 United Network for Organ Sharing, Policy 3.6. Available from: URL: https://optn.transplant.hrsa.gov/governance/policies/
12 **Bruix J**, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022 [PMID: 21374666 DOI: 10.1002/hep.24199]
13 **Martin P**, DiMartini A, Feng S, Brown R, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology* 2014; **59**: 1144-1165 [PMID: 24716201]
14 **European Association For The Study Of The Liver**, European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]
15 **Verslype C**, Rosmorduc O, Rougier P. Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; **23** Suppl 7: vii41-vii48 [PMID: 22997453 DOI: 10.1093/annonc/mds225]
16 **Omata M**, Lesmana LA, Tateishi R, Chen PJ, Lin SM, Yoshida H, Kudo M, Lee JM, Choi BI, Poon RT, Shiina S, Cheng AL, Jia JD, Obi S, Han KH, Jafri W, Chow P, Lim SG, Chawla YK, Budihusodo U, Gani RA, Lesmana CR, Putranto TA, Liaw YF, Sarin SK. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. *Hepatol Int* 2010; **4**: 439-474 [PMID: 20827404 DOI: 10.1007/s12072-010-9165-7]
17 **Kudo M**, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, Okusaka T, Miyayama S, Tsuchiya K, Ueshima K, Hiraoka A, Ikeda M, Ogasawara S, Yamashita T, Minami T, Yamakado K. JSH Consensus-Based Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma: 2014 Update by the Liver Cancer Study Group of Japan. *Liver Cancer* 2014; **3**: 458-468 [PMID: 26280007 DOI: 10.1159/000343875]
18 **Munene G**, Vauthey JN, Dixon E. Summary of the 2010 AHPBA/SSO/SSAT Consensus Conference on HCC. *Int J Hepatol* 2011; **2011**: 565060 [PMID: 21994863 DOI: 10.4061/2011/565060]
19 **Clavien PA**, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol* 2012; **13**: e11-e22 [PMID: 22047762 DOI: 10.1016/S1470-2045(11)70175-9]
20 **Forner A**, Gilabert M, Bruix J, Raoul JL. Treatment of intermediate-stage hepatocellular carcinoma. *Nat Rev Clin Oncol* 2014; **11**: 525-535 [PMID: 25091611 DOI: 10.1038/nrclinonc.2014.122]
21 **Bolondi L**, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, Raoul JL, Sangro B. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. *Semin Liver Dis* 2012; **32**: 348-359 [PMID: 23397536 DOI: 10.1055/s-0032-1329906]
22 **Yao FY**, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; **33**: 1394-1403 [PMID: 11391528 DOI: 10.1053/jhep.2001.24563]
23 **Yao FY**, Xiao L, Bass NM, Kerlan R, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging. *Am J Transplant* 2007; **7**: 2587-2596 [PMID: 17868066 DOI: 10.1111/j.1600-6143.2007.01965.x]
24 **Duffy JP**, Vardanian A, Benjamin E, Watson M, Farmer DG, Ghobrial RM, Lipshutz G, Yersiz H, Lu DS, Lassman C, Tong MJ, Hiatt JR, Busuttil RW. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. *Ann Surg* 2007; **246**: 502-509; discussion 509-511 [PMID: 17717454 DOI: 10.1097/SLA.0b013e318148c704]
25 **Chen JW**, Kow L, Verran DJ, McCall JL, Munn S, Balderson GA, Fawcett JW, Gow PJ, Jones RM, Jeffrey GP, House AK, Strasser SI. Poorer survival in patients whose explanted hepatocellular carcinoma (HCC) exceeds Milan or UCSF Criteria. An analysis of liver transplantation in HCC in Australia and New Zealand. *HPB* (Oxford) 2009; **11**: 81-89 [PMID: 19590628 DOI: 10.1111/j.1477-2574.2009.00022.x]
26 **Toso C**, Kneteman NM, James Shapiro AM, Bigam DL. The estimated number of patients with hepatocellular carcinoma selected for liver transplantation using expanded selection criteria.

Transpl Int 2009; **22**: 869-875 [PMID: 19386075 DOI: 10.1111/j.1432-2277.2009.00882.x]

27 **Volk ML**, Vijan S, Marrero JA. A novel model measuring the harm of transplanting hepatocellular carcinoma exceeding Milan criteria. *Am J Transplant* 2008; **8**: 839-846 [PMID: 18318783 DOI: 10.1111/j.1600-6143.2007.02138.x]

28 **Mazzaferro V**, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T, Roayaie S, Schwartz ME, Grazi GL, Adam R, Neuhaus P, Salizzoni M, Bruix J, Forner A, De Carlis L, Cillo U, Burroughs AK, Troisi R, Rossi M, Gerunda GE, Lerut J, Belghiti J, Boin I, Gugenheim J, Rochling F, Van Hoek B, Majno P. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009; **10**: 35-43 [PMID: 19058754 DOI: 10.1016/S1470-2045(08)70284-5]

29 **D'Amico F**, Schwartz M, Vitale A, Tabrizian P, Roayaie S, Thung S, Guido M, del Rio Martin J, Schiano T, Cillo U. Predicting recurrence after liver transplantation in patients with hepatocellular carcinoma exceeding the up-to-seven criteria. *Liver Transpl* 2009; **15**: 1278-1287 [PMID: 19790142 DOI: 10.1002/lt.21842]

30 **Raj A**, McCall J, Gane E. Validation of the "Metroticket" predictor in a cohort of patients transplanted for predominantly HBV-related hepatocellular carcinoma. *J Hepatol* 2011; **55**: 1063-1068 [PMID: 21354447 DOI: 10.1016/j.jhep.2011.01.052]

31 **Menon KV**, Hakeem AR, Heaton ND. Review article: liver transplantation for hepatocellular carcinoma - a critical appraisal of the current worldwide listing criteria. *Aliment Pharmacol Ther* 2014; **40**: 893-902 [PMID: 25155143 DOI: 10.1111/apt.12922]

32 **Freeman RB**, Mithoefer A, Ruthazer R, Nguyen K, Schore A, Harper A, Edwards E. Optimizing staging for hepatocellular carcinoma before liver transplantation: A retrospective analysis of the UNOS/OPTN database. *Liver Transpl* 2006; **12**: 1504-1511 [PMID: 16952174 DOI: 10.1002/lt.20847]

33 **Shah SA**, Tan JC, McGilvray ID, Cattral MS, Cleary SP, Levy GA, Greig PD, Grant DR. Accuracy of staging as a predictor for recurrence after liver transplantation for hepatocellular carcinoma. *Transplantation* 2006; **81**: 1633-1639 [PMID: 16794527 DOI: 10.1097/01.tp.0000226069.66819.7e]

34 **Grasso A**, Stigliano R, Morisco F, Martines H, Quaglia A, Dhillon AP, Patch D, Davidson BR, Rolles K, Burroughs AK. Liver transplantation and recurrent hepatocellular carcinoma: predictive value of nodule size in a retrospective and explant study. *Transplantation* 2006; **81**: 1532-1541 [PMID: 16770242 DOI: 10.1097/01.tp.0000209641.88912.15]

35 **Kneteman N**, Livraghi T, Madoff D, de Santibañez E, Kew M. Tools for monitoring patients with hepatocellular carcinoma on the waiting list and after liver transplantation. *Liver Transpl* 2011; **17** Suppl 2: S117-S127 [PMID: 21584926 DOI: 10.1002/lt.22334]

36 **Leoni S**, Piscaglia F, Golfieri R, Camaggi V, Vidili G, Pini P, Bolondi L. The impact of vascular and nonvascular findings on the noninvasive diagnosis of small hepatocellular carcinoma based on the EASL and AASLD criteria. *Am J Gastroenterol* 2010; **105**: 599-609 [PMID: 19935786 DOI: 10.1038/ajg.2009.654]

37 **Di Martino M**, De Filippis G, De Santis A, Geiger D, Del Monte M, Lombardo CV, Rossi M, Corradini SG, Mennini G, Catalano C. Hepatocellular carcinoma in cirrhotic patients: prospective comparison of US, CT and MR imaging. *Eur Radiol* 2013; **23**: 887-896 [PMID: 23179521 DOI: 10.1007/s00330-012-2691-z]

38 **Samanci C**, Sobhani F, Ucbilek E, Rakestraw K, Dagher NN, Kamel IR, Gurakar A. Magnetic Resonance Imaging in Diagnosis and Monitoring of Hepatocellular Carcinoma in Liver Transplantation: A Comprehensive Review. *Ann Transplant* 2016; **21**: 68-76 [PMID: 26831626 DOI: 10.12659/AOT.895595]

39 **Rodríguez S**, Balbinotto Neto G, Kiss G, Brandão A. Cost-effectiveness of whole-body bone scans in the pre-liver transplant assessment of patients with hepatocellular carcinoma in Southern Brazil. *Clin Transplant* 2016; **30**: 399-406 [PMID: 26783162 DOI: 10.1111/ctr.12699]

40 **Berry K**, Ioannou GN. Serum alpha-fetoprotein level independently predicts posttransplant survival in patients with hepatocellular carcinoma. *Liver Transpl* 2013; **19**: 634-645 [PMID: 23536495 DOI: 10.1002/lt.23652]

41 **Duvoux C**, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, Francoz C, Compagnon P, Vanlemmens C, Dumortier J, Dharancy S, Gugenheim J, Bernard PH, Adam R, Radenne S, Muscari F, Conti F, Hardwigsen J, Pageaux GP, Chazouillères O, Salame E, Hilleret MN, Lebray P, Abergel A, Debette-Gratien M, Kluger MD, Mallat A, Azoulay D, Cherqui D. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. *Gastroenterology* 2012; **143**: 986-994.e3; quiz e14-15 [PMID: 22750200 DOI: 10.1053/j.gastro.2012.05.052]

42 **Vibert E**, Azoulay D, Hoti E, Iacopinelli S, Samuel D, Salloum C, Lemoine A, Bismuth H, Castaing D, Adam R. Progression of alphafetoprotein before liver transplantation for hepatocellular carcinoma in cirrhotic patients: a critical factor. *Am J Transplant* 2010; **10**: 129-137 [PMID: 20070666 DOI: 10.1111/j.1600-6143.2009.02750.x]

43 **Liu C**, Xiao GQ, Yan LN, Li B, Jiang L, Wen TF, Wang WT, Xu MQ, Yang JY. Value of α-fetoprotein in association with clinicopathological features of hepatocellular carcinoma. *World J Gastroenterol* 2013; **19**: 1811-1819 [PMID: 23555170 DOI: 10.3748/wjg.v19.i11.1811]

44 **Pomfret EA**, Washburn K, Wald C, Nalesnik MA, Douglas D, Russo M, Roberts J, Reich DJ, Schwartz ME, Mieles L, Lee FT, Florman S, Yao F, Harper A, Edwards E, Freeman R, Lake J. Report of a national conference on liver allocation in patients with hepatocellular carcinoma in the United States. *Liver Transpl* 2010; **16**: 262-278 [PMID: 20209641 DOI: 10.1002/lt.21999]

45 **Notarpaolo A**, Layese R, Magistri P, Gambato M, Colledan M, Magini G, Miglioresi L, Vitale A, Vennarecci G, Ambrosio CD, Burra P, Di Benedetto F, Fagiuoli S, Colasanti M, Maria Ettorre G, Andreoli A, Cillo U, Laurent A, Katsahian S, Audureau E, Roudot-Thoraval F, Duvoux C. Validation of the AFP model as a predictor of HCC recurrence in patients with viral hepatitis-related cirrhosis who had received a liver transplant for HCC. *J Hepatol* 2017; **66**: 552-559 [PMID: 27899297 DOI: 10.1016/j.jhep.2016.10.038]

46 **Toso C**, Asthana S, Bigam DL, Shapiro AM, Kneteman NM. Reassessing selection criteria prior to liver transplantation for hepatocellular carcinoma utilizing the Scientific Registry of Transplant Recipients database. *Hepatology* 2009; **49**: 832-838 [PMID: 19152426 DOI: 10.1002/hep.22693]

47 **Toso C**, Meeberg G, Hernandez-Alejandro R, Dufour JF, Marotta P, Majno P, Kneteman NM. Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: A prospective validation. *Hepatology* 2015; **62**: 158-165 [PMID: 25777590 DOI: 10.1002/hep.27787]

48 **Xu X**, Lu D, Ling Q, Wei X, Wu J, Zhou L, Yan S, Wu L, Geng L, Ke Q, Gao F, Tu Z, Wang W, Zhang M, Shen Y, Xie H, Jiang W, Wang H, Zheng S. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria. *Gut* 2016; **65**: 1035-1041 [PMID: 25804634 DOI: 10.1136/gutjnl-2014-308513]

49 The Metroticket Project. Available from: URL: http://www.hcc-olt-metroticket.org/

50 **Cillo U**, Vitale A, Bassanello M, Boccagni P, Brolese A, Zanus G, Burra P, Fagiuoli S, Farinati F, Rugge M, D'Amico DF. Liver transplantation for the treatment of moderately or well-differentiated hepatocellular carcinoma. *Ann Surg* 2004; **239**: 150-159 [PMID: 14745321 DOI: 10.1097/01.sla.0000109146.72827.76]

51 **Pawlik TM**, Gleisner AL, Anders RA, Assumpcao L, Maley W, Choti MA. Preoperative assessment of hepatocellular carcinoma tumor grade using needle biopsy: implications for transplant eligibility. *Ann Surg* 2007; **245**: 435-442 [PMID: 17435551 DOI: 10.1097/01.sla.0000250420.73854.ad]

52 **Colecchia A**, Scaioli E, Montrone L, Vestito A, Di Biase AR, Pieri M, D'Errico-Grigioni A, Bacchi-Reggiani ML, Ravaioli M, Grazi GL, Festi D. Pre-operative liver biopsy in cirrhotic patients with early hepatocellular carcinoma represents a safe and accurate diagnostic tool for tumour grading assessment. *J Hepatol* 2011; **54**: 300-305 [PMID: 21056498 DOI: 10.1016/j.jhep.2010.06.037]

53 **Miltiadous O**, Sia D, Hoshida Y, Fiel MI, Harrington AN, Thung SN, Tan PS, Dong H, Revill K, Chang CY, Roayaie S, Byrne TJ, Mazzaferro V, Rakela J, Florman S, Schwartz M, Llovet JM. Progenitor cell markers predict outcome of patients with hepatocellular carcinoma beyond Milan criteria undergoing liver transplantation. *J Hepatol* 2015; **63**: 1368-1377 [PMID: 26220754 DOI: 10.1016/j.jhep.2015.07.025]

54 **Takada Y**, Kaido T, Shirabe K, Nagano H, Egawa H, Sugawara Y, Taketomi A, Takahara T, Wakabayashi G, Nakanishi C, Kawagishi N, Kenjo A, Gotoh M, Toyoki Y, Hakamada K, Ohtsuka M, Akamatsu N, Kokudo N, Takeda K, Endo I, Takamura H, Okajima H, Wada H, Kubo S, Kuramitsu K, Ku Y, Ishiyama K, Ohdan H, Ito E, Maehara Y, Honda M, Inomata Y, Furukawa H, Uemoto S, Yamaue H, Miyazaki M, Takada T. Significance of preoperative fluorodeoxyglucose-positron emission tomography in prediction of tumor recurrence after liver transplantation for hepatocellular carcinoma patients: a Japanese multicenter study. *J Hepatobiliary Pancreat Sci* 2017; **24**: 49-57 [PMID: 27806426 DOI: 10.1002/jhbp.412]

55 **Asman Y**, Evenson AR, Even-Sapir E, Shibolet O. [18F]fludeoxyglucose positron emission tomography and computed tomography as a prognostic tool before liver transplantation, resection, and locoablative therapies for hepatocellular carcinoma. *Liver Transpl* 2015; **21**: 572-580 [PMID: 25644857 DOI: 10.1002/lt.24083]

56 **Ravaioli M**, Grazi GL, Piscaglia F, Trevisani F, Cescon M, Ercolani G, Vivarelli M, Golfieri R, D'Errico Grigioni A, Panzini I, Morelli C, Bernardi M, Bolondi L, Pinna AD. Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. *Am J Transplant* 2008; **8**: 2547-2557 [PMID: 19032223 DOI: 10.1111/j.1600-6143.2008.02409.x]

57 **Yao FY**, Kerlan RK, Hirose R, Davern TJ, Bass NM, Feng S, Peters M, Terrault N, Freise CE, Ascher NL, Roberts JP. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. *Hepatology* 2008; **48**: 819-827 [PMID: 18688876 DOI: 10.1002/hep.22412]

58 **Yao FY**, Mehta N, Flemming J, Dodge J, Hameed B, Fix O, Hirose R, Fidelman N, Kerlan RK, Roberts JP. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. *Hepatology* 2015; **61**: 1968-1977 [PMID: 25689978 DOI: 10.1002/hep.27752]

59 **Yao FY**, Breitenstein S, Broelsch CE, Dufour JF, Sherman M. Does a patient qualify for liver transplantation after the down-staging of hepatocellular carcinoma? *Liver Transpl* 2011; **17** Suppl 2: S109-S116 [PMID: 21584927 DOI: 10.1002/lt.22335]

60 **Lencioni R**, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010; **30**: 52-60 [PMID: 20175033 DOI: 10.1055/s-0030-1247132]

61 **Lai Q**, Avolio AW, Graziadei I, Otto G, Rossi M, Tisone G, Goffette P, Vogel W, Pitton MB, Lerut J. Alpha-fetoprotein and modified response evaluation criteria in solid tumors progression after locoregional therapy as predictors of hepatocellular cancer recurrence and death after transplantation. *Liver Transpl* 2013; **19**: 1108-1118 [PMID: 23873764 DOI: 10.1002/lt.23706]

62 **Otto G**, Herber S, Heise M, Lohse AW, Mönch C, Bittinger F, Hoppe-Lotichius M, Schuchmann M, Victor A, Pitton M. Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma. *Liver Transpl* 2006; **12**: 1260-1267 [PMID: 16826556 DOI: 10.1002/lt.20837]

63 **Halazun KJ**, Patzer RE, Rana AA, Verna EC, Griesemer AD, Parsons RF, Samstein B, Guarrera JV, Kato T, Brown RS, Emond JC. Standing the test of time: outcomes of a decade of prioritizing patients with hepatocellular carcinoma, results of the UNOS natural geographic experiment. *Hepatology* 2014; **60**: 1957-1962 [PMID: 24954365]

64 **Lo C**. Downstaging of hepatocellular carcinoma before transplantation: an advance in therapy or just another selection criterion. *Am J Transplant* 2008; **8**: 2485-2486 [PMID: 19032218 DOI: 10.1111/j.1600-6143.2008.02466.x]

65 **Cescon M**, Cucchetti A, Ravaioli M, Pinna AD. Hepatocellular carcinoma locoregional therapies for patients in the waiting list. Impact on transplantability and recurrence rate. *J Hepatol* 2013; **58**: 609-618 [PMID: 23041304 DOI: 10.1016/j.jhep.2012.09.021]

66 **Toso C**, Mazzaferro V, Bruix J, Freeman R, Mentha G, Majno P. Toward a better liver graft allocation that accounts for candidates with and without hepatocellular carcinoma. *Am J Transplant* 2014; **14**: 2221-2227 [PMID: 25220672 DOI: 10.1111/ajt.12923]

67 **Wiesner R**, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91-96 [PMID: 12512033 DOI: 10.1053/gast.2003.50016]

68 **Goldberg D**, French B, Abt P, Feng S, Cameron AM. Increasing disparity in waitlist mortality rates with increased model for end-stage liver disease scores for candidates with hepatocellular carcinoma versus candidates without hepatocellular carcinoma. *Liver Transpl* 2012; **18**: 434-443 [PMID: 22271656 DOI: 10.1002/lt.23394]

69 **Feng S**, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, Greenstein SM, Merion RM. Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant* 2006; **6**: 783-790 [PMID: 16539636 DOI: 10.1111/j.1600-6143.2006.01242.x]

70 **Avolio AW**, Cillo U, Salizzoni M, De Carlis L, Colledan M, Gerunda GE, Mazzaferro V, Tisone G, Romagnoli R, Caccamo L, Rossi M, Vitale A, Cucchetti A, Lupo L, Gruttadauria S, Nicolotti N, Burra P, Gasbarrini A, Agnes S. Balancing donor and recipient risk factors in liver transplantation: the value of D-MELD with particular reference to HCV recipients. *Am J Transplant* 2011; **11**: 2724-2736 [PMID: 21920017 DOI: 10.1111/j.1600-6143.2011.03732.x]

71 **Cillo U**, Vitale A, Polacco M, Fasolo E. Liver transplantation for hepatocellular carcinoma through the lens of transplant benefit. *Hepatology* 2017; **65**: 1741-1748 [PMID: 28010048 DOI: 10.1002/hep.28998]

72 **Schaubel DE**, Guidinger MK, Biggins SW, Kalbfleisch JD, Pomfret EA, Sharma P, Merion RM. Survival benefit-based deceased-donor liver allocation. *Am J Transplant* 2009; **9**: 970-981 [PMID: 19341419 DOI: 10.1111/j.1600-6143.2009.02571.x]

73 **Vitale A**, Morales RR, Zanus G, Farinati F, Burra P, Angeli P, Frigo AC, Del Poggio P, Rapaccini G, Di Nolfo MA, Benvegnù L, Zoli M, Borzio F, Giannini EG, Caturelli E, Chiaramonte M, Trevisani F, Cillo U. Barcelona Clinic Liver Cancer staging and transplant survival benefit for patients with hepatocellular carcinoma: a multicentre, cohort study. *Lancet Oncol* 2011; **12**: 654-662 [PMID: 21684210 DOI: 10.1016/S1470-2045(11)70144-9]

74 **Bruix J**, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. *Gut* 2014; **63**: 844-855 [PMID: 24531850 DOI: 10.1136/gutjnl-2013-306627]

75 **Piscaglia F**, Camaggi V, Ravaioli M, Grazi GL, Zanello M, Leoni S, Ballardini G, Cavrini G, Pinna AD, Bolondi L. A new priority policy for patients with hepatocellular carcinoma awaiting liver transplantation within the model for end-stage liver disease system. *Liver Transpl* 2007; **13**: 857-866 [PMID: 17539006 DOI: 10.1002/lt.21155]

76 **Freeman RB**, Edwards EB, Harper AM. Waiting list removal rates among patients with chronic and malignant liver diseases. *Am J Transplant* 2006; **6**: 1416-1421 [PMID: 16686765 DOI: 10.1111/j.1600-6143.2006.01321.x]

77 **Toso C**, Dupuis-Lozeron E, Majno P, Berney T, Kneteman NM, Perneger T, Morel P, Mentha G, Combescure C. A model for dropout assessment of candidates with or without hepatocellular carcinoma on a common liver transplant waiting list. *Hepatology* 2012; **56**: 149-156 [PMID: 22271250 DOI: 10.1002/hep.25603]

78 **Vitale A**, Volk ML, De Feo TM, Burra P, Frigo AC, Ramirez Morales R, De Carlis L, Belli L, Colledan M, Fagiuoli S, Rossi G, Andorno E, Baccarani U, Regalia E, Vivarelli M, Donataccio M, Cillo U. A method for establishing allocation equity among patients with and without hepatocellular carcinoma on a common liver transplant waiting list. *J Hepatol* 2014; **60**: 290-297 [PMID:

24161408 DOI: 10.1016/j.jhep.2013.10.010]
79 **Belli LS**, Berenguer M, Cortesi PA, Strazzabosco M, Rockenschaub SR, Martini S, Morelli C, Donato F, Volpes R, Pageaux GP, Coilly A, Fagiuoli S, Amaddeo G, Perricone G, Vinaixa C, Berlakovich G, Facchetti R, Polak W, Muiesan P, Duvoux C. Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: A European study. *J Hepatol* 2016; **65**: 524-531 [PMID: 27212241 DOI: 10.1016/j.jhep.2016.05.010]
80 **Mazzaferro V**. Squaring the circle of selection and allocation in liver transplantation for HCC: An adaptive approach. *Hepatology* 2016; **63**: 1707-1717 [PMID: 26703761 DOI: 10.1002/hep.28420]
81 **Cillo U**, Burra P, Mazzaferro V, Belli L, Pinna AD, Spada M, Nanni Costa A, Toniutto P. A Multistep, Consensus-Based Approach to Organ Allocation in Liver Transplantation: Toward a "Blended Principle Model". *Am J Transplant* 2015; **15**: 2552-2561 [PMID: 26274338 DOI: 10.1111/ajt.13408]

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