

Enlarged selection criteria for hepatocellular cancer: is the upper limit needed?

Andrea Peloso^{1,2}, Graziano Oldani^{1,3}

¹Division of Abdominal Surgery, Department of Surgery, Faculty of Medicine, University of Geneva, Geneva, Switzerland; ²Division of General Surgery, IRCCS Policlinico San Matteo Foundation, University of Pavia, Pavia, Italy; ³HPB Centre, Geneva University Hospitals, Geneva, Switzerland

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Correspondence to: Graziano Oldani. Department of Surgery, Rue Gabrielle-Perret-Gentil, 1211 Geneva, Switzerland. Email: graziano.oldani@hcuge.ch.

Abstract: Liver transplantation (LT) for hepatocellular carcinoma (HCC) is strategically challenging because the very good mid-term outcomes of this treatment jar with the risk of cancer recurrence. Although Milan criteria (MC) tap the balance on the safe side, they tend to be considered too restrictive and new, enlarged criteria have been conceived in order to enlarge the pool of potential recipients. Some extended criteria are more audacious than others, but they seem to be well tailored on the local reality they are applied to. Being HCC epidemiology and organs availability very variable between regions, a universally valid ‘upper limit’ is yet to be determinable.

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Introduction

Milan criteria (MC) are so far the safest and still the most commonly used way to select early-stage hepatocellular carcinoma (HCC) patients for transplantation. However, in a world facing a constant increase of HCC cases (1), the pressure to enlarge the pool of donors and to extend these criteria is extremely strong. As a result, in the last decade, the use of marginal donors (steatotic and/or older grafts) in association to less restrictive criteria, has certainly reduced the mortality on waiting list (and in the first few years after transplantation) (2,3), but it has been associated to higher rates of tumor recurrence after transplantation (4,5). Being organ shortage a real problem, defining where is the border between an acceptable ‘waste’ and the misuse of a limited resource seems to be mandatory.

Criteria selection for liver transplantation (LT)

Allocation policies

LT for HCC is particularly attractive for its ability to remove at the same time the macroscopic lesions, the undetected micro-disease and the underlying cirrhosis, when present. On the other hand, hepatic resection is still indicated for HCC patients having well-compensated cirrhosis [model for end-stage liver disease (MELD) ≤ 9] (6) and no evidence of portal hypertension, along with an operable liver. In the population of patients without chronic liver disease, resection can yield to 5-year overall survival rates around 50% (7), which looks barely acceptable.

Indication boundaries are constantly evolving, and several studies have compared LT and hepatic resection outcomes, trying to define the best management strategy. Chapman *et al.* (8) for example, demonstrated that LT can

grant an overall and disease-free survival advantage over resection, among patients who qualify for both treatment modalities. This is due to the fact that by transplantation, all the underlying pathologies are treated at once. On the other hand, Vitale *et al.* recommended transplantation as second line treatment for patients with very early stage HCC, in case of recurrence or for parenchymal insufficiency after liver resection (9). This last approach seems to be the most pragmatic, since it allows to spare organs and immunosuppression-related side effects (and costs) on one side, while it identifies the borderline patients who are promptly rescued by transplantation on the other.

LT is the best treatment option not only for early-stage HCC, but for a wide range of pathologies, like chronic and acute hepatitis, or genetically determined metabolic and developmental liver diseases (10). The success of this treatment determines a high demand for grafts, which translates into a chronic organ shortage worldwide. To face this problem, the transplant community has adopted quite strict criteria, in order to prioritize the patients on the waiting list for a transplantation, based on their clinic conditions. MELD is the fairest tool to assess the urgency of a transplantation in cirrhotic patients, based on their risk of mortality in the short period (11). HCC patients get MELD exceptions points, in order to compensate the time-related risk of developing an incurable disease. Exception points are constantly revised based on the outcomes of both HCC and non-HCC patients, aiming to play fair on both sides (12). It was in fact noticed that, based on the initial scoring, the transplantation rate of HCC patients was too high, which was 'unfair' towards non-HCC patients, and unconcerned about tumor aggressiveness (because cancer patients were transplanted too early in their follow-up). In some of the last revisions it was decided to award the exception points six months after the diagnosis (and not right from the start), in order to indirectly assess tumor biology based on its evolution during this reasonably short follow-up (13). Allocation policies when dealing with HCC patients still vary considerably depending on the country (or the area) (14).

MC: are they still valid?

In 1996, Mazzaferro *et al.* (15) taught the world how to select HCC patients for LT. In their series, the 5-year survival rate was >70%, being the conditions to fulfil: a solitary HCC nodule ≤ 5 cm or up to 3 nodules, each one ≤ 3 cm, along with the absence of macroscopic vascular invasion or

spread disease.

The MC have been corroborated by numerous transplant units all over the world and finally adopted by the United Network for Organ Sharing as the gold standard for selecting patients with early-stage HCC for LT.

Although undoubtedly safe to select very good candidates for LT, MC are now considered too strict and unable to identify all the possible suitable patients. In this sense, many extended criteria have been proposed (5).

Beyond MC

Schwartz *et al.* have clearly identified the limitations that reside in the MC patient selection (16). According to their analysis, the fact they only rely on the tumor's (macro) morphological characteristics may lead to misdiagnosis, due to the limitations connected to the imaging technique. Second, tumor aggressiveness is not taken into account. Third, such criteria are too limitative in terms of nodules number and size. Fourth, MC used as a drop-out tool are responsible for an excessive removal of patients from the waiting list.

MC's limitations were also evident to other transplant experts, fueling their motivation to develop more compliant criteria, to which we refer as 'extended'. The most commonly used being University of California San Francisco (UCSF) criteria (17), Up-to-7 criteria (18), total tumor volume/alpha-fetoprotein (TTV/AFP) criteria (19), extended Toronto criteria (ETC) (4), and Kyoto criteria (20). *Table 1* summarizes the characteristics of MC and the most commonly used extended criteria, focusing on their propensity to consider tumor biology and grading.

HCC biological behavior

While UCSF and Up-to-7 criteria represent a cautious extension of MC and still consider macromorphological aspects only, the other proposed criteria try to deal with tumor biological aggressiveness. TTV/AFP criteria, developed between Edmonton and Geneva, use indeed AFP as (surrogate) biological marker of cancer violence. Higher plasma concentrations of this protein are in fact associated to increased tumor burden and enhanced risk of post-transplant recurrence (21).

The Kyoto criteria involve a less exploited molecule: des- γ -carboxyprothrombin (DCP), which has also been associated to increased tumor activity and recurrence risk (22).

Toronto, instead, has completely abandoned morphological criteria and focuses on tumor biological

Table 1 Criteria for the selection of liver transplantation candidates among HCC patients

Transplantation criteria	Tumor morphology	Tumor biology	Tumor grading	Clinic
Milan	Single nodule ≤ 5 cm or 3 nodules all ≤ 3 cm	–	–	–
UCSF	Single nodule ≤ 6.5 cm or 3 nodules all ≤ 4.5 cm with TTD ≤ 8 cm	–	–	–
Up-to-7	Biggest nodule diameter + number of nodules ≤ 7	–	–	–
TTV/AFP	Total tumor volume ≤ 115 cm ³	AFP ≤ 400 ng/mL	–	–
ETC	Size: no limit; number: no limit	–	Biopsy of the largest nodule not poorly differentiated	No cancer-related symptoms
Kyoto	≤ 10 nodules each ≤ 5 cm	DCP ≤ 400 mAU/mL	–	–

HCC, hepatocellular carcinoma; UCSF, University of California San Francisco; TTV/AFP, total tumor volume/alpha-fetoprotein; ETC, extended Toronto criteria; DCP, des- γ -carboxyprothrombin.

behavior, involving direct and indirect measures. ETC include a biopsy of the largest nodule, obtaining the most precise information available about cancer grading and general aggressiveness (differentiation, microvascular infiltration).

Future criteria will probably include ‘liquid biopsies’ (23). This emerging concept is based on the ability to detect specific tumor DNA or cancer cells RNA (exosome) in mainstream blood (and other body fluids) (24). The potential advantage over physical biopsies is dual, as the analysis is not limited to a single nodule, while the risk of dissemination is completely avoided. Exosomes specific to HCC have already been identified (25,26) and challenged on their efficacy in predicting recurrence after LT (27). The results are encouraging and the future of this technology is certainly bright.

An enlarged selection criterion for every situation

All the enlarged selection criteria listed, have been validated on large cohorts of patients. As a consequence, their principles could be applied to the ‘general population’ of HCC patients with predictable outcomes. Conversely, HCC epidemiology varies consistently depending on the region, country or continent (1). Even greater discrepancies exist in terms of organs availability and allocation policies (28).

These differences explain why, assuming that MC are too restrictive and different ones were needed, the transplant

community has not unified under the same new criteria yet (5).

In countries (or regions) with low HCC incidence and very good organs availability, aiming to 10-year overall survival $<40\%$, for example, can be acceptable. In this situation, selection criteria deserve to be sensibly enlarged, because even a ‘sub optimal’ outcome would not be considered as a waste of resources. In contrast to that, regions with high incidence of HCC and a more limited availability of organs, cannot afford to enlarge their selection criteria too much, in order to protect the potential recipients with indications different to HCC. For these reasons it is rational to think that every transplant center will keep on developing its own enlarged criteria, and that the upper limit will be set based on the local epidemiology and resources, instead of by a globally predetermined acceptable outcome.

As shown in *Figure 1*, every extended criterion allows to transplant more patients (green columns). The more permissive the criteria are, the higher the price to pay in terms of survival, compared to MC. UCSF criteria, which are a prudent revision of MC, enlarge the pool of recipients by 10% (17), still allowing for similar disease-free survival and slightly reduced overall survival. The ETC, more bravely, permit to include 40% more recipients. In this case the downside is represented by the disease-free survival, which drops to 30%, being the overall survival still quite high (68%) (4). The team from Toronto can afford such criteria because they were able to extend their pool of donors by the extraordinary implementation of the

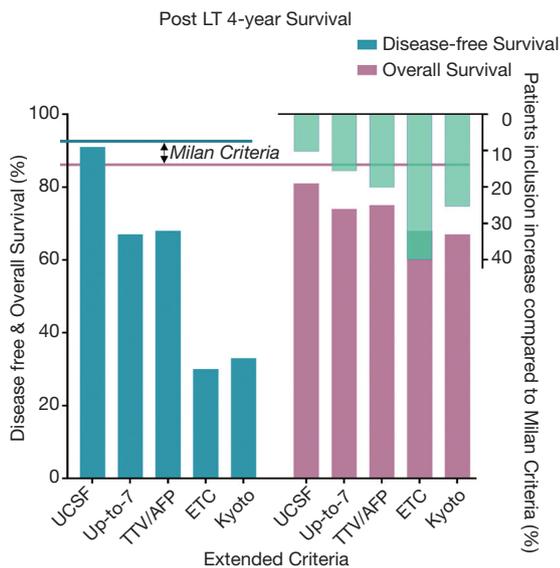


Figure 1 Comparison of extended selection criteria in terms of patients' inclusion, disease-free and overall survival after liver transplantation for HCC (normalized at 4 years). HCC, hepatocellular carcinoma.

living donation (29) and the use of DCD grafts. Similar criteria could not be applied in many other environments, with more traditional donation strategies. On the other hand, TTV/AFP criteria (presently applied in Geneva and Edmonton) represent a more affordable compromise, because they extend the pool of recipients by 20%, reducing the overall survival by only 10% and without affecting the disease-free survival too much (19).

As inclusion criteria for LT of HCC patients will continue to evolve, universally setting an acceptable outcome after LT for HCC does not reflect the current situation, where cancer epidemiology and resources can be extremely variable, depending on the country or the region of interest. As a consequence, even the most extreme enlarged selection criteria should not be considered excessive if they well fit the population and the local means.

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Footnote

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