

Searching the ideal hepatocellular carcinoma patient for liver transplantation: are the Toronto criteria a step in the right direction?

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Since the introduction of Milan criteria by Mazzaferro *et al.* in 1996 (1), many transplant programs and allocation systems use these criteria for the selection of suitable candidates for liver transplantation in hepatocellular carcinoma (HCC) patients. The Milan criteria define a tumor burden of one tumor nodule (with a maximum diameter of 5 cm) or up to three tumor nodules (with a maximum diameter of 3 cm each) as threshold for a beneficial outcome.

Critics of the aforementioned criteria point that a variety of patients, exceeding the Milan criteria, are precluded from a liver transplantation even if they would benefit from this therapy.

Referred to the Eurotransplant region, a patient with one tumor nodule between two and five centimeters or up to three tumor nodules between one and three centimeters, according to a UNOS T2 HCC, are allowed to get a so-called “standard exception (SE)”—MELD. This means that these patients start their waiting time period with a SE-MELD score of 22, increasing every three months if the tumor burden is still inside the criteria. A successful downstaging is not designated to receive a SE-MELD.

However, this implies that the decision of transplanting a HCC patient or not and preferring a HCC patient or not,

respectively, depends on static parameters (tumor size in imaging) on a certain point in time. Biological parameters, like response to a bridging therapy, tumor differentiation or molecular marker, are not taken into account.

Thus, the presented study of Sapisochin *et al.* titled “*The Extended Toronto Criteria for Liver Transplantation in Patients With Hepatocellular Carcinoma: A Prospective Validation Study*” (2) shows a more progressive approach when putting HCC patients on the waiting list. The Toronto criteria include patients with any size or number of tumors provided that they do not have systemic cancer-related symptoms, extrahepatic disease, vascular invasion or poorly differentiated tumors.

The study group overviews 605 patients in a time period between January 1996 and December 2012 who were listed for liver transplantation due to HCC. This cohort was subdivided in two groups depending on the date of listing and again subdivided in a group fulfilling the Milan criteria or exceeding the Milan criteria, respectively.

The long-term outcome in the group exceeding the Milan criteria was (slightly) inferior, the 5- and 10-year patient survival after liver transplantation were 68% and 50% compared to 76% and 60% in the Milan-in group. The risk of HCC recurrence was higher in the group

exceeding the Milan criteria (5- and 10-year cumulative risk of recurrence 30% and 33% versus 13% and 15%). The authors argue that the superior results in the Milan-in group might be justified, beside the lower tumor burden, in the possibility of using radiofrequency ablation instead of transarterial chemoembolization.

Interestingly (and difficult to imagine taking the mid-European relations as a basis), the median waiting time averages between 4 and 6 months. This implies that a response to bridging therapy doesn't play a major role in the Toronto setting. However, the tumor biology plays a role in the results of the present study: an α -fetoprotein (AFP) level >500 ng/mL goes along with a significant worse outcome, independent whether the AFP level was determined at the time of listing or of liver transplantation.

Another interesting fact in the Toronto approach is the mandatory tumor biopsy prior listing (in any case exceeding the Milan criteria) to exclude a poor tumor differentiation.

Many centers are afraid of tumor seeding along biopsy canal. So, the Toronto results are encouraging since none of the patients dropped out due to biopsy related tumor seeding, even though three patients might have had tumor recurrence after liver transplantation due to the biopsy.

However, a 10-year survival rate of 50% (in the group exceeding the Milan criteria) is still an excellent result underlying a malignant disease as main diagnosis. Most oncologic therapies do not touch such results in the slightest. Therefore, it is even hard from an ethical point of view to exclude HCC from a curative treatment option "only" on the basis of an imaging. One might argue that, on the other hand, most transplant regions suffer from a striking organ shortage and many patients die on the waiting list.

So, in our opinion, the transplant community has to solve the following questions in the upcoming years.

Who is the "ideal" HCC patient, who benefits most from a liver transplantation?

The Milan criteria, more than twenty years old, as static parameters should not be the only criterion for decision. The Toronto data are a step in the right direction, underlying tumor parameters (e.g., tumor differentiation) in the decision tree. In our experience, a test of time, in sense of a response to bridging therapy, is another important parameter, although this is born of necessity in Mid-Europe due to increasing waiting times.

How can we avoid a preference and a disadvantage for HCC patients?

In many allocation systems, HCC patients receive an exceptional MELD-score when fulfilling certain criteria (like Milan-in or UNOS T2). But not only HCC patients receive such exceptional points, also certain diagnosis like primary sclerosing cholangitis (PSC) are privileged in certain circumstances. This might be placed to the debit of patients suffering from complications of liver cirrhosis, e.g., therapy-refractory ascites or hepatic encephalopathy, who have a low MELD-score but life-threatening complications as described.

In summary, the patients who fulfilled the Toronto criteria achieved a good long-term outcome after liver transplantation. Therefore, these criteria could be used for selection of appropriate transplant candidates. This means that the tumor biology instead of the tumor burden alone must be in the focus of attention when deciding about suitable HCC patients for liver transplantation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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