# Selection criteria for liver transplantation in patients with hepatocellular carcinoma. Eastern and western experiences, and perspectives for the future

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## Abstract

**Ever since the initial description of the Milan criteria, used for selecting patients with hepatocellular carcinoma (HCC) for liver transplantation (LT), there has been a clear need to go further than solely morphological criteria. Tumours exceeding the Milan criteria, but presenting favourable biological behaviour, might still allow for comparable overall- and disease-free survivals after LT. As it is well established that the presence of microvascular invasion is a major factor that influences HCC recurrence after LT, several serum and tissue biomarkers in addition to imaging studies are attracting wider attention as more refined tools for selecting HCC patients for LT. A thorough review of the recent literature on the subject was conducted. In the future a combination of systemic inflammation markers, biomarkers and morphological criteria may be key to more accurate prediction of HCC recurrence after LT. This may allow LT in patients whose HCC tumours exceed the Milan criteria but have favourable biological behaviour. Further prospective studies are required in order to improve patient selection for transplantation in HCC and these could help a move towards more transparent and improved management.** (Acta gastroenterol. belg., **2019**, 82, **314-318**).

## Introduction

Hepatocellular carcinoma (HCC) is the seventh most common cancer and the third most common cause of cancer-related deaths worldwide. The HCC incidence differs between the Western and the Eastern World mainly due to a difference in the underlying causes, alcohol abuse and hepatitis C virus being more prevalent in the Western hemisphere compared to hepatitis B virus in the Far East. (1,2,3)

Despite parenchyma-preserving surgical techniques and other means to increase the volume of the future remnant liver, surgical resection is a suitable treatment option for only a minority of HCC patients. Locoregional therapies allow tumour control but are limited to small tumours with compensated cirrhosis and have technical limitations concerning tumour volume and localization. Liver transplantation (LT) not only eliminates the tumour itself, but also the tumour-bearing environment of cirrhosis, and offers the best curative option from an oncological viewpoint.

## Evolution of Liver transplantation and Selection criteria for HCC

From the early beginnings of LT until the end of the 1980s, the LT outcome of HCC patients has been rather poor and HCC was even considered a contraindication by the United States Department of Health in 1989 (4). Breakthrough results were published in 1996 by Mazzaferro et al., achieving a 4-year overall survival (OS) and disease-free survival (DFS) of 83% and 75%, respectively, in a selected group of HCC patients, transplanted for either a single tumour not exceeding 5 cm in diameter, or 3 tumours each not exceeding 3 cm (5). These, soon called "Milan criteria", became the benchmark on which later decisions for allocating organs were made.

Over time, and with growing experience in LT, it became apparent that a slight expansion in tumour size and numbers would yield similar outcomes. The team from the University of San Francisco (UCSF) was among the first able to show that by expanding the criteria to 6.5 cm for a single tumour, or for 3 tumours not exceeding 4.5 cm, and with a total tumour volume of less than 8 cm, a 5-year survival of 75% was possible (6). Following these so-called "UCSF criteria", an increasing number of centres began to define extended criteria with similarly encouraging results (7-13) (Table 1). The Milan group described the up-to-seven criteria with seven being the sum of the size of the largest tumour in cm and the number of tumours, achieving a 5-year overall survival of 71% (14).

The question of what constitutes an acceptable outcome by pushing the criteria further and how this impacts the non-HCC waiting list must be addressed in the context of organ donor shortage, especially in the Western hemisphere, where living donor liver transplantation is more marginal. Although debatable, the threshold of a 5-year OS survival of 50% is widely regarded as the minimum acceptable outcome (4).

It has been shown that expanding tumour size and number beyond the Milan criteria comes with a 'price' of reduced survival after LT. This was illustrated in the Metroticket project, that after combining data from multiple European centres, was able in the "HCC forecast chart" to predict

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Table 1. — **Liver transplantation beyond Milan criteria in the Western hemisphere and outcomes (adapted from (12))**

| Authors | n | Milan IN (MI)/ Milan OUT (MO) | Extended criteria | Survival |
|---|---|---|---|---|
| Herrero et al., 2001(7) | 61 | 49/12 | 1 nodule ≤6 cm, or 2-3 nodules each ≤5 cm | 5-year 79% |
| Roayaie et al., 2002 (8) | 31 | 0/31 | 1 or more nodules 5-7 cm | 5-year MO - 55% |
| Kneteman et al., 2004 (9) | 40 | 19/21 | 1 nodule <7.5 cm<br>any number <5 cm | 4-year<br>MI - 87%<br>MO - 83% |
| Onaca et al.,2007 (10) | 1152 | 1038/114 | 1 nodule ≤6 cm<br>2-4 nodules each ≤5 cm | 5-year<br>MI - 62%<br>MO - 54.3% |
| Cillo et al., 2007 (11) | 100 | 60/40 | Number of tumours - 3 ± 1.2<br>Size of largest tumour - 4.0 ±1.6 | 3-year<br>MI - 69%<br>MO - 85% |
| Guiteau et al., 2010 (12) | 445 | 363/82 | 1 lesion <6 cm<br>≤3 lesions none >5 cm<br>total diameter 9 cm | 5-year<br>MI - 72.9%<br>MO - 70.2% |

Table 2. — **Alpha-fetoprotein cut-off levels and selection criteria in Asian centres**

| Author | Country | n | AFP cut-off (ng/ml) | Criteria |
|---|---|---|---|---|
| Yang et al., 2007 (18) | Korea | 63 | 20, 200, 1000 | Tumour number and size, different AFP cut-off levels |
| Zheng et al., 2008 (19) | China | 195 | 400 | Hangzhou criteria :<br>TTD ≤8 or>8, well or moderately differentiated, AFP < 400 |
| Kim et al., 2014 (20) | Korea | 180 | 1000 | Samsung criteria: Up to7 tumours ≤ 6 cm, AFP ≤ 1000 |
| Shimamura et al., 2019 (21) | Japan | 965 | 500 | Nodule size ≤5 cm in diameter, nodule number ≤5, AFP ≤500 |

5-year survival based on tumour size and number on pre-transplant imaging (14,15).

The question as to whether we can afford the 'price' of lower OS and DFS by transplanting more extended HCC based only on size and number has since then been taken on by multiple centres. Several biomarkers, in addition to imaging studies, are attracting an increasing amount of attention as more refined tools for selecting HCC patients for LT.

## New selection criteria

It has become clear that not only HCC size and number but ultimately the biological tumour behaviour determines post-transplant outcome. Similar tumour morphology amongst HCC patients does not correlate to a similar outcome and defining biomarkers has become critical in modern cancer treatment. It is well established that the presence of microvascular invasion is a major factor that influences recurrence after LT for HCC.

In the Eastern hemisphere, with predominately living donor liver transplantation (LDLT), HCC patients can be transplanted without a significant waiting time. This also means that there is no significant period that would allow for the observation of biological tumour behaviour over some time, and this may result in the inclusion of patients with more aggressive tumour biology. In order to help predict outcome in this setting alpha-fetoprotein (AFP) was amongst the first markers to be examined.

## Alpha-fetoprotein

Alpha-fetoprotein is a glycoprotein produced by the dedifferentiation of hepatocytes and liver tumours. It is a surrogate marker for tumour differentiation and is associated with microvascular invasion, subsequent increased recurrence rates and therefore reduced overall survival after liver transplantation (16,17). Different AFP cut-off levels have been described in several Asian centres such as China, Korea and Japan (18-21), and new selection criteria based on different AFP cut-off levels and tumour number and size have been defined (Table 2). In Europe, the Liver Transplantation French Study Group have developed a prognostic model, that combines AFP

Table 3. — **French AFP cut-off levels and selection criteria**

| Author | n | Cut-off levels | Criteria |
|---|---|---|---|
| Duvoux et al. 2012 (15) | 972 | Largest diameter, cm — Points<br>≤3 — 0<br>3-6 — 1<br>>6 — 4<br>Number of nodules<br>1-3 — 0<br>≥4 — 2<br>AFP level, ng/ml<br><100 — 0<br>100-1000 — 2<br>>1000 — 3 | Cut-off variable at 2 separates between patients with low and high risk of recurrence |

Table 4. — **Combined use of DCP and AFP levels with HCC tumour size and number as selection criteria (adapted from (16))**

| Authors | Country | n | Cut-off levels | Selection criteria |
|---|---|---|---|---|
| Takada et al., 2007 (24) | Japan | 125 | DCP 400 | Kyoto criteria: up to 10 tumours ≤ 5 cm and DCP ≤ 400 |
| Soejima et al., 2007 (25) | Japan | 60 | DPC 300 | Kyushu criteria:<br>Any number of tumours <5 cm and DCP < 300 |
| Todo et al., 2007 (26) | Japan | 551 | AFP 200, DPC 100 | A-P level: AFP ≤ 200 and DCP ≤ 100 |
| Yang et al., 2016 (27) | Korea | 88 (training cohort);<br>198 (validation cohort) | AFP: 200;<br>DCP: 200 | A-P 200: AFP ≤ 200 or DCP ≤ 200 |
| Kim et al., 2016 (28) | Korea | 461 | AFP: 150; DCP:100 | -- |

level and HCC tumour size and number with different cut-offs for each variable, that predicts recurrence after LT (22) (Table 3). This model allows for a more improved discrimination between patients with high or low risk of recurrence than the Milan criteria alone. A cut-off level of AFP > 1000 ng/ml would exclude patients from LT whatever the tumour size or number. This model has been adopted into the official liver allocation policy in France since 2013.

## Des-gamma-carboxy prothrombin

Des-gamma-carboxy prothrombin (DCP) is an abnormal form of prothrombin and is additionally known as a protein induced by the absence of vitamin K or antagonist II (PIVKA-II) (23). It is produced during the malignant transformation of hepatocytes and induces the expression of angiogenic growth factors such as epithelial growth factor and vascular endothelial growth factor. DCP-positive tumours present an increased rate of intrahepatic metastases, capsule infiltration and portal vein invasion.

DCP has been put forward as a strong predictor for HCC recurrence. Some Asian centres (24-28) have proposed the combined use of DCP levels with tumour size and number, some also with integrating AFP levels, as selection criteria for transplant candidates (16) (Table 4).

## Systemic inflammation markers

Systemic inflammation markers are known predictors for outcome in several malignancies, and have been associated with HCC recurrence after LT (16,17). Neutrophil lymphocyte-ratio (NLR) and platelet-lymphocyte-ratio (PLR) in peripheral blood are involved in vascular invasion by increasing pro-angiogenic factors, but the broader molecular mechanisms and how they relate to HCC recurrence are still unknown. A recent meta-analysis suggests that reduced NLR at baseline is associated with better recurrence-free survival after LT (29). Different cut-off levels for NLR have been described and a cut-off level of 4 has been recommended (30). The significance of PLR in HCC recurrence has not been so widely described, but high PLR seems to be associated with more HCC recurrence after LT (31).

## Other serum and tissue biomarkers

Several other serum markers have been suggested as being predictors for outcome after LT for HCC. A variant of AFP, the *Lens culinaris* agglutinin fraction (AFP-L3), is correlated to tumour size and seems to be of particular interest in patients with normal serum AFP levels (17). A recent meta-analysis describes an elevated AFP-L3 as an independent predictor of poor OS and DFS (32).

Tissue biomarkers are also rapidly emerging to assess tumour biology and possibly predict response to targeted therapies, despite liver biopsy not being routinely performed for HCC diagnosis. Glypican-3 can be found on more than 90% of AFP-negative tumours and has been described as an independent factor of poor disease-free survival (33,34). Other markers like E-cadherin (35) or osteopontin (36) might be associated with more aggressive tumour biology and reduced survival, but their true role in the selection of HCC patients for transplantation still needs to be established.

In the future a combination of systemic inflammation markers and biomarkers may be key to more accurately predicting HCC recurrence after LT. Nevertheless, the large majority of data are from retrospective studies and are difficult to compare due to different transplant policies in the Eastern and Western hemisphere, such as living donor liver transplantation (LDLT) versus deceased donor liver transplantation (DDLT), as well as different adjuvant bridging treatment schemes.

## Perspectives

There is a clear need to go beyond the Milan morphological criteria in LT for HCC and therefore allow LT in patients whose HCC tumours exceed the Milan criteria but have favourable biological behaviour and a low anticipated risk of recurrence after LT. The use of positron-emission tomography (PET) with various tracers has emerged in recent years as a diagnostic tool for the diagnosis of HCC, risk assessment and therapy monitoring. In a recent meta-analysis, PET using 11C-acetate and radio-labelled choline such as 11C-choline or 18F-fluorocholine show higher sensitivity as compared to 18-fluorodeoxyglucose-positron emission tomography (18-FDG-PET) in the diagnosis of primary or recurrent HCC. These tracers tend to have a higher

uptake in well differentiated HCC (37). The use of a combination of tracers such as 11C-choline and 18-FDG, may rise the sensitivity of HCC detection to up to 93% (38).

18-FDG-PET as a prognostic tool in HCC may help to identify tumours which display poorer grades of differentiation and are more prone to microvascular invasion (38,39).

The interest of 18-FDG-PET was recently pointed out in a retrospective study showing that positive PET-status was an independent clinical predictor of tumour recurrence in patients beyond up-to-seven criteria (39), with a tumour/liver activity ratios (RSUVmax) cut-off value of 1.15 as a strong prognostic indicator (40). Interestingly, the risk of recurrence was not different in HCC Milan-out/FDG-PET negative patients compared to HCC Milan-in/FDG-PET negative patients.

A prospective Belgian national multicentre study has recently been set up and will allow the specific identification and monitoring of these patients through the construction of a prospective database. This unique, original, prospective and multicentre study might have a major impact on HCC selection of candidates for transplantation through PET-CT, and might help a shift towards improved patient management. If this study confirms the hypothesis that Milan-out, up-to-seven-in, PET negative HCC candidates for LT have the same DFS and OS as Milan-in patients, there might be a major impact on the management, listing and allocation of grafts to this group of HCC patients in Belgium and maybe in the wider EUROTRANSPLANT region (41, 42). This study is designed to improve patient selection for transplantation in HCC through PET-CT and could help a move towards more transparent and improved management.

## Conflict of interest

The authors declare not to have any conflict of interest
Key words: hepatocellular carcinoma, Milan criteria, microvascular invasion, biomarkers

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