

# World Journal of *Hepatology*

*World J Hepatol* 2019 March 27; 11(3): 250-334



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*World Journal of Hepatology* (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Responsible Electronic Editor: Yan-Liang Zhang Proofing Editorial Office Director: Ya-Juan Ma

**NAME OF JOURNAL**

*World Journal of Hepatology*

**ISSN**

ISSN 1948-5182 (online)

**LAUNCH DATE**

October 31, 2009

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Ke-Qin Hu, Koo Jeong Kang, Nikolaos Pyrsopoulos

**EDITORIAL BOARD MEMBERS**

<https://www.wjnet.com/1948-5182/editorialboard.htm>

**EDITORIAL OFFICE**

Ya-Juan Ma, Director

**PUBLICATION DATE**

March 27, 2019

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**ARTICLE PROCESSING CHARGE**

<https://www.wjnet.com/bpg/gerinfo/242>

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<https://www.wjnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

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## Hepatocellular carcinoma recurrence after liver transplantation: Risk factors, screening and clinical presentation

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**Author contributions:** Filgueira NA contribute to conception and design, literature review and writing of article.

**Conflict-of-interest statement:** No potential conflicts of interest, no financial support

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**Manuscript source:** Invited manuscript

**Received:** February 6, 2019

**Peer-review started:** February 6, 2019

**First decision:** March 5, 2019

**Revised:** March 6, 2019

**Accepted:** March 16, 2019

**Article in press:** March 16, 2019

**Published online:** March 27, 2019

**P-Reviewer:** Qin J, Tchilikidi KY

**S-Editor:** Cui LJ

**L-Editor:** A

**E-Editor:** Zhang YL

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### Abstract

Liver transplantation is the best treatment option for cirrhotic patients with early-stage hepatocellular carcinoma, but it faces the problem of scarcity of donors and the risk of tumor recurrence, which affects between 15% and 20% of the cases, despite the use of restrictive criteria. The risk of recurrence depends on a number of factors, related to the tumor, the patient, and the treatment, which are discussed in this review. Some of these factors are already well established, such as the histopathological characteristics of the tumor, Alpha-fetoprotein (AFP) levels, and waiting time. Other factors related to the biological behavior of the tumor and treatment should be recognized because they can be used in the refinement of the selection criteria of transplant candidates and in an attempt to reduce recurrence. This review also discusses the clinical presentation of recurrence and its prognosis, contributing to the identification of a subgroup of patients who may have better survival, if they are timely identified and treated. Development of recurrence after the first year, with AFP levels  $\leq 100$  ng/mL, and single site capable of locoregional therapy are associated with better survival after recurrence.

**Key words:** Hepatocellular carcinoma; Liver transplantation; Recurrence; Risk factors; Alpha-fetoprotein; Survival; Prognosis

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**Core tip:** Recurrence of hepatocellular carcinoma (HCC) after liver transplantation usually portends a poor prognosis with short survival. Besides well recognized risk factors for post-transplant HCC recurrence, as tumor staging and vascular invasion, this review discusses other factors strongly associated with the recurrence risk, such as alpha-fetoprotein levels, tumor uptake of FDG in Pet scan, response to locoregional therapy and post-transplant immunosuppression. We present proposals of a screening protocol for tumor recurrence after transplantation and of criteria to identify patients with good prognosis after recurrence, who might benefit from aggressive antitumor therapy.



**Citation:** Filgueira NA. Hepatocellular carcinoma recurrence after liver transplantation: Risk factors, screening and clinical presentation. *World J Hepatol* 2019; 11(3): 261-272  
**URL:** <https://www.wjgnet.com/1948-5182/full/v11/i3/261.htm>  
**DOI:** <https://dx.doi.org/10.4254/wjh.v11.i3.261>

## INTRODUCTION

Liver transplantation (LT) is the treatment of choice for cirrhotic patients with early-stage hepatocellular carcinoma (HCC), because it concomitantly resects the tumor and the underlying liver disease, which is the main risk factor for the appearance of new tumors. The percentage of cases of HCC among patients waiting LT tripled from 2004 to 2015 in the United States, becoming the leading indication of LT in 2015 (23.9% of registrations)<sup>[1]</sup>. However, the shortage of organs for transplantation limits the selection of this therapeutic modality for HCC.

Despite using morphologic criteria, such as the Milan criteria (MC) (single nodule smaller than 5 cm or two or three nodules of up to 3 cm)<sup>[2]</sup>, to select HCC patients for LT, tumor recurrence (TR) still occurs in 15% to 20% of cases, being associated with an unfavorable prognosis<sup>[3-6]</sup>. Therefore, it is necessary to identify other risk factors for TR to refine patient selection and to identify modifiable factors that may reduce the incidence of TR.

## RISK FACTORS FOR TUMOR RECURRENCE

There are numerous studies that have sought to identify the risk factors for HCC recurrence after LT. We shall classify these factors according to the tumor, the patient, or the treatment (Table 1).

### **Factors related to the tumor**

**Staging, number and size of the nodules:** After 15 years of using the MC<sup>[2]</sup> in clinical practice, a systematic review showed that with the compliance of these criteria, cases of well-differentiated tumors were selected, without vascular invasion and with similar 5-year survival rate to that of the transplanted patients for nontumor causes<sup>[7]</sup>.

The increased risk of TR with the higher number of nodules is not linear, because, from three nodules and above, the increase in risk tends to be attenuated<sup>[8]</sup>. Another meta-analysis showed that the risk of TR was proportional to the diameter of the larger nodule, with no association with the number of nodules, probably because multiple nodules, however small, did not present higher frequency of vascular invasion<sup>[9]</sup>. These findings were confirmed in a retrospective cohort study that showed an increase of 36% in the risk of TR for each extra centimeter in the diameter of the larger nodule, with no association with the number of nodules<sup>[10]</sup>.

**Vascular invasion:** Macrovascular tumoral invasion can be identified by imaging exams and is considered a contraindication to the realization of LT. In turn, microvascular invasion (mIV) can only be detected by the analysis of the explant, being, therefore, unavailable in the preoperative period.

However, mIV tends to be associated with tumor staging, being observed in 16.6% of the tumors within the MC, and in 50.2% of those beyond the Up-to-seven criteria group (sum of the diameter of the largest node with the number of nodules smaller than seven)<sup>[8]</sup>.

The mIV is a determining factor in the risk of TR and survival, doubling the risk of death<sup>[8]</sup>. The presence of micro- and macrovascular invasion in the explant was associated with a significant increase in the TR [relative risk (RR), 2.42 and 7.82, respectively] and decreased 5-year recurrence-free survival (RFS) (44% and 13%, respectively, compared to 64% in patients without vascular invasion)<sup>[11]</sup>.

**Degree of differentiation:** Poorly differentiated tumors are found in 11% to 25% of patients who underwent LT<sup>[8,11-13]</sup>, and this frequency seems to increase as we expand the morphological selection criteria<sup>[8]</sup>. Poorly differentiated tumors entail higher risk of TR (39.3% vs 13%) and reduction of RFS by 5 years (39.9% vs 57.7%)<sup>[12]</sup>. However, a percutaneous biopsy presents low sensitivity (29%) and positive predictive value (35%) in the identification of poorly differentiated tumors, not improving the accuracy of the selection of candidates for LT, when associated to the MC<sup>[14]</sup>.

**Table 1 Factors possibly associated with the recurrence of hepatocellular carcinoma after liver transplantation**

Related to the tumor	Related to the patient	Related to the treatment
Tumor staging	Obesity	<b>Pretransplantation:</b>
Vascular invasion	Viral etiology	Percutaneous tumor biopsy
Differentiation's grade	HCV treatment	Waiting time
	NAFLD	Bridging therapy
		<b>Peri-transplantation:</b>
Alpha-fetoprotein		Donor's age
Neutrophil-lymphocyte ratio		Ischemia time
		Surgical technique
		<b>Posttransplantation:</b>
Enhanced uptake in PET scan		Immunosuppression
MRI findings with gadoxetic acid		Adjuvant sorafenib
Response to LRT		

MRI: Magnetic resonance imaging; LRT: Locoregional therapy; HCV: Hepatitis C virus; NAFLD: Non-alcoholic fatty liver disease.

**Alpha-fetoprotein:** Alpha-fetoprotein (AFP) levels are high in approximately 60% of the HCC cases<sup>[15]</sup>. Although losing diagnostic value, its role in the prognosis of HCC is relevant. A retrospective analysis, based on the United Network for Sharing Organs (UNOS) data, observed an inverse relationship between the level of AFP (from 16 ng/mL) and survival post-LT<sup>[16]</sup>.

Duvoux *et al*<sup>[17]</sup> have proposed a simple scoring system, associating the levels of AFP with the size and number of nodules. Using a cutoff value of two points to differentiate low- and high-risk patients, they found the following rates of TR: 8.8% and 50.6%, respectively, after LT.

A recent study reported that in patients with tumors within the MC, a monthly increase in the level of AFP greater than 7.5 ng/mL, in spite of locoregional therapy (LRT), was associated with the presence of mIV [odds ratio (OR) 6.8] and a greater risk of TR [(hazard ratio (HR), 3.9)]<sup>[18]</sup>.

Several authors have reported that the reduction of AFP levels after LRT is associated with a good prognosis<sup>[16,17,19,20]</sup>. Merani *et al*<sup>[21]</sup> showed that patients who achieved AFP levels below 400 ng/mL after LRT were less excluded by tumor progression and attained a higher survival rate than those who already had low values from the onset. Even patients with initial levels of AFP above 1000 ng/mL attained good survival, as long as the AFP levels were reduced with less than 400 ng/mL after LRT.

Some authors proposed the exclusion of patients with AFP levels higher than 1000 ng/mL from undergoing LT, found in 4.7% of the cases with tumors within the MC, which was strongly associated with mIV (OR, 6.8) and 5-year TR (47.3%)<sup>[19]</sup>. A recent study, based on the UNOS database, included 407 patients with HCC who underwent LT with AFP levels > 1000 ng/mL, which corresponded to 3.8% of the total number of cases. Of these, 23.9% achieved a reduction of AFP to less than 500 ng/mL with LRT, which was associated with a marked reduction of TR (13.3% *vs* 35%) and 5-year mortality rate (33% *vs* 51, 2%)<sup>[22]</sup>.

**Neutrophil-lymphocyte ratio:** Some tumors induce an inflammatory response that induces the release of cytokines and inflammatory mediators, increasing the risk of metastasis by inhibition of apoptosis, promotion of angiogenesis, and DNA damage. The neutrophil-lymphocyte ratio (NLR) in the peripheral blood can be a marker of inflammatory response, and its association with the poor prognosis of various tumors has already been demonstrated<sup>[23]</sup>. Some authors have studied the association between the NLR, calculated based on the immediate preoperative exams, and the risk of recurrence of HCC after LT. Halazun *et al*<sup>[24]</sup> found NLR  $\geq 5$  in 9% of the individuals transplanted for HCC, who presented a 5-year RFS of only 25%. They proposed a score by associating the NLR to the diameter of the larger nodule and observed a median survival of only 3 mo in patients with NLR  $\geq 5$  and tumor diameter > 3 cm. A meta-analysis confirmed the association of the NLR with mIV, multifocality, size, poor tumor differentiation, and shorter survival<sup>[25]</sup>.

**Enhanced uptake in positron emission tomography scan:** The diagnostic sensitivity of positron emission tomography scan (Pet scan) for HCC is only 50%, since well-differentiated tumors have comparable glycolytic activity to that of nontumor liver cells. [18F] FDG uptake by the tumor has been used as a marker of HCC aggressiveness, based on the association with mIV and poor tumoral differentiation, greater risk of dropout, greater risk of TR, and lower RFS and overall 5-year survival<sup>[26,27]</sup>.

**Findings from magnetic resonance imaging with gadoxetic acid:** A recent publication described the development of significantly higher TR in patients with satellite nodules (HR, 3.97) and peritumoral hypointensity in the hepatobiliary phase (HR, 4.24). The positive predictive value of these findings in predicting mIV in the explant was 84%, and the difference in RFS over 3 years was significant (27.5% vs 84.6%)<sup>[28]</sup>.

**LRT response:** LRT response may be a marker of the biological behavior of the tumor. LRT can be used pretransplant in the following two scenarios: (1) in tumors beyond MC, with the goal of reducing tumor mass and thus enabling the inclusion criteria (downstaging), or (2) in patients with tumors within the MC, as neoadjuvant therapy [bridging therapy (BT)], to prevent the removal of the patient from the list due to tumor progression (dropout). The treatment modalities that can be performed for LRT are transarterial chemoembolization (TACE), radiofrequency ablation, alcoholization, and radioembolization, depending on the characteristics of the tumor and the patient<sup>[29]</sup>.

Otto *et al*<sup>[30]</sup> observed that the response to TACE allows a better selection of candidates for LT than pathological data, such as tumor size, vascular invasion, and degree of differentiation. Patients who reached downstaging obtained a lower rate of TR (3.3%), while those who presented some degree of tumor progression presented a significantly lower 5-year RFS (22 vs 92%; RR, 21.7).

The University of California's group prospectively included patients with tumors beyond CM in a downstaging program provided they did not present macrovascular invasion and met one of the following criteria: (1) Single nodule less than or equal to 8 cm; (2) two or three nodules smaller than 5 cm, with a sum smaller than 8 cm; or (3) four to five nodules smaller than 3 cm with a sum smaller than 8 cm. About 65% of the cases achieved effective downstaging and were enrolled for LT after 3 mo. When compared to patients with MC tumors from the start, they had a greater 2-year dropout risk (34.2 vs 25.6%), but the RFS was similar<sup>[31]</sup>. A recent meta-analysis confirmed the good results with the downstaging process<sup>[32]</sup>, so much so that the American Association for the Study of Liver Diseases (AASLD) recommends the inclusion of such patients in the LT list<sup>[33]</sup>.

### Factors related to the patient

**Obesity:** In one sample, 25% of patients with HCC who underwent LT were obese and had twice the risk of death, a higher frequency of mIV, and tendency for a higher rate of TR, suggesting that the increased expression of vascular endothelial growth factor (VEGF) induced by the adipose tissue may stimulate tumor angiogenesis<sup>[34]</sup>. Another group has confirmed the increased risk of TR, with smaller RFS among overweight patients, suggesting that obesity induces a pro-oncogenic state, via reduction of adiponectin and increase of leptin, which would stimulate HCC proliferation, migration, and invasion<sup>[35]</sup>.

**Viral etiology:** A study from Taiwan described a strong association between the failure of prophylactic therapy against reactivation of hepatitis B in the posttransplant period and the risk of TR, both of which are related to the presence of a specific mutation of the virus, which seems to induce a pro-carcinogenic state<sup>[36]</sup>. Another study found a 2.45-fold higher risk of TR in patients with hepatitis B and viral load above 5 log, also finding an association between the reactivation of hepatitis B in the post-LT period and the risk of TR<sup>[37]</sup>.

There are controversial reports on the influence of hepatitis C on the risk of TR after LT due to HCC. Bozorgzadeh *et al*<sup>[38]</sup> compared a small group of transplanted HCC patients with and without hepatitis C and reported an association of viral infection with lower 5-year RFS. A group from Taiwan, in turn, found lower RFS in the subgroup of hepatitis C patients who evolved with rapid development of liver fibrosis after living-donor LT<sup>[39]</sup>.

**Hepatitis C virus treatment:** There are few reports on the impact of HCV treatment in the post-LT period on the risk of TR. Small case series have suggested that treatment with interferon-based schemes could be associated with a lower risk of TR<sup>[40]</sup>.

Data on the use of direct-acting antivirals (DAAs) to treat HCV in patients with

HCC who underwent LT are still scarce. In the CUPILT cohort, 314 patients transplanted for HCC were treated with DAAs after ca. 67 mo of transplant, attaining 96.8% sustained virological response (SVR), with only 2.2% of TR<sup>[41]</sup>.

Some authors have reported preliminary results regarding antiviral treatment in patients with HCC during the waiting time for transplantation. Yang *et al*<sup>[42]</sup> observed a tendency for a higher risk of TR in 18 patients treated with DAAs in pre-LT, who presented a surprisingly low rate of virologic response (50%), observing an association with histological features of poor prognosis, early TR, and extrahepatic metastases.

On the other hand, an Italian cohort achieved 94% SVR after treatment during the waiting time, with TR being observed in only 8.5% of them after 20 mo of follow-up<sup>[43]</sup>. Another study compared patients treated or not with DAAs while awaiting transplantation, with no difference in dropout risk, characteristics of the explant, or TR<sup>[44]</sup>.

**Non-alcoholic fatty liver disease:** Recently, some authors have described a more indolent biological behavior in HCC associated to non-alcoholic fatty liver disease (NAFLD). Lewin *et al*<sup>[45]</sup> analyzed the UNOS database and observed that the cases with HCC secondary to NAFLD presented a 32% lower rate of high-risk characteristics for TR. A study from the University of Toronto and University of San Francisco noted that among patients with tumors beyond MC, bearers of NAFLD showed a 80% lower rate of TR<sup>[46]</sup>.

### Factors related to treatment

**Percutaneous tumor biopsy:** Although the current consensus allows the diagnosis of HCC by imaging methods in most of the cases, percutaneous biopsy may still be necessary in cases with atypical radiological pattern<sup>[29,33]</sup>. In 2005, a Spanish group reported that the accomplishment of percutaneous biopsy was associated with a higher risk of TR, especially extrahepatic<sup>[47]</sup>. Lopez *et al*<sup>[48]</sup> studied patients with HCC who underwent biopsy and radiofrequency ablation before LT, finding no tumor implant in the needle path in patients who underwent the two procedures at the same time, while 16.7% of those who underwent radiofrequency after biopsy showed TR in the thoracic wall.

**Time to transplantation:** Studies based on the UNOS database reported an association between a short time to transplantation and increased risk of TR in the post-LT, with decreased survival. The authors suggested that the rigorous image monitoring during the waiting time could select the tumors with more favorable biological behavior<sup>[49,50]</sup>. A multicenter study found a dropout rate of 3.2% and 12.4% when the time between HCC diagnosis and LT was greater than 6 and 18 mo, respectively, despite the completion of LRT. The risk of 5-year TR was greater in patients transplanted before 6 mo or after 18 mo of diagnosis of HCC<sup>[51]</sup>.

**BT:** There are controversial reports on the benefits of BT, but an international conference recommended it when the likely waiting time is longer than 6 mo<sup>[52]</sup>, and the AASLD suggests BT in patients with tumors within the MC<sup>[33]</sup>. In their meta-analysis, Kulik *et al*<sup>[32]</sup> found no significant reduction in the risk of dropout after LRT in patients within the MC, while no impact on the risk of TR and RFS was observed.

A multicenter study examined 3601 transplanted patients with HCC, of which 79.3% received LRT, and did not observe difference in TR and RFS compared to those without these therapies. However, a greater risk of TR in those who developed only partial necrosis of the nodule was seen when compared to those without LRT<sup>[53]</sup>.

Another group confirmed the similarity of TR rates in patients within the MC who underwent LRT or did not and the higher risk of TR in patients with partial necrosis of the tumor, when compared to those with complete necrosis and without necrosis. They also found an association between partial necrosis of the tumor and increased risk of lymph node metastases, demonstrating that the partial necrosis was accompanied by greater density of peritumoral lymphatic vessels and increased expression of VEGF. These authors raised the hypothesis that tumor necrosis stimulates the production of growth factors and neoangiogenesis, facilitating the progression and lymphatic dissemination of the remaining tumor cells<sup>[54]</sup>.

A recently published retrospective cohort study found a 64% reduction in the risk of TR in patients undergoing TACE when adjusted by the initial size of the lesion, not observing this association in patients who underwent radiofrequency, suggesting that the greatest benefits would be achieved in patients with tumors with a diameter greater than 4 cm<sup>[10]</sup>.

**Donor's age:** One study observed higher median age of the donor among patients who evolved with TR after LT, which remained significant after multivariate analysis,

which led them to speculate if older livers would have less tolerance to the preservation injury and increased susceptibility to cold ischemia<sup>[55]</sup>. A similar result was observed in a survey of the UNOS database, in which a 70% higher risk of TR was found in patients who received grafts from donors older than 60 years, regardless of the etiology of liver disease<sup>[56]</sup>.

**Ischemia time:** Warm and cold ischemia times are related with the intensity of ischemia-reperfusion injury, which stimulates immune and inflammatory phenomena. Nagai *et al*<sup>[57]</sup> observed a gradual increase in the risk of TR with the increase of the ischemia time, with a significant difference after 10 h of cold ischemia and 50 min of warm ischemia. A German group found an association between a warm ischemia time greater than 50 minutes and the risk of TR<sup>[58]</sup>. It is speculated that ischemia-reperfusion injury can accelerate growth and implantation of HCC micrometastases present at the time of LT.

**Surgical technique:** The preservation of the vena cava in piggyback procedures reduces the hemodynamic instability and the warm ischemia time. On the other hand, the preservation of the cava theoretically could increase the risk of persistence of tumor-affected margins, and the greater manipulation of the patient's liver could increase the spread of tumor cells. Mangus *et al*<sup>[59]</sup> found no difference in the frequency of TR nor RFS according to the technique of venous reconstruction, while a Polish study found a higher risk of TR in patients undergoing the conventional technique<sup>[60]</sup>.

The technique of living-donor LT implies piggyback anastomosis between the receiver and the partial graft of the donor. A meta-analysis reported ca. 60% greater RFS in patients who underwent cadaver LT than those who underwent living-donor LT<sup>[61]</sup>. The possible explanations for the worse prognosis of living-donor LT in the treatment of HCC would be the following: (1) Shorter waiting list, which would prevent the identification of more aggressive tumors; (2) greater surgical manipulation, which could contribute to the spread of neoplastic cells; and (3) rapid hepatic regeneration after living-donor LT, which would release growth factors and cytokines that could contribute to the TR<sup>[62]</sup>.

**Immunosuppression:** In the transplantation scenario for the treatment of a neoplasia, a balance must be sought between immunological risks (graft rejection) and oncological risks (TR). The association between the serum level of tacrolimus in the first month after LT with the risk of TR has already been demonstrated, and it was observed that patients with a level above 10 ng/ml presented a 2.8-fold higher risk of TR<sup>[63]</sup>.

As mTOR inhibitors (sirolimus and everolimus) inhibit cell proliferation and angiogenesis, it has been postulated that these drugs could reduce the risk of TR after LT. A meta-analysis of five cohort studies found 70% lower risk of TR in patients who used sirolimus associated to a calcineurin inhibitor<sup>[64]</sup>. Another meta-analysis including 42 studies showed a lower frequency of TR among patients treated with an mTOR inhibitor, although this difference was only significant among patients with tumors within the MC<sup>[65]</sup>. However, both meta-analyses assumed that these studies were of low quality.

A randomized, prospective, multicenter trial (SILVER trial) included 525 patients transplanted for HCC, associating or not sirolimus, from 4 to 6 weeks of LT, with the traditional immunosuppression scheme of each participating center. Although the 5-year TR rate was similar between the groups, those treated with sirolimus showed a higher percentage of RFS in the first 4 years, and from the end of the first year, the risk of TR was 50% lower. When an analysis of subgroups was performed, the addition of sirolimus was beneficial in patients with tumors within the MC. In general, the addition of sirolimus to the immunosuppressive regimen was associated with a gain of 6.4 mo in the RFS<sup>[66]</sup>.

Another study using a historical control group evaluated the use of everolimus from the third week after LT on the risk of TR, with no significant difference between the groups<sup>[67]</sup>.

**Adjuvant sorafenib:** Sorafenib is a multiple tyrosine kinase inhibitor that exerts an antiangiogenic effect through the inhibition of VEGF and platelet-derived growth factor and was the first drug to provide increased survival for patients with advanced HCC<sup>[68]</sup>. Its use as an adjuvant therapy after LT in order to reduce the risk of TR began to be described from 2010 in small case-control studies, with varying results, but at the expense of toxicity that required a reduction of dose in 75% to 82% of cases<sup>[69-71]</sup>.

## MONITORING OF THE PATIENT AFTER LT FOR HCC

There is no consensus on the protocol for monitoring TR after LT, without definition on the modality of exams to be performed and frequency or duration of follow-up. Most authors monitored the patients with thoracic-abdominal computed tomography (CT) and AFP levels with 3- to 6-mo intervals in the first 2 or 3 years, increasing the interval between exams from that date. Bone scintigraphy is usually reserved for those cases that present with symptoms or TR. There is also no consensus on the duration of screening of TR<sup>[5,6,72,73]</sup>. A consensus conference published a vague recommendation of a combination of imaging exams (CT or magnetic resonance imaging), and AFP every 6 to 12 mo<sup>[54]</sup>.

A multicenter study has proposed a protocol of postoperative monitoring, stratified according to the risk of TR, which would be estimated by the RETREAT score, calculated according to the following three simple data: AFP on the occasion of the LT, vascular invasion, and sum of diameter with the number of viable nodules (Table 2)<sup>[74]</sup>.

## CLINICAL PRESENTATION OF HCC RECURRENCE AFTER LT

The recurrence of HCC after LT usually occurs early, with a median RFS of 12 to 16 mo. In most cases, TR is of poor prognosis with a median survival after recurrence of 7 to 16 mo<sup>[4-6,72,73]</sup>.

Approximately 75% of the TR occur during the first 2 years after the LT, and only 10% of them are detected after the fourth year<sup>[6]</sup>. Most authors consider early TR the one that develops during the first year after LT. From a pathophysiological point of view, early TR occurs due to pretransplantation staging failure, which fails to identify existing metastases, or by implantation and growth of circulating tumor cells in another organ. On the other hand, late TR would arise as a result of late seeding of cells that remained latent and in less number for a long time after LT<sup>[3]</sup>.

The clinical course of TR after LT tends to be dramatic, because it involves tumoral dissemination in immunosuppressed patients. TR after LT must be considered a systemic event, because it is restricted to the graft in only 30% of cases<sup>[75]</sup>. The organs most commonly involved in TR are the lungs, liver, bones, lymph nodes, and adrenal glands. Involvement of more than one organ is observed in more than 50% of the cases<sup>[6]</sup>.

RFS has a strong impact on survival after TR, since the early TR usually denotes greater tumor burden and more aggressive biological behavior<sup>[5,6,73]</sup>. Other factors seem to impact survival after TR including the following: nutritional status on the occasion of the TR<sup>[4]</sup>, bone metastases<sup>[6,72]</sup>, level of AFP after TR<sup>[4-6]</sup>, lymphopenia<sup>[4]</sup>, the involvement of multiple organs<sup>[76]</sup>, and impossible treatment with curative intent of TR<sup>[5]</sup>.

The use of therapy with curative intention, such as surgical resection or ablation by radiofrequency, is usually possible in patients with TR with less aggressive behavior, represented by late TR, lower levels of AFP, lower number and size of tumor nodules, and single TR site, which is associated with a significantly higher survival rates (22 *vs* 9 mo)<sup>[77]</sup>.

A Euro-American study developed a prognostic score after TR, based on the presence of the following three signs of poor prognosis: TR during the first year after LT (HR, 1.6), AFP level higher than 100 ng/mL at TR (HR, 2.1), and tumor not susceptible to curative therapy (HR, 4.7). Patients without any of these poor prognostic factors achieved a 5-year survival rate of 50% (Table 3)<sup>[5]</sup>. This score was recently validated in another multicenter study, which confirmed its usefulness in predicting survival after TR<sup>[77]</sup>.

## CONCLUSION

LT is the best treatment option for cirrhotic patients with early-stage HCC, but it faces the problem of scarcity of donors and the risk of TR, which affects between 15% and 20% of the cases, probably because morphologic criteria do not predict the tumor biological behavior. Besides well recognized risk factors for HCC recurrence after LT, as tumor staging and vascular invasion, some other factors are strongly associated with the recurrence risk, such as AFP levels, tumor uptake of FDG in Pet scan and response to LRT. Some therapy-related risk factors may be modified to reduce recurrence risk, as waiting time and post-transplant immunosuppression. Tumor recurrence after transplantation usually portends a poor prognosis with a median

**Table 2 RETREAT score to estimate the risk of tumor recurrence after liver transplantation in patients with tumors within the Milan criteria and proposed protocol for tumor recurrence screening<sup>[74]</sup>**

Risk factor	Score
Alpha-fetoprotein level before LT	
0–20 ng/mL	0
21–99 ng/mL	1
0–999 ng/mL	2
> 1000 ng/mL	3
Microvascular invasion	2
Sum of the diameter of the largest viable tumor and the number of viable nodules	
0	0
1.1–4.9	1
5.0–9.9	2
≥ 10	3
<b>RETREAT Score</b>	<b>Screening Protocol</b>
0 points	Screening not needed
1–3 points	Screening every 6/6 mo for 2 yr
4 points	Screening every 6/6 mo for 5 yr
≥5 points	Screening every 3–4 mo for 2 yr Exams every 6 mo between the 2nd and 5th year

TR: Tumor recurrence; LT: Liver transplantation.

survival of 7 to 16 mo. Although there are no structured studies on the treatment of HCC recurrence after LT, it is important to modify the paradigm that TR is always fatal. The implementation of a regular screening protocol may allow the establishment of diagnosis at an early stage, which might provide effective treatment for some patients, improving the dismal prognosis of this clinical condition.

**Table 3** Prognostic score for the prediction of survival after hepatocellular carcinoma recurrence after liver transplantation<sup>[77]</sup>

Poor prognostic variables		
Early tumor recurrence (during the first year after transplantation)		
AFP ≥ 100 ng/mL at the time of the TR		
Tumor not susceptible to curative therapy		
Score	Prognostic score	1st year survival after TR
No variable	Good prognosis	73%
1 or 2 variables	Moderate prognosis	55%
3 variables	Poor prognosis	17%

TR: Tumor recurrence.

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