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**Liver transplantation for hepatocellular carcinoma - factors influencing outcome and disease-free survival**

Fahrner R *et al*. Liver transplantation in HCC

René Fahrner, Felix Dondorf, Michael Ardelt, Yves Dittmar, Utz Settmacher, Falk Rauchfuß

**René Fahrner, Felix Dondorf, Michael Ardelt, Yves Dittmar, Utz Settmacher, Falk Rauchfuß,** Department of General, Visceral and Vascular Surgery, Jena University Hospital, 07740 Jena, Germany

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**Correspondence to: Falk Rauchfuß, MD, MSc,** Department of General, Visceral and Vascular Surgery, Friedrich-Schiller-University Jena, Jena 07747, Germany. [falk.rauchfuss@med.uni-jena.de](mailto:Falk.Rauchfuss@med.uni-jena.de)

**Telephone:** +49-3641-9322695

**Fax**: +49-3641-9322602

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**Abstract**

Hepatocellular carcinoma is one of the leading causes of cancer-related death worldwide. Liver transplantation can be a curative treatment in selected patients. However, there are several factors that influence disease-free survival after transplantation. This review addresses the pre-, intra- and postoperative factors that influence the risk of tumor recurrence after liver transplantation.

**Key words:** Liver transplantation; Hepatocellular carcinoma; Recurrence; Survival; Risk factor; Diagnostics

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**Core tip****:** Hepatocellular carcinoma is one of the leading causes of cancer-related death worldwide. Liver transplantation can be a curative treatment in selected patients. This review addresses the pre-, intra- and postoperative factors that influence disease-free survival and the risk of tumor recurrence after liver transplantation. Furthermore, novel diagnostic methods are presented and discussed.

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**INTRODUCTION**

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide[[1](#_ENREF_1),[2](#_ENREF_2)]. Most HCC co-occurs with liver cirrhosis, and the etiology of liver cirrhosis leading to HCC differs among global regions, *e.g.*, hepatitis C virus infection in North America, Europe and Japan and hepatitis B virus infection in China, South Korea and Taiwan[[1](#_ENREF_1)].

Depending on hepatic function, liver transplantation is a curative option for selected HCC patients. However, the recurrence rate after liver transplantation is reported to be between 5% and 23%[[3-6](#_ENREF_3)].

This review addresses the issue of HCC recurrence after liver transplantation and is subdivided into three sections: preoperative, intraoperative and postoperative factors.

**Preoperative factors**

***Size and number of HCC nodules***

In 1996, Mazzaferro *et al*[[7](#_ENREF_7)] introduced the Milan criteria (MC), which shows a survival benefit in HCC patients with one tumor nodule < 5 cm diameter or three tumor nodules with a maximum diameter < 3 cm for each nodule. The MC remain the gold standard for decision-making in liver transplantation settings for HCC patients.

The MC have been challenged by different authors and work-groups aiming at an expansion of the criteria (see Table 1). However*,* there is only a consensus that “modest expansion of the criteria should consider the dynamics of the waiting list and whether a worse prognosis could be tolerated, if there is no prejudice for patients without HCC”[[4](#_ENREF_4)].

What we do know is the so-called “Metroticket paradigm”: the larger the tumor burden, the lower the post-transplant expected survival. However, reliance on tumor size and number of nodules is not the most ideal approach because biological parameters such as the response to local-ablative therapy or tumor grading are not included.

In practice, there are two important pipelines in liver allocation: center-based allocation, meaning that a graft is offered to a center that chooses the ideal recipient for a donor organ, and MELD-based allocation, which involves a waiting list where patients with a high MELD score receive an organ sooner than patients with a low MELD score. This is important in HCC patients because most have good hepatic function and subsequently a low MELD score. These patients have the chance of requesting an “exceptional” MELD score when fulfilling certain criteria. This phenomenon brings us back to the MC: in most countries around the world, the MC is the deciding tool for an exceptional MELD request (see Table 2).

However, there is increasing evidence that a decision on organ allocation based only on radiological findings does not reflect the reality of tumor biology. A large single-center study of over 800 patients undergoing LT because of HCC revealed that in addition to tumor size, other clinicopathological parameters are helpful and necessary to identify patients with a lower risk of tumor recurrence[[8](#_ENREF_8)]. Varona *et al*[[5](#_ENREF_5)] showed that the French prognostic model, including pre-transplant α-fetoprotein (AFP), tumor size and number of nodules, was better at detecting patients with HCC recurrence after liver transplantation than the MC or up-to-7 criteria. Yao *et al*[[9](#_ENREF_9)] showed that expanded tumor size had no negative effect on patient survival or tumor recurrence. In conclusion, the development of the MC was an important step towards improved outcome after LT in HCC, but these criteria are likely too narrow, and further adaptations are necessary.

***α-Fetoprotein***

The biomarker AFP, which is encoded in humans by the AFP gene located on chromosome 4[[10-12](#_ENREF_10)], is a frequently used serum parameter for the detection of HCC. Unfortunately, the sensitivity of AFP is limited because non-tumor liver diseases are also associated with high serum AFP levels[[13](#_ENREF_13),[14](#_ENREF_14)], and AFP levels are not always increased in HCC[[15](#_ENREF_15)]. Generally speaking, the higher the tumor differentiation, the lower the AFP level. However, elevated AFP levels predict HCC recurrence in a multi-predictive model, together with elevated liver enzymes, lactate dehydrogenase, small resection margins and advanced tumor stage[[16](#_ENREF_16)]. In an analysis of approximately 1.500 patients with liver cirrhosis, AFP levels showed a sensitivity of 99% and a specificity of approximately 72% to detect HCC in combination with ultrasound[[17](#_ENREF_17)]. Recently, several studies showed that during hepatitis treatment, AFP levels were helpful to detect HCC development[[18-20](#_ENREF_18)].

The recurrence of HCC after liver transplantation is a problem; therefore, patients with a high risk of recurrence must be detected. A retrospective cohort study showed that a combination of biomarkers such as AFP and the MC was more sensitive for predicting tumor recurrence than the MC alone[[21](#_ENREF_21)]. In a multivariate analysis, AFP was the only pre-transplant predictor of HCC recurrence and mortality in a cohort of 1.074 patients transplanted for HCC[[22](#_ENREF_22)]. Grat *et al*[[23](#_ENREF_23)] analyzed 121 patients undergoing liver transplantation for HCC and demonstrated that the combination of up-to-7 criteria and University of California, San Francisco (UCSF) criteria with AFP levels less than 100 ng/ml was associated with a minimized risk for tumor recurrence. Previously, in a small cohort of 20 patients, a cut-off level of 100 ng/ml for AFP has been shown to be a predictor for HCC recurrence after liver transplantation[[24](#_ENREF_24)].

AFP remains the gold standard biomarker for HCC detection and a prognostic marker for post-transplant tumor recurrence, particularly in combination with other morphological tumor criteria or diagnostic tools.

***Response to bridging***

To avoid tumor progression and waitlist drop-off, patients waiting for liver transplantation undergo local bridging therapies[[25](#_ENREF_25)] such as transarterial chemoembolization (TACE), which has been shown to be effective and was first proposed as a treatment option in 1977[[26](#_ENREF_26)]. TACE produces a combination of localized chemotherapy and ischemia due to occlusion of feeding vessels with concomitant tumor necrosis[[27](#_ENREF_27)]. Other bridging treatments are selective internal irradiation (SIRT) or radiofrequency ablation (RFA)[[28](#_ENREF_28),[29](#_ENREF_29)]. The question of who is likely to benefit from locoregional therapy remains controversial, but currently the proposed optimal candidates for TACE have almost normal liver function, a tumor localized to the liver, an estimated survival of 16 mo[[30](#_ENREF_30)], tumors of > 3 cm in size, and signs of hypervascularization[[31](#_ENREF_31)]. Some authors noted that poor liver function, vascular invasion, extrahepatic tumor load, bilobar tumors, arterioportal fistula, portal vein thrombosis or renal dysfunction are contraindications for TACE[[30](#_ENREF_30),[32](#_ENREF_32)]. A systematic review analyzed the different techniques and substances used for TACE[[33](#_ENREF_33)]. Doxorubicin, epirubicin or cisplatin alone or in combination are used as local chemotherapy. In addition to these drugs, lipiodol, gelatin sponge particles or beads are injected after the chemotherapeutic substance to embolize the tumor-supplying artery. This should be performed in a selective or superselective manner to avoid damage to the nontumorous liver[[31](#_ENREF_31),[33](#_ENREF_33)]. Acute liver failure, acute renal failure, gastrointestinal bleeding and abscess formation are reported side effects of TACE, and a treatment related mortality rate of 2.4% was reported[[33](#_ENREF_33)], mainly because of liver failure. The timing of TACE before liver transplantation remains unclear[[34](#_ENREF_34)]. Decaens *et al*[[35](#_ENREF_35)] showed that TACE only had a beneficial effect in patients with a waiting time longer than four months. Others showed a positive effect of TACE on survival and tumor recurrence in patients with at least 6 months on the waiting list[[34](#_ENREF_34),[36](#_ENREF_36)]. The complete response is reported to be up to 30%[[37](#_ENREF_37)], but rates of progressive disease following treatment have been reported to be 20%[[38](#_ENREF_38)]. Overall, several studies have demonstrated that TACE prior to liver transplantation was associated with a good response rate for advanced tumor stages with acceptable survival rates after liver transplantation of 40% to 90% after at least four years, even in patients with HCC outside the MC[[39-43](#_ENREF_39)]. A recently published study investigated 204 patients with HCC undergoing liver transplantation and showed a reduced survival of patients with TACE prior to transplantation. The authors concluded that this might be because of a higher amount of pulmonary and distant metastasis[[44](#_ENREF_44)]. Although most results appear promising, there are no controlled prospective trials to investigate the benefits of TACE prior to liver transplantation; thus, this issue will remain controversial.

In contrast to TACE, SIRT is more effective in cases of large and multifocal HCC[[28](#_ENREF_28)]. Negative side effects are rare[[45-47](#_ENREF_45)]. Portal vein thrombosis is not an absolute contraindication for selective internal irradiation and therefore offers an alternative to TACE[[48](#_ENREF_48)]. Selective internal irradiation leads to downstaging or tumor size reduction in 32% to 56% of patients with HCC[[49](#_ENREF_49),[50](#_ENREF_50)]. Selective internal irradiation therapy is useful in bridging patients with HCC until liver transplantation[[49](#_ENREF_49),[51](#_ENREF_51)].

During local tumor therapy with RFA, the tumor is destroyed because of local hyperthermia or chemical injury. RFA is performed percutaneously or during a surgical procedure[[29](#_ENREF_29)]. Thus far, RFA has been shown to be a safe and effective procedure as a bridging therapy prior to transplantation[[29](#_ENREF_29),[52-55](#_ENREF_52)]. A combination of different bridging therapies such as RFA and TACE are safe and effective regarding tumor necrosis[[56](#_ENREF_56)]. However, a Cochrane analysis demonstrated that there is a lack of randomized clinical trials and no evidence of the superiority of RFA for bridging therapy[[57](#_ENREF_57)].

***Positron emission tomography***

Positron emission tomography (PET) measures the metabolic activity of tumor tissue. In most oncologic cases, the tracer 18F-fluorodeoxyglucose (18F-FDG), an analog of glucose, is used[[58](#_ENREF_58)].

The role of 18F-FDG-PET as a diagnostic tool in HCC patients is controversial. One of the first studies dealing with PET in HCC was published by Teefey *et al*[[59](#_ENREF_59)]. In this work, ultrasound, computed tomography, magnet resonance imaging and PET were compared. PET showed the worst sensitivity but displayed good specificity. A Chinese group noted the value of PET scans for the diagnosis of HCC lymph node metastases in a pre-transplant setting and for the detection of tumor recurrence after liver transplantation[[60](#_ENREF_60)]. A study by Lee *et al*[[61](#_ENREF_61)] showed an excellent predictive value for the ratio of the maximum standard uptake volume of the tumor to the maximum standard uptake volume of non-tumoral liver tissue, which predicted tumor recurrence after liver transplantation. Similar results were confirmed by several workgroups[[62-66](#_ENREF_62)].

In non-transplant settings, 18F-FDG-PET is useful for estimating tumor differentiation[[67](#_ENREF_67)], the probability of microvascular invasion[[68](#_ENREF_68)], the diagnosis of bone metastases[[69](#_ENREF_69),[70](#_ENREF_70)] and the estimation of tumor-free or overall survival[[67](#_ENREF_67),[71-77](#_ENREF_71)].

One major issue is the dependency of PET results on tumor grade. Well-differentiated tumors have nearly the same metabolic activity as the surrounding liver tissue and therefore have similar tracer uptake.

However, as shown above, 18F-FDG-PET correlated well with microvascular invasion and post-transplant outcome. 18F-FDG-PET is a good marker for the biological behavior of HCC[[58](#_ENREF_58)]. Therefore, 18F-FDG-PET appears to be a promising approach to evaluate the aforementioned findings using a prospective approach.

***Metabolomics, proteomics, transcriptomics***

AFP is the standard serum biomarker for the detection of HCC. As previously mentioned, AFP is not specific for HCC, and therefore diagnosis on the basis of this biomarker is limited. However, until now, no other marker has replaced AFP to become the new standard in clinical routine use. To overcome this dilemma, new and more sensitive markers have been investigated using metabolomic, transcriptomic and proteomic techniques.

Metabolomics is a global unbiased analysis of biomarkers that identifies small molecular metabolites reflecting normal biological or pathological processes in biological fluids, tissues, organs and organisms[[78-81](#_ENREF_78)]. Metabolomics can measure the metabolite complements in living and diseased systems[[81](#_ENREF_81)]. In contrast, proteomics is able to analyze all proteins within a biological system[[82](#_ENREF_82)].

Thus far, several metabolites have been investigated and proposed as potential biomarkers for HCC, such as the aspartate metabolism pathway[[83](#_ENREF_83)], 1-methyladenosine[[81](#_ENREF_81)], and aberrant lipid metabolism[[84](#_ENREF_84)]. Urinary liquid chromatography-hybrid triple quadrupole linear ion trap mass spectrometry (LC-QTRAP MS) revealed that butyrylcarnitine and hydantoin-5-propionic acid were markers to distinguish patients with HCC from patients with liver cirrhosis without HCC[[85](#_ENREF_85)]. Huang *et al*[[86](#_ENREF_86)] showed that betaine and propionylcarnitine in tissue and serum could distinguish HCC from hepatitis or cirrhosis better than AFP alone. A combination of metabolomics and transcriptomics reported reduced cellular glucose levels and reduced metabolites of cellular energy production in HCC[[87](#_ENREF_87)]. A proteomic analysis detected 87 differently expressed proteins in patients with early HCC recurrence involved in catalytic pathways, signal transduction and cell organization[[88](#_ENREF_88)] and quantified novel phosphorylation sites that might be important for tumor progression in HCC[[89](#_ENREF_89)]. The fields of metabolomics, transcriptomics and proteomics are still emergent fields in cancer research. For most candidate metabolites or proteins, a definite role in HCC development and tumor progression is unclear, and further investigations are required. Thus far, we do not have a clinically applicable biomarker for HCC detection other than AFP.

***Micro-RNAs***

Micro-RNAs (miRNAs) are small noncoding RNA molecules that are not transcribed into proteins but consist of a few nucleotides that are important for regulating the stability and translation of protein-coding messenger RNAs[[90](#_ENREF_90),[91](#_ENREF_91)]. In 1993, miRNAs were first described[[92](#_ENREF_92),[93](#_ENREF_93)]; since then, hundreds of miRNAs have been identified. miRNAs play an important role in tumorigenesis[[94-96](#_ENREF_94)]. In HCC, a number of miRNAs have been identified with partially prognostic significance[[90](#_ENREF_90),[97](#_ENREF_97),[98](#_ENREF_98)]. These miRNAs can be down-regulated, *e.g.*, miR 122[[99](#_ENREF_99),[100](#_ENREF_100)] and miR 199[[101](#_ENREF_101),[102](#_ENREF_102)], or up-regulated, *e.g.*, miR 21[[103](#_ENREF_103)], miR 221[[104](#_ENREF_104),[105](#_ENREF_105)], and miR 222[[104](#_ENREF_104),[106](#_ENREF_106),[107](#_ENREF_107)]. This list includes only some of the previously reported miRNAs. Therefore, miRNAs could be important diagnostic and therapeutic targets in the future of cancer and HCC therapy.

***Circulating tumor cells***

Circulating tumor cells (CTCs) in the blood are thought to be responsible for tumor recurrence and tumor metastasis after complete surgical resection[[108](#_ENREF_108),[109](#_ENREF_109)]. Despite the radical resection of localized HCC with hepatectomy or liver transplantation, postoperative tumor recurrence and metastasis are frequently observed[[110](#_ENREF_110),[111](#_ENREF_111)], with the transplanted liver the most frequent site of early recurrence[[112](#_ENREF_112)]. After access of the primary tumor cells to the blood stream, CTCs are postulated to be responsible for this tumor recurrence[[112](#_ENREF_112),[113](#_ENREF_113)]. Several methods have been investigated in the past to detect CTCs, mainly based on the identification of tumor-specific antigens or epithelial cell surface antigens that are present on the primary tumor[[114](#_ENREF_114),[115](#_ENREF_115)]. One of the most frequently used markers for the detection of circulating tumor cells is the epithelial cell adhesion molecule (EpCAM), which is only expressed on a small proportion of HCC tumors[[116](#_ENREF_116)]. In addition, in one-third of patients, only low numbers of CTCs are detectable[[117](#_ENREF_117)]. Therefore, this technique is not suitable for the routine detection of HCC CTCs[[118](#_ENREF_118)]. Novel approaches to detect CTCs showed promising results[[119](#_ENREF_119),[120](#_ENREF_120)], but until CTC detection is able to guide the therapy of HCC patients, further basic and clinical research is required.

**Intraoperative factors**

***Ischemia time***

Intraoperative factors are less likely to be associated with a tumor recurrence in the long-term. However, there is some evidence that ischemia times play a significant role in the recurrence of HCC.

A recent published study by Nagai *et al*[[121](#_ENREF_121)] showed a significant effect of both cold (CIT) and warm ischemia time (WIT) on post-transplant HCC recurrence. In the multivariate analysis, a CIT of more than 10 hours and a WIT of more than 50 min were risk factors for the development of a recurrent HCC[[121](#_ENREF_121)]. These results were confirmed by a Munich workgroup[[122](#_ENREF_122)].

This observation is explained by ischemia-reperfusion injury, which leads to hepatic microcirculatory barrier dysfunction and activates cell signals related to invasion and migration[[121](#_ENREF_121)]. Furthermore, a cellular cascade leading to angiogenesis, cellular proliferation and growth is activated by ischemia.

This theory is confirmed by an analysis by Croome *et al*[[123](#_ENREF_123)], who showed an inferior outcome in HCC patients who received an organ from a donor who underwent cardiac death. These grafts are exposed to additional WIT.

***Transfusion***

Bleeding during liver transplantation remains a major problem, and sometimes large amounts of blood products are required[[124-127](#_ENREF_124)]. Over the last decades, there has been a significant reduction in the need for transfusions[[128](#_ENREF_128)]. Several studies showed that blood loss and transfusion during liver transplantation were associated with the decreased overall survival of patients and increased complications[[129](#_ENREF_129),[130](#_ENREF_130)]. In addition, perioperative transfusion is associated with earlier tumor recurrence and cancer-related mortality in colorectal cancer resection[[131-135](#_ENREF_131)] and liver resection for colorectal liver metastases[[136](#_ENREF_136),[137](#_ENREF_137)]. Shiba *et al*[[138](#_ENREF_138)] showed that a reduction of blood supply during liver resection for HCC was associated with increased survival. In a meta-analysis of 5.635 patients undergoing surgery for HCC, survival, tumor recurrence and complications were negatively correlated with blood transfusion[[139](#_ENREF_139)]. However, the use of intraoperative autotransfusion during liver surgery because of malignancy showed no negative effects in terms of survival or tumor dissemination[[140](#_ENREF_140),[141](#_ENREF_141)]. Several studies have investigated the safety of blood salvage autotransfusion regarding tumor recurrence during liver transplantation in HCC patients. The authors concluded that in cases where nonruptured HCC tumor cells were filtered, or particularly when a leukocyte depletion filter was used, no higher risk of tumor recurrence was present[[142-144](#_ENREF_142)].

**Postoperative factors**

***Immunosuppression***

There is a relationship between the inflammatory state and carcinogenesis[[7](#_ENREF_7),[145](#_ENREF_145)]. Pro-inflammatory cells and cytokines play a pivotal role in tumor growth, tumor invasion and tumor spread[[146](#_ENREF_146),[147](#_ENREF_147)]. Therefore, immunosuppression after transplantation can modify the inflammatory state and influence tumor recurrence. Most immunosuppression has a negative effect on the outcome of patients with HCC undergoing liver transplantation. Steroids[[148](#_ENREF_148)], basiliximab[[149](#_ENREF_149)] and calcineurin inhibitors (CNIs)[[150](#_ENREF_150)] are postulated to be associated with an increased risk of HCC recurrence. In contrast, several studies reported that mammalian targets of rapamycin inhibitors (mTORi) have positive effects on tumor recurrence and are favored drugs in HCC patients after liver transplantation[[151-153](#_ENREF_151)]. A meta-analysis analyzing five studies demonstrated a decreased recurrence rate and increased recurrence-free and overall survival in patients with sirolimus-based immunosuppression compared to patients with CNIs[[154](#_ENREF_154)]. One reason for the positive effect of mTOR could be the inhibition of the PI3K/Akt/mTOR pathway, which is a key regulator of the cell cycle and is responsible for cell proliferation and cancer[[155](#_ENREF_155)]. However, thus far, randomized controlled prospective studies with long-term follow-up investigating the influence of the immunosuppression treatment are lacking[[156](#_ENREF_156)].

***Adjuvant treatment***

Even after the use of a potentially curative treatment of gastrointestinal tumors, adjuvant treatment is used in most cases depending on the tumor stage. For HCC, this concept was not accepted for a long time[[157](#_ENREF_157)]. A review by Duvoux *et al*[[158](#_ENREF_158)] showed the problem with adjuvant therapy protocols after liver transplantation: most studies were small and retrospective with a low level of evidence. The authors concluded that the homogeneous and ethical selection of patients with a high risk of recurrence, stratification by confounding factors such as pre-transplant therapies and post-transplant immunosuppression, relevant endpoints focusing on recurrence, and appropriate follow-up are the key points for appropriate studies on this issue. Nearly the same conclusions were drawn two years later by Fujiki *et al*[[159](#_ENREF_159)].

Even recently published trials lack the inclusion of a sufficient number of patients:

a study by Teng *et al*[[160](#_ENREF_160)] showed a beneficial effect of sorafenib in a case-control study. However, sorafenib was used in only eleven patients with HCC beyond the MC in either a curative intervention (*n* = 5) or a palliative regime after liver transplantation. Another prospective trial also showed a benefit of sorafenib application after LT in seven patients with HCC beyond the MC compared to a historic control group[[161](#_ENREF_161)].

The increased toxicity of sorafenib in patients after liver transplantation should be taken into account. This increased toxicity, which is not mechanistically understood, should lead to a dose reduction in affected patients[[162](#_ENREF_162)].

In addition to sorafenib, Licartin has been discussed as a potential adjuvant treatment for HCC[[158](#_ENREF_158),[159](#_ENREF_159)]. One Chinese study evaluated Licartin, an 131I-radiolabeled murine monoclonal antibody, in a transplantation setting with excellent results regarding the tumor recurrence rate and the overall survival in the treatment group[[163](#_ENREF_163)]. More data or even multicenter data for Licartin after liver transplantation are unfortunately still lacking.

Some authors have used conventional chemotherapy protocols for the treatment of HCC after liver transplantation. Zhang *et al*[[164](#_ENREF_164)] showed good short-term (one year) results for a treatment protocol using the FOLFOX regime. The overall survival was even better in the midterm (three years), but the recurrence rate did not differ significantly from the control after this time period. Wu *et al*[[165](#_ENREF_165)] performed a randomized three-arm study and showed that the gemcitabine regimen and conventional chemotherapy significantly improved the survival rate and disease free survival rate of HCC patients who had major vascular invasion and/or microvascular invasion after liver transplantation compared to a best supportive care group.

In summary, the best approach for adjuvant treatment protocols has not been identified. Large, prospective, randomized studies should be performed in the future.

**CONCLUSION**

Liver transplantation is the treatment of choice for selected patients. There are several factors that should be taken into account, particularly in preoperative settings. The previously used selection criterion of pure morphometric variables should be changed to include biological parameters, which offer a better risk stratification for tumor recurrence.

In addition to intraoperative parameters that influence the post-transplant prognosis (ischemia times, transfusion), immunosuppression is an important tool to prevent or at least reduce the recurrence of hepatocellular carcinoma. Adjuvant protocols have not yet been established.

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**Table 1 Overview of the selection criteria for liver transplantation**

|  |  |  |
| --- | --- | --- |
| **Name** | **Criteria** | **Reference** |
| Milan | * 1 tumor < 5 cm in diameter OR * ≤ 3 tumor nodules, each ≤ 3 cm in diameter * No extrahepatic manifestation * No vascular invasion | Mazzaferro *et al*[[7](#_ENREF_7)] |
| Up-to-seven criteria (“new Milan”) | * Seven as the sum of the size of the largest tumor (in cm) and the number of tumors | Mazzaferro *et al*[[166](#_ENREF_166)] |
| Kyoto | * ≤ 10 tumors, all ≤ 5 cm in diameter * Pivka-ii ≤ 400 mau/ml | Takada *et al*[[167](#_ENREF_167)] |
| UCSF | * Solitary tumor ≤ 6.5 cm OR * ≤ 3 nodules with largest lesion ≤ 4.5 cm and total tumor diameter ≤ 8 cm * No gross vascular invasion | Yao *et al*[[9](#_ENREF_9)] |
| Shanghai Fudan | * Solitary tumor ≤ 9 cm in diameter OR * ≤ 3 lesions with the largest ≤ 5 cm and total tumor diameter ≤ 9 cm | Fan *et al*[[168](#_ENREF_168)] |
| Hangzhou | * Total tumor diameter ≤ 8 cm OR * Total tumor diameter more than 8 cm with histopathological grade I or II and preoperative AFP ≤ 400 ng/ml | Zheng *et al*[[169](#_ENREF_169)] |
| Asan | * Largest tumor diameter ≤ 5 cm * Hcc number ≤ 6 * No gross vascular invasion | Lee *et al*[[170](#_ENREF_170)] |

**Table 2 Overview of prioritization systems in different transplant regions worldwide**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Region** | **Country** | **Basic listing** | **Standard exception** | **Patient benefit** |
| Eurotransplant | Germany |  | - 1 tumor > 2 and < 5 cm  - up to 3 tumors > 1 and < 3 cm | Initial listing with MELD 22; upgrading every 3 mo by 10% mortality risk |
| The Netherlands |  | - 1 tumor > 2 and < 5 cm  - up to 3 tumors > 1 and < 3 cm | Initial listing with MELD 20, upgrading every 3 mo by 10% mortality risk.  However, “test of time”: patient must have been on the waiting list for 6 months prior |
| Austria | Possible (if Milan Criteria are met); however, irrelevant with center-based allocation | no |  |
| Europe | United Kingdom | - single lesion < 5 cm  - up to 5 lesions < 3 cm  - single lesion between 5 and 7 cm without progression over 6 mo  - no extrahepatic tumor  - no macrovascular invasion - AFP < 1000 U/l |  | No prioritization on the waiting list |
| France | Complex French Liver Allocation Score under consideration of  - lab-MELD-Scores  - tumor stage (T2 ranked higher than T1)  - elapsed waiting time  - distance between donor and recipient hospital |  |  |
| Switzerland |  | - 1 tumor > 2 and < 5 cm  - up to 3 tumors > 1 and < 3 cm | Lab-MELD + 1.5 points per month |
| North America | United States |  | - 1 tumor > 2 and < 5 cm  up to 3 tumors > 1 and < 3 cm | Initial listing with MELD 22; upgrading every 3 mo by 10% mortality risk |
| South America | Brazil |  | - 1 tumor < 5 cm  - up to 3 tumors of less than 3 cm each | Initial listing with 20 points, increase to 24 points after 3 mo and 29 points after 6 mo |