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MINIREVIEWS

Liver transplantation for hepatocellular carcinoma: Where do we stand?

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Abstract

Hepatocellular carcinoma represents an important cause of morbidity and mortality worldwide. It is the sixth most common cancer and the fourth leading cause of cancer death. Liver transplantation is a key tool for the treatment of this disease in human therefore hepatocellular carcinoma is increasing as primary indication for grafting. Although liver transplantation represents an outstanding therapy for hepatocellular carcinoma, due to organ shortage, the careful selection and management of patients who may have a major survival benefit after grafting remains a fundamental question. In fact, only some stages of the disease seem amenable of this therapeutic option, stimulating the debate on the appropriate criteria to select candidates. In this review we focused on current criteria to select patients with hepatocellular carcinoma for liver transplantation as well as on the strategies (bridging) to avoid disease progression and exclusion from grafting during the stay on wait list. The treatments used to bring patients within acceptable criteria (down-staging), when their tumor burden exceeds the standard criteria for transplant, are also reported. Finally, we examined tumor reappearance following liver transplantation. This occurrence is estimated to be approximately 8%-20% in different studies. The possible approaches to prevent this outcome after transplant are reported with the corresponding results.

Key words: Hepatocellular carcinoma; Liver transplantation; Bridging; Down-staging; Milan Criteria

Core tip: Liver transplantation is an important tool for the treatment of hepatocellular carcinoma in human. In this review we focused on the main debated issues in this field including: (1) Criteria for candidate selection; (2) Bridging therapy to transplant; and (3)

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Down-staging of patients exceeding transplant criteria. Tumor recurrence rate in the graft and strategies to prevent this occurrence, are also discussed.

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INTRODUCTION

Hepatocellular carcinoma (HCC) represents the most prevalent primary liver tumor in the world and is consequently a relevant health issue. With 841080 diagnosed cases and 781631 deaths in 2018, and an age-adjusted worldwide incidence of 9.3 cases per 100000 people/year, HCC is the sixth most frequent tumor and the fourth leading cause of cancer death[1]. HCC occurs mostly in the setting of chronic liver disease and cirrhosis, and its incidence is growing[2-4].

In general, liver transplantation (LT) is the best treatment for early-stage HCC, since it simultaneously treats the tumor and the underlying liver disease (the main risk factor for the development of new tumors); thus, the number of patients transplanted for HCC is increasing, with LT for HCC representing 15-50% of all LT performed in most centres[5-7]. Although LT is an outstanding therapy for HCC, due to organ shortage, the careful selection and management of patients who may have a major survival benefit after LT remains a fundamental question. Indeed, the limitation of tumor recurrence after LT is a way to optimize a scarce resource. The present review focuses on current strategies of selection, organ allocation, and management of patients transplanted for HCC.

SELECTION CRITERIA AND SURVIVAL

The milestone study by Mazzaferro in 1996 established deceased donor LT as an important therapeutic strategy for HCC[8]. The study showed that when transplantation was performed in the early-stage of the disease (one nodule ≤ 5 cm or ≤ 3 lesions, none > 3 cm and absence of gross vascular invasion, metastases or lymph nodes involvement), the four-year survival accounted for 75%, with a recurrence rate < 10%-15%. These LT outcomes are not different from those observed in non-HCC cirrhotic subjects. The so called Milan criteria were then widely applied to indicate LT in patients with HCC[8]. However, the Milan criteria are seen as too restrictive and exclude many patients from the transplant list; thus, considerable interest has arisen in their extension[9-13].

As demonstrated by a study held at the University of California in San Francisco (UCSF), HCC patients transplanted with extended criteria corresponding to: (1) Single nodule ≤ 6.5 cm; or (2) ≤ 3 nodules with the largest ≤ 4.5 cm and total sum of diameters ≤ 8cm (UCSF criteria), had an outcome similar to those transplanted within Milan criteria[9]. Nevertheless, a retrospective study by Decaens *et al*[14], showed that the five-year survival was 45.6% for patients who met the UCSF criteria but not the Milan criteria, and 60.1% for patients who met both criteria. Even if this difference was not statically significant, possibly for a lack of power in the analysis, the trends observed suggest that selection on the base of USCF criteria could be associated with a lower success rate.

In another study, data on 1112 patients who underwent LT for HCC at different centres worldwide, despite exceeding the Milan criteria, were recorded *via* a web-based survey. Data were analyzed in order to identify tumor features exceeding the Milan criteria but not affecting survival rates. The so-called up-to-seven criteria were identified with this approach. With these criteria the cut-off value is set to seven and the score is calculated by considering the total number of lesions plus the diameter (in cm) of larger nodule (for instance: 4 nodules + larger diameter 3 cm, up-to-seven score = 7). The comparison between patients (n = 283) matching the up-to-seven criteria with subjects (n = 444) transplanted within the canonical Milan criteria did not show significant difference in term of five-year survival after grafting[12]. However, the prognostic value of up-to-seven criteria was inadequate in the presence of

microvascular invasion, since the survival rate was significantly worse in comparison with what predicted by the score. Unfortunately, in common clinical practice, the presence of microvascular invasion is not assessable before grafting, thus limiting the routine application of up-to-seven criteria in everyday LT activity.

An interesting way to select LT candidates is based on a composite of the total tumor volume (TTV) and alpha-fetoprotein (AFP) level. Indeed, Toso *et al*[11] showed in a prospective study that HCC LT candidate selection could be expanded to patients with TTV ≤ 115 cm^3 and AFP ≤ 400 ng/mL, without macrovascular invasion or extrahepatic disease. An increased risk of dropout from the waiting list can be expected for these patients, but with a post-transplant survival equivalent to that of patients within the Milan criteria.

Since 2004, the University of Toronto has adopted their proper extended Toronto criteria (ETC). According to this system, transplantation is offered in disregard of any HCC size or number providing that patient does not present extra-hepatic disease extension or a very large tumor poorly differentiated at the pathological examination. In a validation cohort of patients transplanted according to the ETC, the five-year actuarial patient survival from the time of LT was 68%, which is slightly decreased in comparison with that of patients transplanted according to the Milan criteria, but not statistically different. However, HCC recurrence rate was higher in the ETC group[10].

A group from Kyoto proposed the following Kyoto criteria of LT for HCC: ≤ 10 tumors; ≤ 5 cm; and des-gamma-carboxy prothrobine (DCP) ≤ 400 mAU/mL[15]. Using this system, 5 year survival and recurrence rates were 80% and 7%, respectively, when all patients (Milan-in or Kyoto-in) were analysed[13]. Examining the different survival rates according to the adopted heterogeneous selection systems, a question comes to mind: What is the minimum acceptable five-year survival rate in patients undergoing LT for HCC? An expected 50% survival rate at 5 years was suggested as the lowest cut-off for inclusion of a patient on the waiting list[16,17]. However, in a study regarding the competitive allocation of grafts between HCC and non-HCC patients, using a Markow model, a minimal five-year survival rate of 61% for HCC LT was proposed to avoid disadvantage to non-HCC patients on the waiting list[18]. In fact, at a 2010 conference on HCC and transplantation, held in Zurich, a 50% five-year survival was regarded as unsatisfactory[19]. Milan criteria are, at present, the gold standard to select HCC patients for a successful LT and the reference to assess the validity of other suggested criteria[20].

Alternative expanded criteria for HCC LT did not reach a consensus nowadays, and the question remains outstanding and closely linked to the length of the waiting list, the system of allocation of organs, and availability of alternative sources of grafts (such as living donors, domino LT, and marginal organs). Characteristics and results of the different allocation systems adopted for LT in HCC are summarized in Table 1.

ALLOCATION OF ORGANS TO HCC PATIENTS

The limited availability of donor livers has determined the adoption of criteria, whereby LT priority is based on the risk of wait-list mortality. The model for end-stage liver disease (MELD) score[21], a statistical model that considers the international normalized prothrombin ratio and bilirubin and creatinine serum levels, has been adopted in most allocation systems worldwide. According to this scoring system, higher scores identify patients with a worse short-term prognosis[22].

For patients with HCC, the traditional MELD score is of scarce utility. The original criteria were in fact designed to predict mortality in subjects with end-stage liver cirrhosis rather than subjects affected by a liver neoplasm. Many HCC patients have well-compensated liver disease, characterized by a low MELD score, and their dropout risk from the waiting list is mainly related to progression of the tumor rather than occurrence of liver failure. For these reasons, modified scoring systems with respect to HCC have been developed and adopted by different centres. This policy was engaged to include the same waiting list patients with neoplasm and patients with liver failure without disadvantage to one group or the other. Prioritization scores for patients with HCC are based mainly upon the characteristics of the tumor (size, number, and AFP level) and the waiting time (additional points are given to patients who have had longer waiting periods)[23].

All allocation systems should undergo a constant assessment and revision during time, in order to accomplish their targets with respect to transplant benefits[24]. The system for HCC allocation can be regarded as a "dynamic issue" to be modified in the various geographic areas over time according to the candidate, type of disease, and donor pool characteristics.

Table 1 Characteristics and results of the different allocation systems adopted for liver transplantation in hepatocellular carcinoma

Selection system	Year of proposal	Criteria	Survival/years of follow-up
Milan criteria	1996	Single lesion ≤ 5 cm; up to three separate lesions, none larger than 3 cm; no evidence of gross vascular invasion; and no regional nodal or distant metastases	85%/4[8]
University of California, San Francisco criteria	2007	Single nodule up to 6.5 cm or up to three lesions, the largest of which is 4.5 cm or smaller and the sum of the diameters no larger than 8 cm	80.9%/5[9]
Up-to-seven criteria	2009	Sum of size (in cm) of larger tumor plus number of tumors ≤ 7	71.2%/5[12]
Total tumor volume and alpha-fetoprotein criteria	2009	Total tumor volume ≤ 115 cm^3 and alpha-fetoprotein ≤ 400 ng/mL, without macrovascular invasion or extrahepatic disease	74.6%/4[11]
Kyoto criteria	2013	≤ 10 tumors; ≤ 5 cm; and des-gamma-carboxy prothrobine ≤ 400 mAU/mL	65%/5[13]
Extended Toronto criteria	2016	Any size or number of tumors, without systemic cancer-related symptoms, extrahepatic disease, vascular invasion, or a poorly differentiated largest lesion at percutaneous tumor biopsy.	68%/5[10]

BRIDGING THERAPY

Management of patients with HCC on the waiting list aims to avoid disease progression with possible exclusion from grafting. Despite the lack of data from randomized placebo-controlled trials, the recent European guidelines recommend neoadjuvant therapies to reduce the dropout risk due to tumor progression. This strategy is especially suggested when the expected waiting time is six months or longer[20].

Updated guidelines from the American Association for the Study of Liver Disease (AASLD) suggest some form of bridging therapy in patients listed for LT within T2 (Milan criteria) without considering the estimated time on the waiting list; however, there is no recommendation for one particular form of neoadjuvant therapy. For patients with cirrhosis awaiting LT who develop a T1 HCC (a single nodule ≤ 1.9 cm), observation with follow-up imaging is suggested prior to any bridging treatment[25].

The rationale for bridging therapy is evident, since the dropout rate from list, related to tumor extension, is reported to occur in 10%-20% of cases[26-28]. Moreover, further positive effects of neoadjuvant therapy may be expected in this clinical setting[29]. In fact, in patients with HCC response (intended as complete or ≥ 60% tumor necrosis) after locoregional therapy, an improved LT outcome has been described by uncontrolled studies[30,31]. The possible beneficial effect of bridging therapy, in HCC patients waiting a short time in list, remains however, to be established[32]. Given the heterogeneity of populations and therapeutic criteria observed in the different research protocols, is not possible to draw a definitive conclusion on the net effect of bridging therapy for HCC. On the other hand, since beneficial effects were frequently reported, it seems wise to consider this option in HCC patients on waiting list[33,34].

Unfortunately, no randomized controlled trials are available regarding this issue. Bridging therapy depends on the tumor location, size, number, and hepatic function and includes liver resection, percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), microwave ablation, trans-arterial chemoembolization (TACE), radio-embolization, and stereotactic radiotherapy.

The overall results of bridging with TACE are rather inconsistent. Some studies described a clinical benefit without a negative impact on post-transplantation survival[35,36]. One of the most positive studies enrolled 48 patients within the Milan criteria; none of the patients treated with TACE had tumor progression or were withdrawn from the waiting list. Furthermore, the five-year survival after LT was 93%. One hundred and seventy-eight days was the mean waiting time for grafting[35]. In contrast, TACE benefit resulted uncertain in other studies[37,38]. A systematic review concluded that good quality evidence was not available to indicate that TACE: (1) Improved post-LT survival; or (2) Modified LT complication; or (3) In–list dropout

rates[39].

For selected patients with small tumors and adequate liver function, another strategy may be pursued, consisting of initial surgical tumor resection followed by close surveillance, and "salvage" transplantation if tumor recurrence or deterioration of liver function occur. In a retrospective analysis of HCC patients undergoing LT as compared with others submitted to initial resection and then LT (due to recurrent HCC, or progression to end-stage liver disease), the surgical procedure, the postoperative course and the overall or disease-free survival were not different[40].

Conversely, a French observational study on salvage LT after initial resection reported an increase in operative mortality and HCC recurrence. Moreover, a worse five-year overall and disease-free survival, as compared with primary LT, was observed. The authors concluded that, even when HCC is amenable of resection, LT still remains the ideal option for a cirrhotic patient with HCC[41]. For all the above, even if a definitive indication should not be drawn, initial tumor resection in patients with well-preserved liver function appears to be a reasonable approach[42-44].

PEI, RFA, and microwave ablation have also been studied as bridging therapies[45-47]. When RFA was employed in fifty-two patients as a bridging therapy, encouraging results were observed. Three patients only (5.8%) dropped out from list, due to tumor progression (mean time in list in the study = 13 mo). Forty-one patients underwent LT with one- and three-year survival rates of 85% and 76%, respectively. HCC recurrence during follow-up did not occur in any patient[45]. Microwave ablation has also been successfully applied as a bridging therapy, although less data are available[48].

Few data are available on radioembolization with yttrium 90-labeled microspheres in comparison with other techniques, however, this procedure has been shown to limit tumor progression and dropout from transplantation programs[49]. The experience with stereotactic body radiotherapy (SBRT) as a bridging therapy is limited, but encouraging. One study compared SBRT with TACE and RFA with respect to dropout rate, postoperative complications, and one-, three- and five-year survival rates after LT. The results were similar among the groups[50].

DOWNSTAGING THERAPY

The majority of treatments used as bridging therapies have also been employed as downstaging therapies. For a comparison see Table 2. "Downstaging" describes treatment used to bring patients within acceptable criteria when their tumor burden exceeds the standard criteria for LT.

Several studies have demonstrated that successful downstaging of HCC to within Milan criteria reduces tumor recurrence with a survival rate, after grafting, comparable with those meeting the Milan criteria at the beginning[51-54]. Regarding this setting, a recent study in 276 patients undergoing locoregional treatment prior to LT showed that a remnant vital tissue ≥ 2 cm was an important predictor of post-LT recurrence[55,56].

There is no universal agreement on the optimal method for downstaging; most of the data have been gathered on TACE or radioembolization. A systematic review on downstaging for HCC, including the data of 950 patients, showed an overall success rate of 48% (95% confidence interval 39%-58%). The difference between TACE and radioembolization was not statistically significant[57]. Other reports have achieved higher success rates (60%) combining different strategies (TACE plus either RFA or radioembolization)[58]. Interestingly, the response to downstaging is an important indirect marker of the biological aggressiveness of the tumor[59].

There is no consensus regarding list-priority of patients re-entering the accepted criteria for LT after downstaging. An Italian consensus conference on liver allocation proposed prioritization according to the risk of progression and the response to bridging/downstaging therapies[60]. Guidelines for treatment of HCC from the AASLD suggest that patients beyond the Milan criteria (≥ T3) should be considered for grafting after an effective downstage of the disease[25].

TUMOR RECURRENCE

HCC tumor recurrence following LT is estimated to be approximately 8%-20%[8,10,61,62]. A multicentre study on explant pathology staging showed that the risk of HCC recurrence is higher when the criteria for size or number of HCC are more expanded[12]. Tumor recurrence is mostly extrahepatic (lungs and bones) [63,64] and likely due to the growth of occult metastases[65]. Tumor-related variables appear to be

Table 2 Techniques employed for bridging or downstaging patients with hepatocellular carcinoma before liver transplantation and their efficacy

	Bridging	Downstaging
TACE	0-35% (39)	24%-77% (57)
Radioembolization	NA (49)	11%-43% (57)
RFA	16.8% (50)	NA
SBRT	16.7% (50)	NA
Resection	NA (40, 42)	NA
Combined approach (TACE + RFA or radioembolization)	NA	56% (58)

Bridging column: Percentages (when present) indicate the drop-out rate from list despite bridging therapy; corresponding reference between commas. Downstaging column: Percentages (when present) indicate the success rate with downstaging; corresponding reference between commas. TACE: Trans-arterial chemoembolization; RFA: Radiofrequency ablation; SBRT: Stereotactic body radiotherapy; NA: Not assessed.

associated with prognosis following LT. Size and number of tumors[9,11], tumor marker serum levels, such as AFP[66] and DCP[67], and inflammation index (neutrophil-to-lymphocyte ratio)[68] have been related to recurrence.

Several studies have analyzed the tumor features in the explanted livers that could influence the development of HCC recurrence; unfortunately, these parameters cannot be used in the pre-transplant setting. In fact, in current clinical practice, the majority of HCC diagnoses are obtained based on radiological findings. The most relevant characteristics of explant pathology are micro- and macroscopic vascular invasion, satellite lesions, and tumor differentiation[69,70].

Investigators at the University of California, San Francisco, have developed a prognostic scoring system [Risk Estimation of Tumor Recurrence After Transplant (RETREAT)] using data from 721 patients who met the Milan criteria. Three variables were independently associated with disease recurrence: microvascular invasion, serum AFP level at the time of transplantation, and diameter of the largest nodule plus the total number of nodules on the explanted liver. These parameters defined a scoring system with the aim of predicting the one- and five-year HCC recurrence risk. The RETREAT score was able to estimate the probability of recurrence, with a risk < 3% corresponding to a score = 0 and ≥ 75% with a score ≥ 5[71].

Concern was raised by a Spanish study in which a temporal association between hepatitis C virus (HCV) therapy employing direct-acting antivirals (DAAs) and recurrent disease was noted in patients previously resected or ablated for HCC[72]. However, more recently, a large prospective study in HCV patients with compensated or decompensated cirrhosis found that the sustained virological response after DAA treatment decreases the incidence of HCC after a mean follow-up time of 14 mo[73]. Therefore, based on these findings, treatment of HCV infection is presently recommended in HCC patients waiting for LT.

A role in HCC recurrence is also played by immunosuppressive regimens containing calcineurin inhibitors, such as tacrolimus and cyclosporine (CSA)[74,75]. It is possible to hypothesize that over-exposure to these drugs soon after LT may inhibit the immune system and prevent the detection and elimination of residual HCC cells[76]. In a retrospective review of HCC patients (n = 70) undergoing transplant and receiving CSA as immunosuppressant, increased serum CSA levels were observed in those who had recurrent disease in comparison with the others[74].

PREVENTION OF TUMOR RECURRENCE

Inhibitors of the mammalian target of rapamycin (mTOR) pathways, sirolimus and everolimus, are immunosuppressive agents that display intriguing properties in the setting of HCC. *In vitro* and *in vivo* studies suggest that this class of drug counteracts HCC proliferative activity, probably interfering with vascular endothelial growth factor. Sirolimus has been demonstrated to inhibit the growth and metastatic progression of HCC[77,78]. Several single-institution retrospective and case-control studies reported a reduced tumor recurrence in patients with HCC treated with sirolimus in comparison with those treated with other types of immunosuppressive agents[79-81].

A meta-analysis based on the available data, stated that the use of a sirolimus-based immunosuppression significantly decreases overall tumor recurrence and

recurrence-related mortality[82]. However, a prospective phase III international multicentre randomized-controlled trial has given negative results. In this randomized study, HCC patients were allocated to a sirolimus or a sirolimus-free regimens following LT. The five-year disease-free survival was not different between groups[83].

Adjuvant therapy may theoretically represent a benefit for HCC subjects undergoing LT. In fact LT surgery requires extensive manipulation of recipient graft thus exposing the patient to a significant risk of tumor cells seeding. Moreover, after LT immunosuppressed state may enhance tumor growth; when this occurs, post-transplantation recurrence tends to develop more rapidly following LT rather than after resection[84]. However, chemotherapy with drugs, such as cisplatin or 5-fluorouracil, did not show any clear benefit[85-87].

Sorafenib, an oral multitargeted tyrosine kinase inhibitor counteracting HCC neo-angiogenesis, cell proliferation and tumor survival, is the recommended therapy for advanced tumor[88]. A small retrospective case-control match analysis appeared to demonstrate the safety and a potential effect of this molecule in reducing HCC recurrence after grafting thus improving disease-free and overall survival rates when administered in high-risk LT subjects[89]. Nevertheless, a phase III double-blinded placebo-controlled trial of sorafenib versus placebo as an adjuvant therapy for HCC after resection or ablation, did not show any significant effect[90]. Several other active agents have been identified, and in some cases approved, for the treatment of advanced HCC, such as regorafenib, nivolumab, and lenvatinib[91-93], but none of these drugs have been investigated as adjuvant therapies.

CONCLUSION

LT is an important curative option for patients with early-stage HCC; nevertheless, organ shortage imposes careful selection of patients. Although a growing interest in admitting patients with larger tumors to LT is understandable, the Milan criteria remains the cornerstone to select HCC patients for transplant. Bridging and downstaging therapies are useful for limiting the dropout of patients awaiting LT, even if the benefit has not been proven in controlled trials. The role of immunosuppressive regimens using inhibitors of mTOR in the prevention of recurrence after LT remains controversial. Currently, though several biomarkers have been proposed, no one has proved strong validity to predict tumor recurrence. Extensive research into predictors of recurrence, such as microvascular invasion, could make refinement of selection criteria possible. Encouraging data are coming from molecular analysis of HCC in regard to disease features. A study evidenced a genetic pattern (genetic signature composed by 35 genes) with a negative predictive value of 0.77 for HCC microvascular invasion[94]. Another recent research proposed two prognostic molecular subtypes among patients with HCC with different vascular invasion and tumor differentiation[95]. However, given the heterogeneity of HCC, efforts are to be commended in future to identify consistent prognostic biomarkers before and after LT.

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