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## Bridging and downstaging treatments for hepatocellular carcinoma in patients on the waiting list for liver transplantation

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### Abstract

Several therapeutic procedures have been proposed as bridging treatments for patients with hepatocellular carcinoma (HCC) awaiting liver transplantation (LT). The most used treatments include transarterial chemoembolization and radiofrequency ablation. Surgical resection has also been successfully used as a bridging procedure, and LT should be considered a rescue treatment in patients with previous HCC resection who experience tumor recurrence or post-treatment severe decompensation of liver function. The aims of bridging treatments include decreasing the waiting list dropout rate before transplantation, reducing HCC recurrence after transplantation, and improving post-transplant overall survival. To date, no data from prospective randomized studies are available; however, for HCC pa-

tients listed for LT within the Milan criteria, prolonging the waiting time over 6-12 mo is a risk factor for tumor spread. Bridging treatments are useful in containing tumor progression and decreasing dropout. Furthermore, the response to pre-LT treatments may represent a surrogate marker of tumor biological aggressiveness and could therefore be evaluated to prioritize HCC candidates for LT. Lastly, although a definitive conclusion can not be reached, the experiences reported to date suggest a positive impact of these treatments on both tumor recurrence and post-transplant patient survival. Advanced HCC may be downstaged to achieve and maintain the current conventional criteria for inclusion in the waiting list for LT. Recent studies have demonstrated that successfully downstaged patients can achieve a 5-year survival rate comparable to that of patients meeting the conventional criteria without requiring downstaging.

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**Key words:** Hepatocellular carcinoma; Bridging treatment; Downstaging; Liver cirrhosis; Liver transplantation; Liver resection; Waiting list; Waiting time; Dropout rate

**Core tip:** The bridging treatments for patients with hepatocellular carcinoma within Milan criteria listed for liver transplantation are useful in decreasing dropout rate from the waiting list and the experiences reported to date suggest a positive impact on post-transplant tumor recurrence and patient survival. The response to treatments may represent a surrogate marker of tumor biological aggressiveness and could be evaluated to prioritize hepatocellular carcinoma candidates in the waiting list. Advanced hepatocellular carcinoma may be downstaged to achieve the current conventional criteria for inclusion in the waiting list and successfully

downstaged patients can achieve an excellent 5-year survival rate.

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## INTRODUCTION

Liver transplantation (LT) is the treatment of choice for patients with unresectable hepatocellular carcinoma (HCC) complicating liver cirrhosis because it allows the cure of both the tumor and the underlying chronic liver disease. HCC classified within the so-called Milan criteria (MC) (1 nodule smaller than 5 cm or no more than 3 nodules smaller than 3 cm)<sup>[1]</sup> is recognized everywhere as the standard indication for LT. However, after admission to the waiting list for LT, HCC patients can experience tumor growth beyond the conventional transplant criteria. Indeed, there is a high cumulative probability of drop-out from the waiting list for HCC patients due to intrahepatic or extrahepatic tumor progression. This probability has been reported to range between 7% and 11% at 6 mo and to be approximately 38% at 12 mo following enrollment by two papers published at the end of the 1990s by Llovet *et al.*<sup>[2]</sup> and Yao *et al.*<sup>[3]</sup>. The probability has been correlated with tumor characteristics, geographic origin, and length of time waiting for LT<sup>[4-6]</sup>.

Allocation policies for HCC patients awaiting LT remain controversial in the era of the model for end-stage liver disease (MELD) for the management of the LT waiting list. Different models have been developed to quantify the risk of death in neoplastic and non-neoplastic patients<sup>[7-11]</sup>. As the neoplastic risk assessment is not considered in MELD, patients with unresectable HCC with a neoplasm fulfilling the MC have been considered exceptions in the American allocation system. According to this rule, patients with T2-HCC fulfilling the MC (a single tumor of 2-5 cm or 2-3 tumors each < 3 cm) enter the waiting list with a MELD score equal to 22 and are therefore given priority over patients with less decompensated disease who enter the waiting list according to their laboratory MELD score (6 to 21). In addition, T2-HCC patients also receive incremental points for every 3 mo spent on the waiting list<sup>[12,13]</sup>. A similar approach has been implemented in other allocation systems<sup>[14,15]</sup>. The 22 threshold has been set to offer to HCC patients the same drop-out probability of patients without malignancy<sup>[16]</sup>. More detailed studies based on a dynamic prognosis parallelism have been published, and more complex allocation models aimed at balancing the risk of death in HCC and non-HCC patients have been proposed; however, they have not been applied in clinical practice<sup>[7,17-21]</sup>. According to these studies, LT can-

didates with HCC have dropout rates lower than non-HCC candidates, although the rate is similar to that of standard MELD candidates with a score of less than 21. Therefore, HCC patients appear to have an advantage in the current system, raising the question of whether a calculated continuous HCC priority score should be developed that also considers some biological features of the tumor such as the  $\alpha$ -fetoprotein (AFP) value, size, and rate of growth<sup>[17,18]</sup>. Indeed, HCC patients with a high AFP level achieve acceptable LT outcomes if their AFP levels can be reduced with locoregional therapy during the waiting period<sup>[22,23]</sup>. Furthermore, an inadequate response to HCC bridging therapy was shown to be a strong predictor of dropout probability in three single-center Italian studies<sup>[10,14,24]</sup>, whereas both the serum AFP level and the response to locoregional therapy were related to tumor recurrence and death in a retrospective international multicenter cohort study<sup>[25]</sup>.

Lastly, the development of the survival-benefit approach, which proposes ranking priority according to the benefit in survival between standard care and LT rather than crude survival figures, changed the perspective of the outcome evaluation system<sup>[26-28]</sup>. The practice most widely used since 2005, which is in accordance with the United Network for Organ Sharing rules, gives HCC patients with unresectable T1 neoplasms (a single nodule smaller than 2 cm) the same priority as patients listed for non-neoplastic diseases.

In this scenario, several therapeutic procedures have been proposed and largely used in the past as bridging neo-adjuvant treatments for patients listed for LT with HCC within the MC<sup>[29]</sup>. The rationale for their use is the possible decrease of the waiting list drop-out rate before transplantation and of HCC recurrence after transplantation, which is less than 15% in patients with HCC within the MC undergoing LT without any prior tumor treatment<sup>[30]</sup>. These beneficial effects could also improve the overall survival of transplanted patients. Both surgical resection and locoregional therapies can be used not only as bridging procedures to LT in T2-HCC patients but also to downstage HCC patients who do not initially meet the conventional transplant criteria<sup>[31]</sup>. According to this approach, patients can be safely listed for LT if they can reach and maintain for an adequate follow-up period the MC or slightly expanded criteria such as the University of California San Francisco criteria (UCSF) (a single HCC  $\leq$  6.5 cm or  $\leq$  3 tumors with the largest being  $\leq$  4.5 cm and a total tumor burden  $\leq$  8 cm)<sup>[32]</sup> or the up-to-7 criteria [HCCs with 7 as the sum of the size of the largest tumor (in cm) and the number of tumors]<sup>[33]</sup>. The aim of downstaging is to select HCC patients with reasonably low rates of tumor recurrence after LT among those who are initially excluded according to the current number-size criteria<sup>[34]</sup>.

In this paper, we analyzed the indications and results of the various neo-adjuvant treatment modalities currently administered to HCC patients awaiting LT to avoid exceeding the MC while on the waiting list as well as those used to downstage patients who do not meet

the conventional transplant criteria.

## NEO-ADJUVANT BRIDGING PROCEDURES FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA AWAITING LIVER TRANSPLANTATION

### **Surgical resection**

Liver resection (LR) can be theoretically used as a first-line bridging procedure to LT. However, in most transplant centers, transarterial chemoembolization (TACE) and percutaneous ablation therapies are the preferred bridging therapies. The theoretical advantages of surgery in this setting are twofold. The first advantage is the best possible control of tumor growth, as TACE and percutaneous treatments do not always achieve complete tumor necrosis. The second advantage is the possibility of selecting patients in whom pathological analysis of the resected specimen shows features suggesting poor prognosis in terms of tumor recurrence, such as undifferentiated histotype, satellitosis, microvascular invasion, or capsular effraction, who should immediately undergo evaluation for LT<sup>[35]</sup>. However, compared to non-surgical therapies, the surgical bridging approach to patients listed for LT implies higher costs, entails more peri-procedural risks, can only be proposed in well-compensated patients without severe portal hypertension, and can make the ensuing LT technically more difficult, with a higher risk of post-operative complications<sup>[36]</sup>.

Moreover, important issues regarding tumor resectability should also be considered. Single exophytic or at least subcapsular neoplasms are easier to resect than multiple neoplasms or those located adjacent to the hilum or vena cava<sup>[37,38]</sup>. Furthermore, a location in the left lobe represents a more favorable condition, and the progress achieved in the laparoscopic resection of the liver has reduced the number of HCC patients with an absolute indication for LT<sup>[39]</sup>. However, the combination of LR and LT over time appears to be a reasonable strategy; HCC patients within the MC who have preserved liver function can undergo LR, limiting LT as a rescue treatment in cases of tumor recurrence or liver function failure (salvage LT)<sup>[40]</sup>. This approach allows a consequent saving of grafts, which can then be more efficaciously transplanted in other patients, and is supported by the discrepancy between the limited donor pool and the enormous number of LT candidates. However, there are important differences in access to LT according to cadaveric organ availability, blood group of the recipient, implementation of a living donor program, and degree of donor-recipient matching<sup>[41-44]</sup>.

Although during the initial experience with LR, the overall survival and disease survival rates of patients undergoing secondary LT after HCC resection were significantly lower (due to higher perioperative mortality unrelated to HCC) than those observed in cirrhotic patients with HCC undergoing primary LT<sup>[45]</sup>, favorable results

have more recently been reported by Belghiti *et al.*<sup>[46]</sup>. They showed that postoperative course, complications, and the 3- and 5-year survival rates did not differ significantly between cirrhotic HCC patients undergoing primary LT or secondary LT after resection. Similarly favorable results for salvage LT have been subsequently reported by other groups in patients initially submitted to LR within the MC<sup>[15,47]</sup> or the UCSF criteria<sup>[48]</sup>.

Salvage LT has been shown to be effective not only in the setting of deceased donor LT but also in the setting of living donor LT, particularly in Asian countries. Compared to deceased donor LT, the main advantage of living donor LT is the reduction of the waiting list time, whereas the main drawback is represented by the occurrence of severe life-threatening complications among donors in approximately 1% of cases<sup>[49]</sup>. Indeed, Hwang *et al.*<sup>[50]</sup> have shown that the combination of prior recipient hepatectomy and a living donor liver graft is feasible and provides excellent long-term survival in treated patients, and their results have recently been confirmed by other groups<sup>[51,52]</sup>.

Notably, the option of salvage LT cannot be offered to all patients initially treated by LR, primarily due to HCC recurrence overcoming the conventional LT criteria, age over 65 years at the time of recurrence, and the presence of comorbidities preventing the feasibility of LT. In a series reported by Poon *et al.*<sup>[53]</sup>, approximately 80% of patients were still eligible for salvage LT at the time of tumor recurrence. In a recent paper by Liu *et al.*<sup>[48]</sup>, among 71 patients with HCC recurrence within the UCSF criteria, salvage LT could be performed in 39 patients (54.9%). Compared to 180 HCC patients who underwent primary LT, patients treated with salvage LT for HCC recurrence showed greater intraoperative blood loss and required more blood transfusions; however, perioperative mortality, post-transplant complications, HCC recurrence rates, and overall survival did not differ significantly between the two groups.

### **Transarterial chemoembolization**

TACE is considered the standard treatment for patients with intermediate-stage HCC according to the Barcelona-Clinic Liver Cancer classification<sup>[54]</sup>, and it achieves a partial response in 15%-55% of patients and an improvement of median survival from 16 to 20 mo<sup>[55]</sup>. The most widely used conventional TACE procedure consists of an arterial infusion of a lipiodol emulsion with a chemotherapeutic agent (*e.g.*, doxorubicin or cisplatin) followed by embolization with gelfoam. However, conventional TACE is not a standardized procedure, and the optimal chemotherapeutic/embolizing agent and retreatment strategy have yet to be determined<sup>[56]</sup>. In particular, it is well known that TACE requires treatment repetition either at regular intervals or “a la demande” and that repeating conventional TACE may damage non-cancerous hepatocyte functions and affect the clinical course. Indeed, liver toxicity is a major limitation of conventional TACE regimens, and superselective TACE

is recommended in the setting of patients waiting for LT to minimize ischemic injury to non-tumoral liver tissue. Promising new data have been obtained using drug-eluting beads (DEBs), which are particles of variable size that are able to bind and elute doxorubicin in a predictable manner<sup>[57]</sup>. Compared to conventional techniques, DEBs appear to be a more standardized approach to TACE with less liver-related toxicity and fewer systemic adverse events<sup>[58]</sup>.

TACE has been extensively used in the past as a bridging treatment to LT, and a number of studies have shown that it is an effective therapy in terms of adequate tumor necrosis achievement at explant analysis. Analyzing the largest available series indicates that the rate of patients treated by TACE reaching complete tumor necrosis is quite uniform, ranging between 27% and 57% in patients within the MC<sup>[59-67]</sup>.

Interestingly, the rate of tumor necrosis appears to be higher in patients with single nodules when compared with patients with multiple nodules, in patients submitted to superselective TACE when compared with lobar TACE (complete necrosis achieved in 53.8% *vs* 29.8% of cases, respectively), and in patients with nodules 3-5 cm in size compared with patients with nodules smaller than 3 cm<sup>[65]</sup>. This last finding confirms the result obtained by Alba *et al*<sup>[64]</sup> and may be explained considering that larger nodules are typically fed by larger arteries, whereas in some instances, smaller nodules lack fully developed arterial neoangiogenesis; as a result, chemoembolization may be more effective in the former<sup>[65]</sup>. Accordingly, Kwan *et al*<sup>[66]</sup> have recently shown that the development of > 90% lesion necrosis upon pathological analysis of explanted liver was associated with avid lesion enhancement and the presence of a feeding vessel larger than 0.9 mm in diameter on the pre-TACE visceral angiogram. On post-TACE computed tomography images, a lack of residual contrast enhancement, a decrease in lesion size, a high lesion density due to an accumulation, and a diffuse distribution of ethiodized oil throughout the lesion were also correlated with near-complete lesion necrosis.

A recent small retrospective study compared tumor response in explanted liver after treatment with DEBs or standard TACE. TACE with DEBs achieved complete necrosis in 77% of the lesions, which was significantly higher than that reached after standard TACE (27.2%). More data are needed to address the better performance of DEBs compared to standard TACE in the transplant setting<sup>[68]</sup>.

Another important point to clarify is the evaluation of TACE safety in patients awaiting LT. Because arteritis of the celiac and hepatic arteries may complicate TACE as a result of endovascular trauma caused by guides and catheters, recipients could be exposed after the transplant to an increased occurrence of complications such as arterial thrombosis. However, the prevalence of such serious complications has not been found to be increased in some studies comparing patients with or without TACE performed before LT<sup>[69-71]</sup>.

### Radiofrequency ablation

Radiofrequency thermal ablation (RFA) has gained widespread use over recent years as an effective procedure for small HCCs not amenable to surgical resection. Thermal ablation may be performed using cool-tip or hook needles with comparable results<sup>[72]</sup>. Some studies have described the use of RFA as a bridge to transplantation in HCC patients in recent years. These studies have reported complete tumor necrosis at pathological evaluation of the explanted liver in 47%-75% of cases, with a mean value of 58%<sup>[73-77]</sup>. A clear difference in effectiveness can be observed when analyzing tumors according to size. Indeed, the rate of complete necrosis ranges between 50% and 78% in HCCs up to 3 cm and between 13% and 43% in larger neoplasms<sup>[73-75,77]</sup>. Furthermore, in two studies, a tumor size larger than 3 cm was the only risk factor identified for HCC persistence after treatment<sup>[73,75]</sup>.

Regarding RFA-related complications in the setting of HCC patients awaiting LT, an analysis of the largest available series demonstrated that the procedure is quite safe. In fact, considering 5 large series, the mean rate of post-ablation major complications was only as high as 4.6%, including one case of death due to peritoneal bleeding, two cases of acute peritonitis/cholecystitis, and one case each of severe liver failure treated by urgent transplantation, severe persistent liver failure, biliary stenosis, arterial hemorrhage, and small bowel perforation<sup>[73-76,78]</sup>. Additionally, the risk of tumor seeding at the level of the abdomen wall appears to be low; however, occasional cases of tumor seeding along the needle track diagnosed after LT in patients submitted to RFA as a bridging procedure have been reported in the literature<sup>[79,80]</sup>.

### Other treatments

TACE and RFA are the most used bridging treatments to LT in HCC patients, although other therapeutic options have been proposed (Table 1). Percutaneous ethanol injection (PEI) is the oldest and most used technique for the local treatment of HCC, but it has been rarely used as a bridging treatment to transplantation. In our multicenter survey, the rate of complete necrosis in tumors smaller than 3 cm was 30%<sup>[75]</sup>. Castroagudín *et al*<sup>[81]</sup>, in a series of 20 nodules in 19 patients, showed that in patients with small tumors (*i.e.*, less than 3 cm), ethanol injection induced complete necrosis in 58% of the cases. In a more recent paper, Branco *et al*<sup>[82]</sup> reported a complete necrosis rate of 64% in 59 patients within the MC and a mean tumor size of 2.4 cm (range: 0.5-5.5 cm). In these studies, PEI was not affected by procedure-related major complications and did not provide total necrosis in most tumors larger than 3 cm.

Percutaneous laser ablation (PLA) performed using multiple tiny laser fibers has recently been shown to be an effective technique for the thermal ablation of HCC in patients in whom surgical resection is not possible or appropriate<sup>[83,84]</sup>. We recently showed that in HCC patients awaiting LT, PLA provided results comparable

**Table 1 Advantages and disadvantages of the bridging and downstaging procedures for hepatocellular carcinoma in cirrhotic patients who are candidates for liver transplantation**

	Advantages	Disadvantages
Resection	Higher complete effectiveness than non-surgical procedures More simple in cases with peripheral subglissonian nodules	Unfeasible in patients with decompensated liver disease or severe portal hypertension
TACE	More effective using the selective/superselective technique in well-vascularized nodules with large feeding arteries	Unfeasible in patients with severely reduced portal vein flow, intratumoral arteriovenous fistula, or renal failure (creatinine clearance < 30 mL/min)
TARE	Possible better effectiveness than TACE in cases with multiple nodules	Less experience with TARE than TACE High cost
RFA	More effective in nodules ≤ 3 cm	Potentially dangerous in patients with impaired clotting parameters or lesions located superficially or near the gallbladder, major bile ducts, or bowel loops
PEI	More effective in nodules ≤ 3 cm Suitable in patients with impaired clotting parameters or lesions located in dangerous sites for thermal ablation	Less effective than RFA for nodules > 2 cm
PLA	More effective in nodules ≤ 3 cm Suitable in patients with impaired clotting parameters	Less experience with PLA than RFA Technically complex Potentially dangerous in cases of lesions located superficially or near the gallbladder, major bile ducts, or bowel loops
MWA	Possible better effectiveness than RFA in nodules ≥ 3 cm or located near large vessels	Less experience with MWA than RFA Potentially dangerous in patients with impaired clotting parameters or with lesions located superficially or near the gallbladder, major bile ducts, or bowel loops

TACE: Transarterial chemoembolization; TARE: Transarterial radio embolization; RFA: Radiofrequency ablation; PEI: Percutaneous ethanol injection; PLA: Percutaneous laser ablation; MWA: Microwave ablation.

to those of RFA; the rate of complete necrosis found at explant analysis in a series of 13 nodules up to 3 cm was 62%<sup>[85]</sup>. Due to the use of fine needles, the possible advantages of PLA in respect to RFA include the treatment of patients with either nodules in high-risk sites (*i.e.*, near vital structures)<sup>[86]</sup> or severe clotting impairment, in whom RFA may be contraindicated, and the lower overall cost of the procedure.

Microwave ablation (MWA) has been shown to be an effective thermal ablation procedure for the percutaneous treatment of HCC. Compared to RFA, this technique could theoretically provide a larger volume of necrosis and be more effective when treating nodules adjacent to large vessels; however, a clear advantage of MWA with respect to RFA has not been demonstrated<sup>[87,88]</sup>. The use of MWA as a bridging procedure to LT or a downstaging procedure in HCC patients appears to be promising. In a recent preliminary study, 6 patients with 6 HCC nodules ranging between 2.5 and 5.0 cm (mean 3.5 cm) in diameter underwent MWA before LT. At explant analysis, all of the nodules showed complete necrosis without intraoperative evidence of tumor spread in all cases or evidence of tumor recurrence at a one-year follow up in the 5 patients who could be evaluated<sup>[89]</sup>.

The effectiveness of transarterial radioembolization (TARE) with <sup>90</sup>Yttrium microspheres has recently been evaluated by Riaz *et al.*<sup>[90]</sup>, who studied 38 nodules in 35 patients. Of 15 patients with T2-HCC, none progressed to T3-HCC (one nodule > 5 cm or up to three nodules with one > 3 cm) before LT, whereas 8 of 10 patients were downstaged from stage T3 to stage T2. At explant analysis, 23 of the 38 target lesions (61%) showed complete tumor necrosis, and its achievement was af-

ected by the size of the target lesion; indeed, complete necrosis was detected in 89%, 65%, and 33% of lesions smaller than 3 cm, between 3 and 5 cm, and larger than 5 cm, respectively.

Data regarding the use of external conformal radiotherapy (CRT) as a bridging treatment to LT in HCC patients are scarce. In a recent paper, CRT was delivered in five or six fractions to 10 patients with HCC awaiting LT with tumor diameters ranging from 2.5 to 10.8 cm. Nine patients completed the treatment, and it was well tolerated in all cases. Two tumors remained stable; the rest had 10%-50% regression, which was sustained on follow-up imaging. Five patients underwent LT, and at explant pathology, tumor necrosis ranging between 40% and 90% was demonstrated. No patients showed tumor recurrence after LT (median follow-up period of 6 mo). The main conclusions of the paper were that CRT is a safe and efficacious local bridging therapy for patients with HCC who are on the waiting list for LT and that further studies are warranted to compare the effectiveness of CRT to other local treatment regimens<sup>[91]</sup>.

### Combined treatments

Experiences with combined therapies such as TACE followed by RFA<sup>[92-94]</sup> or RFA shortly after TACE<sup>[95]</sup> have been published in recent years, typically in the setting of unresectable HCC larger than 3 cm. The rationale for the use of combined treatment rather than a single treatment is to reach a higher local tumor control rate due to higher rates of complete tumor necrosis. In this context, the question arises of how TACE and RFA should be sequenced. The advantage of performing TACE prior to RFA is the reduced heat-sink effect with the ability to create larger ablation zones more easily. The advan-

tage of using TACE after RFA is that RFA generates a hyperemic rim surrounding the ablation area, which can consequently be targeted by transarterial means more effectively. The approach of combined treatment may be applied even as a bridge to LT. A recent experience with combined TACE followed by RFA in a series of 44 HCC patients within the MC reported the absence of major complications and a 76.9% rate of complete necrosis in the 16 patients with 26 nodules who underwent LT<sup>[96]</sup>.

## IMPACT OF BRIDGING TREATMENTS ON DROPOUT FROM THE LIVER TRANSPLANTATION WAITING LIST

The impact of bridging treatments on waiting list dropout is uncertain due to the absence of prospective comparative studies, but the dropout data of treated patients should be compared with the features of HCC patients awaiting LT without any bridging treatment. In the latter case, the dropout rates were greater than 30% 12 mo after being added to the list<sup>[2,3]</sup>. In 2006, Lesurtel *et al*<sup>[97]</sup> published an interesting paper dealing with the usefulness of TACE in HCC patients undergoing LT according to the criteria of evidence-based medicine. The question was whether TACE impacted the waiting list dropout rate. They found insufficient evidence to answer this question. Hayashi *et al*<sup>[61]</sup> reported a discouraging 35% dropout rate in patients with TNM stage 1 or 2 HCC and a mean waiting time of 340 d after treatment with TACE. Similarly, among 54 listed HCC patients who underwent TACE prior to LT, Maddala *et al*<sup>[98]</sup> revealed drop-out rates of 15% and 25% at 6 and 12 mo, respectively. However, the most recent series including patients treated with TACE before LT have indicated that the dropout rate due to tumor progression is lower and ranges between 3.0% and 9.3%, with a mean waiting time on the transplantation list exceeding 6 mo in the largest available studies<sup>[63,64,69]</sup> (Table 2).

Less data are available in this setting for patients submitted to RFA. In a preliminary study published in 2002, Fontana *et al*<sup>[99]</sup> reported a dropout rate of 21% over a mean waiting period of 7.9 mo among 33 patients treated with RFA prior to LT. In more recent papers including larger numbers of patients, the dropout rate due to HCC progression was found to be 0% after a mean waiting time of 9.5 mo in one study<sup>[73]</sup> and 5.8% at 12 mo in another study<sup>[74]</sup> (Table 2). In a large study including only HCC patients within the MC awaiting LT, 77 patients who underwent RFA were compared to 93 patients without any bridging treatment; a non-specific trend toward a higher dropout rate for tumor-specific events was detected among RFA patients (21% *vs* 11%), but the mean waiting time was significantly higher in the RFA group. Using survival analysis modeling, there was no significant difference in the time to dropout between the RFA and no-treatment groups for all causes<sup>[78]</sup>.

Encouraging data have been reported following the application of multimodal schedules of treatment; in a series of 44 listed HCC patients within the MC who systematically underwent TACE followed by RFA, the intention-to-treat cumulative dropout rates were 5.5% and 11.0% at 12 and 24 mo, respectively<sup>[96]</sup>.

Lastly, the short-term response to bridging treatment has recently been reported to be crucial in the prediction of dropout. In a recent report by De Giorgio *et al*<sup>[24]</sup>, 170 HCC patients awaiting LT within the MC who underwent percutaneous ablation, TACE, or surgery as a bridging treatment were analyzed. Total tumor diameter and recurrence or persistence of tumor activity at the 6-wk follow-up after therapy were significantly correlated with progression beyond the MC and dropout from the waiting list. The finding of a significantly decreased dropout probability among T2 patients achieving a complete or partial response to bridging treatment compared with patients with an inadequate or no response to treatment has also been confirmed in two other large studies<sup>[10,14]</sup>.

In summary, there is sufficient evidence to conclude that bridging treatments yielding complete or subtotal HCC necrosis on imaging effectively reduce the rate of dropout from the waiting list.

## IMPACT OF BRIDGING TREATMENTS ON RECURRENCE OF HEPATOCELLULAR CARCINOMA AFTER LIVER TRANSPLANTATION

A less than 15% recurrence rate has been reported for HCC in patients within the MC undergoing LT without any treatment<sup>[30]</sup>. Whether the application of bridging therapies while on the waiting list decreases this rate is controversial. Again, prospective multicenter comparative studies are lacking in this field, and the only available data were obtained in single-center retrospective case series.

Regarding TACE, in a cohort of 111 HCC patients undergoing LT (54 treated preoperatively with TACE), Majno *et al*<sup>[59]</sup> showed that downstaging of tumors > 3 cm and total necrosis of the nodule at explant analysis were associated with better 5-year disease-free survival than either an inadequate response to TACE or no TACE before LT. Thereafter, low recurrence rates of 7.6% and 10.7% were reported in two large series of HCC patients within the MC who were treated with TACE before LT<sup>[63,64]</sup>. A clear trend toward longer recurrence-free survival has also been observed by Millonig *et al*<sup>[63]</sup> in patients with complete tumor necrosis when compared with patients with viable tumor at explant analysis. More recently, Tsochatzis *et al*<sup>[67]</sup> evaluated 150 consecutive patients with HCC within the MC who underwent LT. Sixty-seven patients (45%) underwent transarterial embolization (TAE) with polyvinyl alcohol particles or TACE before LT, and the remaining 83 patients were not treated before

**Table 2** Selected studies on non-surgical bridging therapy for hepatocellular carcinoma before liver transplantation *n* (%)

Ref.	Treatment	Patients	HCC stage	Dropout rate -Total -HCC progression	HCC recurrence after LT	Intention-to-treat survival	Survival after LT
Fontana <i>et al</i> <sup>[99]</sup>	RFA	33 (15 LT)	MC (30 pts)	NA	2 (13)	NA	85% at 3 yr
Graziadei <i>et al</i> <sup>[60]</sup>	TACE	48 (41 LT)	MC	0	1 (2.4)	94% at 5 yr	94% at 5 yr
Hayashi <i>et al</i> <sup>[61]</sup>	TACE	20 (12 LT)	MC	6 (35)	NA	61% at 3 yr	100% at 4 yr
Maddala <i>et al</i> <sup>[98]</sup>	TACE	54 (46 LT)	MC (47 pts)	8 (14.8)	5 (13.3)	61% at 5 yr	74% at 5 yr
				6 (11.1)			
Mazzaferro <i>et al</i> <sup>[73]</sup>	RFA	50 (50 LT)	MC (40 pts)	0 (0)	2 (4)	NA	83% at 3 yr
Lu <i>et al</i> <sup>[74]</sup>	RFA	52 (41 LT)	MC (42 pts)	6 (12)	0 (0)	74% at 3 yr	76% at 3 yr
				3 (5.8)			
Castrogaudin <i>et al</i> <sup>[81]</sup>	PEI	34 (23 LT)	UNOS T1-T2 (30 pts)	5 (14.7)	1 (4.3)	NA	19/23 (82.6%) alive (median FU 21 mo)
				2 (5.9)			
Pompili <i>et al</i> <sup>[75]</sup>	RFA, PEI	40 (40 LT)	MC (37 pts)	NA	3 (7.5)	NA	85.4% at 3 yr
Porrett <i>et al</i> <sup>[79]</sup>	TACE, RFA, TARE	31 (31 LT)	UNOS T1-T2	NA	7 (22.6)	NA	84% at 3 yr
Brillet <i>et al</i> <sup>[76]</sup>	RFA	21 (16 LT)	MC	5 (23.8)	1 (6.3)	NA	11/16 (69%) alive (median FU 25 mo)
				3 (14.3)			
Millonig <i>et al</i> <sup>[63]</sup>	TACE	68 (66 LT)	MC	2 (3)	5 (7.6)	70% at 5 yr	NA
Majno <i>et al</i> <sup>[69]</sup>	TACE	43 (43 LT)	MC	12 (27.9)	4 (9.3)	NA	NA
				4 (9.3)			
Rodríguez-Sanjuán <i>et al</i> <sup>[77]</sup>	RFA	28 (28 LT)	MC (25 pts)	NA	2 (7.1)	NA	NA
Alba <i>et al</i> <sup>[64]</sup>	TACE	63 (56 LT)	MC	7 (11)	6 (10.7)	NA	60.4% at 5 yr
				3 (4.8)			
Branco <i>et al</i> <sup>[82]</sup>	PEI	62 (59 LT)	MC	3 (4.8)	3 (5.1)	64.4% at 3 yr	67.7% at 3 yr
DuBay <i>et al</i> <sup>[78]</sup>	RFA	77 (51 LT)	MC	19 (25)	1 (2)	NA	> 80% at 3 yr
				16 (21)			
Ashoori <i>et al</i> <sup>[96]</sup>	TACE + RFA	36 (16 LT)	MC	6 (16.7)	0 (0)	NA	11/16 alive (median FU 29.9 mo)
				4 (11.1)			
Tsochatzis <i>et al</i> <sup>[67]</sup>	TACE, TAE	67 (67 LT)	MC	NA	4 (6)	NA	NA

HCC: Hepatocellular carcinoma; LT: Liver transplantation; RFA: Radiofrequency ablation; MC: Milan criteria; NA: Not available; TACE: Transarterial chemoembolization; PEI: Percutaneous ethanol injection; UNOS: United Network for Organ Sharing; TARE: Transarterial radio embolization; TAE: Transarterial embolization.

LT. HCC recurrence after LT was significantly lower in the TAE-TACE group (6%) than in the no TAE-TACE group (18.1%) (Table 2). Furthermore, post-transplant HCC recurrence was independently associated with no neo-adjuvant transarterial therapy and the total radiological size of the HCC nodules.

HCC recurrence after LT has been evaluated in 7 studies of patients who underwent RFA as the only bridging treatment. In total, 231 patients were evaluated over follow-up periods of 15-41 mo (mean 28 mo). Overall, HCC recurrence was detected in 8 patients (3.5%), and the rate of recurrence ranged between 0% and 13%<sup>[73-78,99]</sup> (Table 2).

Some recent single-center studies appear to confirm a positive impact of bridging treatments on HCC recurrence after LT. In a series of 147 HCC candidates (38% outside the MC) who underwent RFA, TACE, or multimodal treatment before LT, a complete or partial response was observed in 57.8% of cases. Transplanted patients with stable disease or no response to pre-LT HCC treatment had a significant 6-fold increase in tumor recurrence after LT compared with patients with a complete or partial response (13% *vs* 2%)<sup>[10]</sup>. In another study that included 315 HCC patients who were candidates for LT (17% outside the MC) and underwent TACE, RFA, PEI, or surgical resection, a

complete response to treatment was observed in 49.1% of cases; transplanted patients with a partial or no response to bridging treatments showed a significantly higher risk of HCC recurrence compared with patients with a complete response (19.4% *vs* 5.5%)<sup>[14]</sup>. Among 137 transplanted patients (42 outside the MC) who underwent locoregional bridging treatments such as resection, TACE, RFA, and PEI before LT, AFP > 400 ng/mL was the only significant pre-transplant factor linked to HCC recurrence after LT. Conversely, the use of locoregional treatments was a significant protective factor, and the best 5-year tumor-free survival was observed in patients within the MC who underwent locoregional treatment<sup>[100]</sup>. Lastly, within a group of 93 consecutive HCC patients (36 beyond MC) who underwent LT, 59 underwent pre-transplant TACE or RFA. The 5-year tumor-free survival did not significantly differ between treated and untreated patients (78% *vs* 68%). However, among the treated patients, the presence of more than 50% necrosis of the target lesions at explant analysis was associated with a significantly better 5-year tumor-free survival rate (96% *vs* 21%)<sup>[101]</sup>.

Overall, a trend toward a decreased recurrence rate after LT appears to emerge in patients achieving a total or subtotal response to the treatment administered before LT.

## IMPACT OF BRIDGING TREATMENTS ON SURVIVAL AFTER LIVER TRANSPLANTATION

Independent of the treatment administered, a key question remains to be answered: do bridging treatments improve survival in HCC patients who undergo LT? There is insufficient evidence of a beneficial effect of TACE because data obtained from prospective randomized studies are lacking<sup>[97]</sup>. A multicenter retrospective case control study from France compared 100 HCC patients who underwent TACE before transplantation and 100 HCC patients transplanted without any prior treatment. The 5-year survival (59% in both groups) and 5-year disease free survival (69% *vs* 64%) rates were not significantly different. At explant analysis, greater than 80% total or subtotal HCC necrosis was found in 30% of treated patients, and this subgroup showed a non-significant trend toward a better 5-year survival compared with a matched untreated control group (63% *vs* 54%)<sup>[62]</sup>. It can be reasonably argued that patients with total/subtotal tumor necrosis might receive a significant survival benefit from TACE before LT, perhaps due to a decreased risk of post-transplant HCC recurrence. This hypothesis appears to have been confirmed in a study by Millonig *et al*<sup>[63]</sup> that included 116 HCC patients who underwent TACE before transplantation. Most of the patients were within the MC, and complete tumor necrosis was found in 27% of the cases. The 5-year survival rate was higher in patients with completely necrotic tumors than in patients with partial necrosis (86% *vs* 66%), although this difference did not reach statistical significance.

The influence of neo-adjuvant treatments on post-LT survival should be analyzed independent of the treatment used; however, the only available data come from single-center retrospective series and provide contradictory results. In a study by Bharat *et al*<sup>[102]</sup>, 46 HCC patients undergoing various bridging treatments before LT were compared to 46 matched HCC patients transplanted without any treatment. The 5-year survival rate was significantly higher in the treated group (82% *vs* 52%), although the survival advantage was evident only for patients with T2-T4 tumors, not for patients with T0-T1 tumors. Even the 5-year disease-free survival rate was slightly higher in the treated group (84% *vs* 76%), although this difference was not significant. In a study by Lao *et al*<sup>[103]</sup>, 91 untreated HCC patients who underwent LT were compared to 33 patients with HCC who underwent TACE, RFA, or PEI before LT. HCC recurred only in 9 untreated patients, and the only factors significantly linked to tumor recurrence were a MELD score < 14, AFP > 1000 ng/mL, and the absence of pre-LT bridging treatment. The disease-free survival showed a non-significant trend toward a better outcome in treated patients, whereas the cumulative survival did not differ. Heckman *et al*<sup>[104]</sup> compared the outcomes of 50 HCC patients undergoing bridging therapy before LT to those of 73 HCC patients transplanted without any

prior treatment; they found a non-significant trend toward improved 5-year survival in treated patients (81% *vs* 71%). Porrett *et al*<sup>[79]</sup> compared 30 treated patients to 33 untreated patients before transplant. Their study failed to show any survival difference between the groups, but it should be noted that only 20% of the treated patients had complete HCC necrosis at explant analysis. Lastly, in the previously cited study by DuBay *et al*<sup>[78]</sup>, no differences in 5-year overall or tumor-free survival from the list date or transplant were identified when comparing 77 patients treated with RFA to 93 matched untreated patients. No data were provided about the achievement of complete necrosis in the ablated tumors at explant analysis.

Although a definitive conclusion cannot be made, a positive impact of pre-LT treatments on post-LT survival could be present. Indeed, in the United States, data on liver transplant activity for HCC from 1997 to 2006 demonstrated a higher 3-year post-LT survival in patients who underwent ablative procedures compared with patients who did not<sup>[105]</sup>. Moreover, studies reporting no difference between treated and untreated patients also tend to report shorter waiting times for LT<sup>[29]</sup>.

## DOWNSTAGING OF HCC BEYOND THE CONVENTIONAL LIVER TRANSPLANTATION CRITERIA

Downstaging of HCC to within the MC or the UCSF criteria is an attractive alternative to expanding the tumor size limits for LT. Theoretically, the downstaging process allows the selection of tumors with a more favorable biology that will likely respond to downstaging treatments and will also do well following LT<sup>[106]</sup>.

In recent years, several papers have been published defining successful downstaging as fulfilling the MC<sup>[107-114]</sup> or the UCSF criteria<sup>[106]</sup>. However, different criteria for successful treatment have been used in other studies, including fulfilling the MC without a serum AFP level higher than 400 ng/mL<sup>[115]</sup>, a 30%-50% decrease in the size of treated nodules<sup>[60,116]</sup>, or no tumor progression during the downstaging treatment in patients with well or moderately differentiated HCC<sup>[4,117]</sup> (Table 3). In some of these studies, only TACE<sup>[60,108,110,112-114]</sup> or transarterial chemoinfusion<sup>[107]</sup> was used as the downstaging procedure, whereas in other studies, a multimodal approach was used, including TACE, RFA, PEI, or surgical resection<sup>[4,106,114,115,117]</sup>. TARE as a single downstaging procedure was retrospectively compared to TACE in a study by Lewandowski *et al*<sup>[109]</sup>. Better performance was observed for TARE in terms of the downstaging success rate and 3-year intention-to-treat post-HCC treatment survival.

Significant factors for unsuccessful downstaging related to biological tumor features have been reported by some of these papers. In the study by Yao *et al*<sup>[106]</sup>, AFP > 1000 ng/mL was the only significant negative prognostic factor. Barakat *et al*<sup>[111]</sup> showed that the mean

**Table 3** Selected studies on downstaging therapy for hepatocellular carcinoma before liver transplantation *n* (%)

Ref.	Treatment	Pts	Inclusion criteria <sup>1</sup>	Successful downstage -Criteria -Rate	Transplanted pts	Recurrence free survival after LT	Intention to treat survival	Survival after LT
Graziadei <i>et al</i> <sup>[60]</sup>	TACE	36	HCC > 5 cm	Decreased size > 50% 11/36 (31)	10	Recurrent HCC: 3 pts (30)	31% at 5 yr	41% at 4 yr
Otto <i>et al</i> <sup>[116]</sup>	TACE	62	Beyond MC	Decreased size ≥ 30% 34/62 (55)	27	68% at 5 yr	NA	73.2% at 5 yr
Cillo <i>et al</i> <sup>[4]</sup>	TACE, RFA, PEI, Resection	40	Beyond MC WD or MD HCC	Maintenance of selection criteria NA	31	Recurrent HCC: 0 pts	79% at 5 yr	> 90% at 3 yr
Chapman <i>et al</i> <sup>[108]</sup>	TACE	76	Beyond MC	MC 18/76 (24)	17	50% at 5 yr	NA	93.8% at 5 yr
Yao <i>et al</i> <sup>[106]</sup>	TACE, RFA, Resection	61	1 HCC 5-8 cm 2-3 HCCs 3-5 cm, total diameter ≤ 8 cm 4-5 HCCs ≤ 3 cm total diameter ≤ 8 cm	UCSF 43/61 (71)	35	92% at 2 yr	69% at 4 yr	92% at 2 yr
Ravaioli <i>et al</i> <sup>[115]</sup>	Multimodal (TACE, PEI, RFA, Resection)	48	1 HCC 5-8 cm 2 HCCs 3-5 cm, total diameter ≤ 8 cm 3-5 HCCs ≤ 4 cm to- tal diameter ≤ 12 cm	MC and AFP < 400 ng/mL 32/48 (67)	32	71% at 3 yr	62% at 3 yr	NA
Lewandowski <i>et al</i> <sup>[109]</sup>	TACE (43 patients) TARE (43 patients)	86	UNOS T3	MC TACE 11/35 (31) TARE 25/43 (58)	TACE 11 TARE 9	TACE 73% at 1 yr TARE 89% at 1 yr	TACE 19% at 3 yr TARE 59% at 3 yr	NA
De Luna <i>et al</i> <sup>[107]</sup>	TACI	27	Beyond MC	MC 17/27 (63)	15	NA	84.1% at 3 yr	78.8% at 3 yr
Jang <i>et al</i> <sup>[110]</sup>	TACE	386	Beyond MC	MC or complete tumor necrosis 160/386 (41.5)	37	66.3% at 5 yr	NA	54.6% at 5 yr
Barakat <i>et al</i> <sup>[111]</sup>	TACE, TARE, RFA, Resection	32	Beyond UCSF (18 pts) Beyond MC (14 pts)	UNOS T2 18/32 (56.3)	13	Recurrent HCC: 2 pts (15.4%)	NA	75% at 2 yr
Bargellini <i>et al</i> <sup>[112]</sup>	TACE	33	Beyond MC	Complete or partial response, or stable disease according to mRECIST criteria NA	33	74.4% at 5 yr	NA	72.5% at 5 yr
Bova <i>et al</i> <sup>[113]</sup>	TACE, TAE	48	Beyond MC	MC AFP < 100 ng/mL 19/48 (39)	9	Recurrent HCC: 1 pt (11.1%)	NA	NA
Lei <i>et al</i> <sup>[114]</sup>	TACE, RFA, Resection, HIFU	58	Beyond MC Within UCSF	MC NA	58	63.8% at 5 yr	NA	74.1% at 5 yr

<sup>1</sup>Patients with vascular invasion or extrahepatic tumor spread at baseline excluded in all series. HCC: Hepatocellular carcinoma; LT: Liver transplantation; TACE: Transarterial chemoembolization; MC: Milan criteria; NA: Not available; RFA: Radiofrequency ablation; PEI: Percutaneous ethanol injection; WD: Well differentiated; MD: Moderately differentiated; UCSF: University of California San Francisco; AFP:  $\alpha$ -fetoprotein; TARE: Transarterial radio embolization; UNOS: United Network for Organ Sharing; TACI: Transarterial chemoinfusion; mRECIST: Modified Response Evaluation Criteria in Solid Tumors; TAE: Transarterial embolization; HIFU: High-intensity focused ultrasound; pts: Patients.

AFP level and the rate of infiltrative tumors were significantly higher in patients who did not achieve successful downstaging. An AFP level lower than 100 ng/mL and the 3-year survival probability calculated using the Metroticket calculator<sup>[33]</sup> were the only independent predictors of successful downstaging in the study by Bova *et al*<sup>[113]</sup>. An AFP slope > 15 ng/mL per month and tumor progression according to the Modified Response Evaluation Criteria in Solid Tumors (mRECIST)<sup>[118]</sup> were independent risk factors for HCC recurrence and patient death in an international retrospective multicenter European study performed by Lai *et al*<sup>[25]</sup> that included

MC-within (316 cases) and MC-outside (116 cases) patients who underwent LT after locoregional therapy. We should also highlight that after successful downstaging, some authors have recommended that patients undergo a 3-mo observation period before listing to assess the stability of neoplastic disease<sup>[4,106,115]</sup>. This “test of time” will identify rapidly recurring lesions, vascular invasion, and distant metastasis, thereby decreasing the risk of tumor recurrence and poor overall results after LT<sup>[34]</sup>.

Overall, according to the presently available data, the successful downstaging rate ranges between 24% and 71% (Table 3). The proportion of patients transplanted

ranges between 10% and 67%, and the average waiting time to LT ranges between 2 and 10.9 mo<sup>[29]</sup>. Additionally, the reported survival rates range from 78.8% to more than 90% and from 54.6% to 93.8% at 3 and 5 years, respectively<sup>[119]</sup>. Two prospective studies have demonstrated that survival after LT in patients with large tumors successfully downstaged within the MC<sup>[115]</sup> or the UCSF criteria<sup>[106]</sup> is similar to that of patients who initially met the criteria for transplantation. Six studies<sup>[4,60,107,108,114,116]</sup> compared patients who were downstaged successfully within the MC with those who initially met the MC. Five of these studies<sup>[4,107,108,114,116]</sup> reported no significant difference in absolute or disease-free survival between groups, whereas one study<sup>[60]</sup> reported that patients who were downstaged successfully had significantly worse survival at 1, 2, and 5 years after LT. Lastly, in a recent study, no significant differences in postoperative complications, tumor recurrence, or survival rate were reported between two groups of patients with advanced HCC who underwent deceased donor LT (52 patients) or living donor LT (31 patients) after successful downstaging therapy<sup>[42]</sup>.

## CONCLUSION

Currently, locoregional therapies play a crucial role in the treatment of patients awaiting LT. For patients listed within the MC (stage T2-HCC), a delay of LT over 6-12 mo without bridging treatment is a well-recognized risk factor for tumor progression and dropout from the list or interval dissemination with post-transplant tumor recurrence<sup>[2,3,16]</sup>. For this reason, the optimal strategy for T2-HCC patients awaiting LT should be to transplant within 6 mo without pre-transplant therapy<sup>[120]</sup>. However, if a longer waiting time is needed, following the current guidelines of the American Association for the Study of Liver Disease and the European Association for the Study of the Liver for the treatment of HCC<sup>[121,122]</sup> and the recommendations of a recent international consensus conference on the management of HCC patients who are LT candidates<sup>[123]</sup>, the use of bridging treatments is recommended, as several studies in recent years have documented their usefulness in preventing tumor progression. There is, however, no evidence that bridging treatments are useful in patients with T1-HCC<sup>[123]</sup>.

In patients who underwent previous liver resection and experienced tumor recurrence but are within the currently accepted transplant criteria or those with liver function failure, salvage LT using deceased donor livers yields an acceptable long-term survival rate and can be considered<sup>[6,25]</sup>. Salvage LT using living donors has also been successfully performed in centers with high-volume living donor programs, and they appear to provide long-term results comparable to those obtained using deceased donor grafts<sup>[48]</sup>.

Regarding non-surgical bridging therapies, no recommendation can be made for one type of locoregional therapy over others<sup>[123]</sup>. However, RFA could be the first-

line treatment for lesions up to 3 cm, in which complete tumor necrosis has been shown in more than 50% of cases at explant analysis. The risk of major complications related to RFA in this patient setting appears to be quite low, but it is good clinical practice to limit needle insertions and to avoid the treatment of superficially located lesions. PEI appears to show lower efficacy and can be reserved for small lesions located in sites considered “dangerous” for RFA (*e.g.*, near the gallbladder or bowel loops). TACE should be preferred for treating lesions > 3 cm because its effectiveness appears to be better in well-vascularized tumors with large feeding arteries; selective and superselective TACE should be preferred, and the possible advantage of DEBs-TACE over lipiodol-TACE should be investigated in future studies. Multimodal treatment strategies, including sequentially applied TACE and RFA, appear to be promising, although the role of alternative treatments such as PLA, MWA, TARE, and CRT needs to be investigated in a larger number of patients. Regardless, all ablation procedures should be better evaluated with caution in patients with decompensated liver function to avoid irreversible liver failure and severe complications precluding LT.

The response of HCC to neoadjuvant treatments should be evaluated using the mRECIST criteria<sup>[118]</sup>. The RECIST criteria<sup>[124]</sup> were amended to the mRECIST in 2008<sup>[125]</sup> in the setting of HCC based on the concept that the evaluation of the treatment response should consider the amount of necrosis when estimating the decreased tumor load, not only the reduction in tumor size. However, it should also be considered that computed tomography and magnetic resonance imaging, which are currently used to assess the results of the ablation bridging procedures, tend to overestimate treatment effectiveness. In several studies, the concordance in the diagnosis of complete necrosis between the last imaging evaluation before LT and the pathological assessment at explant analysis of the target lesions has been reported to range between 50% and 83%; this is primarily due to the persistence of microscopic avascular neoplastic foci that are primarily located peripherally and cannot be detected by contrast-enhanced imaging techniques<sup>[74,75,77,85,106,115,126,127]</sup>.

Although no solid conclusions may be drawn due to the absence of prospective comparative studies, it appears reasonable to state that bridging treatments decrease the dropout rate from the waiting list of T2-HCC patients and could have a positive impact on post-LT HCC recurrence and overall survival, at least in patients with complete or subtotal necrosis of the targeted lesions and a longer waiting period<sup>[29,105]</sup>. Furthermore, the response to pre-LT treatments may represent a surrogate marker of tumor biology and should be considered in the selection and prioritization of candidates for LT. That is, the transplant priority of T2-HCC candidates could be reduced after successful bridging therapy and a 3-6 mo period of observation confirming inactive neoplastic disease, and patients showing stable or progressive disease after treatment could then be prioritized.

However, if an advantage is given on the waiting list to non-responding patients, a worsening in the outcome of LT in terms of overall survival, primarily due to an increased incidence of HCC recurrence after transplantation, should be considered. Whether this risk is acceptable is a matter of debate, and this issue should be further addressed in future studies<sup>[14,29,128]</sup>.

HCC downstaging using exclusively TACE or multimodal sequential therapies to meet the conventional criteria for LT among carefully selected patients yields promising results in terms of overall and disease-free survival. In particular, some recent papers have demonstrated that patients successfully downstaged within the MC or the UCSF criteria can achieve a 5-year survival rate comparable to that of patients meeting the above-mentioned criteria without requiring downstaging<sup>[123]</sup>. A follow-up period of 3 mo demonstrating stable disease after successful downstaging is suggested before inclusion on the waiting list for transplantation.

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