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TOPIC HIGHLIGHT

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Neo-adjuvant therapy for hepatocellular carcinoma before liver transplantation: Where do we stand?

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Abstract

Liver transplantation (LT) for hepatocellular carcinoma (HCC) within Milan criteria is a widely accepted optimal therapy. Neo-adjuvant therapy before transplantation has been used as a bridging therapy to prevent drop-out during the waiting period and as a down-staging method for the patient with intermediate HCC to qualify for liver transplantation. Transarterial chemoembolization and radiofrequency ablation are the most commonly used method for locoregional therapy. The data associated with newer modalities including drug-eluting beads, radioembolization with Y90, stereotactic radiation therapy and sorafenib will be discussed as a tool for converting advanced HCC to LT candidates. The concept "ablate and wait" has gained the popularity where mandated observation period after neo-adjuvant therapy allows for tumor biology to become apparent, thus has been recommended after down-staging. The role of neo-adjuvant therapy with conjunction of "ablate and wait" in living donor liver transplantation for intermediate stage HCC is also discussed in the paper.

Key words: Bridging therapy; Neo-adjuvant therapy; Locoregional therapy; Intermediate stage; Living donor liver transplantation; Ablation; Transarterial chemotherapy; Transarterial radioembolization; External beam radiotherapy

Core tip: Transarterial chemoembolization (TACE) and radiofrequency ablation are effective in down-staging intermediate staged hepatocellular carcinoma (HCC) to fulfill Milan criteria for liver transplantation (LT). New techniques using drug eluting beads-TACE, transarterial radioembolization and stereotactic radiation therapy have shown promising results in the treatment for advanced HCC over conventional TACE. In current practice, use of multimodality approach, taking advantage of the benefits of different locoregional therapy for HCC have been adopted as down-staging and bridging therapy for LT. Use of mandatory observation period prior to LT can exclude highly aggressive liver cancer that might not benefit from LT.

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INTRODUCTION

Hepatocellular carcinoma (HCC) in cirrhotic patients

has been considered to be a contraindication for liver transplantation (LT) due to poor clinical outcome post-transplant until Bismuth *et al*[1] reported good 5-year survival after LT for HCC with early stage. Mazzaferro *et al*[2] validated this outcome using the Milan criteria (one lesion ⩽ 5 cm, or two to three lesions ⩽ 3 cm) and showed that outcomes of LT for HCC within the criteria to non HCC patients was equivalent. Currently the Milan criteria (MC) is widely adopted as a criteria of LT for HCC, therefore the priority to the organ from deceased donor has been given to HCC patients within Milan criteria world wide[3-5].

Use of neo-adjuvant therapy on HCC patients prior to LT has two objectives. First rationale is to prevent drop-out from the waiting list due to tumor progression. The concept of "bridging therapy" is now the standard of care in most transplant centers. "Bridging strategies might be appropriate for patients with United Network for Organ Sharing (UNOS) T2 (one nodule 2-5 cm or two or three nodules each ⩽ 3 cm) HCC and a likely waiting time longer than 6 mo." However, there is no evidence that bridging therapies are of any benefit in patients with UNOS T1 (one nodule < 2 cm) or short waiting time.

Another indication of neo-adjuvant therapy for possible transplant candidates is down-staging HCC with intermediate stage into the Milan criteria or other criteria which allows entry to the waiting list for LT. Various locoregional therapy (LRT) for HCC have evolved during the past two decades, and made down-staging feasible with reasonable success rates[6-8]. Grown literatures have demonstrated the efficacy of LRT with transarterial chemotherapy (TACE) and radiofrequency ablation (RFA) for down-staging as well as bridging purposes[9,10]. Several other promising LRT and systemic therapy that have been used in advanced HCC have now been brought into the field of neo-adjuvant therapy for transplant candidates. These modalities include TACE using drug-eluting beads (DEB-TACE), transarterial radioembolization (TARE) with Y90, external beam radiotherapy (EBRT), and sorafenib[11-15].

The goal of down staging HCC in transplant candidates is to achieve comparable post-transplant outcomes with that of non-HCC patients. Five-year survival after LT for non-HCC was 65%-87% according to the reports from European Liver Transplant Registry (ELTR), Organ Procurement and Transplantation Network (OPTN), and Australia and New Zealand Liver Transplant Registry (ANZLTR)[16-19]. Based on this, a 5-year post-transplant survival rate of approximately 60% would be necessary for outcomes that would justify LT for patients with intermediate staged HCC[16]. Two prospective studies showed that post-transplant survival in patients with intermediate HCC successfully down staged with LRT was comparable to survival in patients who initially met the criteria for LT[6,8]. These studies proved that even patients with large tumor burden can possibly become acceptable candidates for LT after successful down stage strategy, although cumulated evidence level in this area is still scarce compared to bridging therapy.

Pre-operative predictors for post-transplant HCC recurrences includes tumor volume, histologic grade, and serum AFP level[20-24]. In addition to these well-known predictors, recent studies indicated that observing tumor stability over a period of time after the treatment is useful to select low risk candidates in terms of post-transplant recurrences[6,25,26]. This concept "ablate and wait" has gained popularity among transplant centers. Several groups advocate the mandated observation time after successful down stage when LT is offered for the patients with advanced HCC[3].

In this article, we review the current evidences of neo-adjuvant therapy for HCC before LT for both bridging and down staging purposes. The concept of "ablate and wait" after neo-adjuvant therapy for deceased donor liver transplantation (DDLT) as well as living donor liver transplantation (LDLT) are discussed.

CONVENTIONAL LRT WITH TACE AND RFA

The most commonly used LRT in transplant candidates is conventional TACE followed by RFA[6,27-29]. Most evidence in the field of neo-adjuvant therapy for transplant candidates are based on studies mainly using these two modalities.

The concept of LRT prior to LT was first introduced in 1997 with the study using TACE[30]. The study showed successful down-stage rate of 62%, and down-staging of tumors > 3 cm (19 of 35 patients, 54%) was associated with better 5-year disease-free survival than either incomplete response to TACE or no TACE (71 % *vs* 29% and 49%, $P = 0.01$ and 0.09). Successful down-staging rates with TACE have been reported to range from 31% to 61%[12,25,31,32].

TACE is now widely accepted as the most popular LRT for bridge therapy and down-staging prior to LT. Pathological studies showed a marginal advantage for RFA over TACE in terms of tumor necrosis. The ideal indications of RFA include the tumor size ⩽ 3 cm, ⩽ 3 nodules, and no major vascular or biliary structure near the target lesions[33,34]. RFA has been used mainly as a bridge therapy rather than for down-staging because of its limited efficacy for large tumors. Two large single center studies using RFA for neo-adjuvant therapy were published in 2000's. The study by Mazzaferro *et al*[33] reported 50 transplant candidates with HCC, 40 of which are within MC after treatment with single RFA session. Four patients (8%) had major complications that required admissions. No drop out was reported with a mean waiting time of 9.5 mo. The UCLA group reported another series containing 52 patients in which 43 patients were within Milan criteria after treatment with RFA[34]. Three patients (5.8%) experienced significant treatment related complications, and 3 patients (5.8%) were reported to drop out due to tumor progression

with a mean waiting time of 12.7 mo.

Currently there is no level 1 evidence to support one LRT modality over another. Based on this, international consensus stated that no recommendation can be made for any type of LRT in patients listed for LT or in those entering a down-staging protocol[16].

EMERGING LRT; DEB-TACE, TARE, AND EBRT

Recent advance in trans-arterial and ablative treatments have widened the choice of LRT for intermediate staged HCC. These modalities include DEB-TACE, TARE and EBRT. Generally recent modalities tend to be more tolerable compared to conventional TACE. These modalities have been used in non-transplant setting first, and are now introduced to neo-adjuvant therapy for transplant candidates. In this section, the studies of these emerging LRTs in non-transplant setting are summarized along with several important studies in neo-adjuvant setting.

DEB-TACE

TACE with drug-eluting beads (DEB-TACE) uses beads loaded with chemotherapy agents which are gradually released to reduce systemic side effects and to enhance tumor drug delivery. The PRECISION study compared DEB *vs* conventional TACE. Among 212 intermediate staged HCC in non-transplant setting, the study demonstrated comparable disease control [complete response (CR) + partial response (PR) + stable disease (SD)] rate (63.4% *vs* 51.9%) and comparable adverse events[35]. However, sub-set analyses of the study showed that in patients with more advanced disease (Child Pugh B, ECOG 1, bilobar or recurrent disease), disease control rates were significantly higher in DEB-TACE ($P = 0.026$). Recent subanalysis of the trial revealed that liver toxicity and cardiac toxicity were significantly lower in DEB-TACE[36]. A recent study of 104 patients treated with DEB-TACE also validated the safety (9.6% major complication rate) and efficacy (median survival 48.6 mo) of DEB-TACE[37].

In the transplant setting, there is one small retrospective study comparing tumor response in explanted livers after DEB-TACE *vs* bland embolization that showed favoring DEB-TACE in CR rate without significant adverse effects[11].

These studies indicate that DEB-TACE is equally effective and safer compared with conventional TACE especially for the patients with advanced liver disease with comorbid diseases. These studies showed the DEB-TACE can also be incorporated into neo-adjuvant setting for transplant candidates as well.

Trans-arterial radio-embolization

Radioembolization with Yttrium-90 is a novel liver-directed brachytherapy using insoluble microspheres. There are two available devices for Yttrium-90 administration; TheraSphere® (glass based) and SIR-Spheres® (resin based). Radiolabeled particles are trapped at the precapillary level within the tumor vasculature, thus limits exposure to the surrounding normal parenchyma. Thereby this allows higher dose delivery than with an external beam radiation therapy. Glass based microspheres have smaller particle size and lower number of spheres than resin based microspheres. Therefore, TheraSphere® has less embolic effect compared to SIR-Spheres®[38]. Clinical experience with TheraSphere® has shown a low incidence of post-embolization syndrome, directly supporting its minimally embolic effect[39].

One advantage of TARE is its use in HCC with portal vein thrombosis (PVT). Majority of PVT is bland (non-malignant) thrombus due to cirrhosis. Regardless the nature of PVT (bland or malignant), TheraSphere® has been widely used safely in the setting of PVT without compromising blood flow to the hepatic parenchyma[40,41]. SIR-Spheres® has been also used in the patient with PVT as well[42].

In non-transplant setting, there have been growing literatures supporting the role of TARE over conventional TACE in intermediate HCC especially with PVT. Two large cohort studies of TARE for unresectable HCC showed excellent partial response rate of 57%-70% based on European Association for the Study of the Liver (EASL) criteria with acceptable bilirubin toxicity (19%-31%)[39,40]. Kulik *et al*[40] reported a phase Ⅱ trial of 108 HCC patients treated with TARE, 37% with PVT. There was no increased risk of hepatic failure, encephalopathy or hyperbilirubinemia in patients with branch PVT compared to no PVT.

Recently a comparative analysis was published including 463 patients with intermediate HCC treated with either TACE or TARE[43]. The case with PVT was excluded for comparison because it was contraindication for TACE, leaving 123 TARE and 122 TACE treated patients without PVT. Response rate based on EASL criteria were similar (TARE 72% *vs* TACE 69%, $P = 0.75$), although TARE had significantly better time to progression than TACE (13.3 mo *vs* 8.4 mo, $P = 0.046$).

Utilization of TARE as a neo-adjuvant therapy before LT is limited. Lewandowski *et al*[12] compared down-staging efficacy of glass based TARE ($n = 43$) *vs* TACE ($n = 43$) from T3 stage HCC to T2 to make patients transplant candidates. Partial response and down staging to T2 stage were significantly better in the TARE group (61% *vs* 37%, 58% *vs* 31%, respectively). Furthermore, time to progression favored TARE *vs* TACE (33.3 mo *vs* 18.2 mo).

Barakat *et al*[44] used resin-based TARE in their multimodal treatment protocol for down-staging advanced HCC to Milan criteria. TARE was used after TACE in patients with large (> 6 cm), multifocal (≥ 4) lesions or with residual lesions that failed to respond to combined TACE and RFA. Thirty two patients underwent multimodality treatment, and 18 of them (56%) were successfully down-staged to Milan criteria. Fourteen patients

Table 1 Studies of external beam radiotherapy for hepatocellular carcinoma before liver transplant

Ref.	*n*	Medial dose (Gy)/ fractions (*n*)	Tumor (*n*)	Size of tumor (cm)	Child C *n* (%)	Patients who failed previous LRT	Radiological CR/PR	Transplanted after EBRT	HCC recurrence after LT
Sandroussi *et al*[50]	10	33/6	2 (1-10)	6.3 (2.2-10.8)	1 (10)	5	0/7	5	0
Andolino *et al*[13]	60	48/3	1 (1-3)	3.1 (1.0-6.5)	0	23	18/24	23	2
Katz *et al*[14]	18	50/10	1 (1-2)	4.0 (1.2-6.5)	4 (22)	3	0/4	11	0
O'Connor *et al*[49]	10	51/3	1 (1-2)	3.4 (2.5-5.5)	1 (10)	4	NA	10	0

HCC: Hepatocellular carcinoma; LRT: Locoreginal therapy; CR: Complete response; PR: Partial response; EBRT: External beam radiotherapy; NA: Not available.

underwent LT after down-stage.

TARE is a novel modality with lower post-embolization syndrome, less hospitalization and equivalent response rates, thus seems to be promising modality for neo-adjuvant therapy before LT especially in patients with large tumor or bland PVT. In the case with PVT, tumor thrombus must be ruled out since it is an absolute contraindication of LT.

EBRT

The relative radiosensitivity of the liver has traditionally limited the use of radiation therapy in HCC. However, the recent development of three-dimensional conformal radiotherapy (3D-CRT) made it feasible to deliver the radiation to large HCC without damaging the surrounding normal liver tissue. Stereotactic body radiation therapy (SBRT) uses fewer fractions of potent doses with high geometric precision[15]. With these technical advances, EBRT is being recognized as an effective therapy for intermediate/advanced HCC, although clinical experience of EBRT is still very limited.

EBRT has been used in intermediate HCC and reported to have excellent radiological response with mild adverse effect. It was noted that EBRT alone treatment resulted in more intrahepatic tumor recurrences outside the irradiated volume compared to the combined treatment with TACE[45,46]. Combined use of EBRT with other modalities such as TACE and sorafenib was employed with intent to reduce the intrahepatic recurrence outside the irradiated volume[47,48]. Additionally, reduction of tumor volume after TACE may allow less irradiation for normal liver parenchyma, permitting the use of higher doses of radiation with less toxicity[15].

A recent meta-analysis of 17 Asian trials comparing TACE in combination with EBRT *vs* TACE alone for unresectable HCC involving 1476 patients showed significant improvement with combined therapy with higher CR rate and 5-year survivals with comparable adverse effects[47].

EBRT is now being evaluated as a neo-adjuvant therapy. However, the experience of EBRT in LT candidates is limited to small single center cohort studies[13,14,49,50] (Table 1). Most of neo-adjuvant EBRT were performed in Child A/B patients with T2-3 tumors. The results showed excellent local control. No patients experienced ⩾ Grade 3 toxicity or radiation induced liver disease in these series. Pathological CR rates were reported to be 0%-30% in explant examinations[13,49].

The group of University of Toronto used 3D-CRT as a neo-adjuvant therapy in 10 HCC patients (Child A/B/C, 4/5/1) who failed prior LRT (3 TACE, 2 RFA) and were considered unsuitable for other modalities due to advanced liver disease or because of anatomical reasons[50]. Eight out of the 10 patients were beyond Milan criteria. Local tumor control was 100% (PR in 7 patients) with the median follow up of 14 mo, but two patients developed metastatic lesions outside the field. Five patients underwent LT with standard vascular reconstructions except one case in which jump arterial graft was used.

The largest case series was reported from Indiana University that contained 60 Child A/B patients[13] treated with SBRT. Eight patients (13%) experienced an increase in hematologic/hepatic dysfunction greater than 1 grade. Radiological CR and PR were 30% and 40%. Among them, 23 patients underwent LT with a median time to transplant of 7 mo. Before LT, no patient experienced local control failure, but 4 patients developed new intrahepatic HCC outside the irradiated volume. Following transplant, 2 patients developed distant metastases.

Rochester University reported neo-adjuvant SBRT on 18 patients (including 4 patients with Child C) with 21 HCC[14]. Three of 18 patients dropped out due to tumor progression. Eleven patients underwent LT, and one patient underwent liver resection after completion of SBRT. All patients were disease-free after LT or hepatic resection at a median follow-up of 19.6 mo.

The role of EBRT has been gradually expanded from a palliative intent to a curative intent in intermediate HCC. EBRT is being recognized as an effective therapy for HCC in adjunct to other modalities especially for patients who failed LRT or large tumors not suitable for other LRT. Although its clinical experience is still limited, EBRT can potentially become a viable option for bridging or down-staging therapy especially for those who failed other LRT.

Sorafenib

Sorafenib is an oral multikinase inhibitor with anti-angiogenic activity, which has shown to prolong survival in advanced HCC patients based on two large randomized studies[51-53].

However due to its low response rate, sorafenib single therapy has not been used as a neo-adjuvant therapy prior

to LT. However, because of its anti-angiogenic effect, sorafenib is expected to have synergistic effect when combined with LRT[54]. For example, several *ex vivo* studies indicated that radiation alone may enhance HCC cell invasiveness through PI3K signaling pathway[55] which may explain increased intrahepatic recurrence after EBRT. Sorafenib may suppress this process[56] thus reducing the risk of recurrence outside the radiation field. Combination of TACE and sorafenib also represent a potentially powerful therapeutic approach. TACE blocks blood flow, causing necrosis and angiogenic conditions, while sorafenib inhibits angiogenesis and slows tumor progression.

At present, there are multiple ongoing clinical trials evaluating outcomes with combining sorafenib and other modalities including EBRT, TACE, and TARE in the adjuvant setting or following transplant for high-risk patients[15,57-59].

DOWN-STAGING INTERMEDIATE STAGE HCC BEFORE LT

For the last decade, there has been world-wide effort to expand the criteria of LT for HCC beyond the Milan criteria[20,22,23,60,61]. In Asian countries where live donor is the main organ source, transplant programs tend to have more extended institutional criteria because of the less need to share the organ from deceased donation pool[20,60,61]. In the Western hemisphere, where limited deceased donor is the largest source of transplants, down-staging advanced HCC to Milan criteria is the favored approach. Several studies using neo-adjuvant therapy as a method of down-staging were published from Western countries[10,24,28,32,62,63] (Table 2).

In 1997, Majno *et al*[30] first reported the use of TACE as a neo-adjuvant therapy in 113 patients with unresectable HCC before liver resection or liver transplantation. The study compared 54 patients treated with TACE *vs* 57 patients without treatment. Both groups included all stages of HCC, not limited to HCC beyond Milan criteria. The results showed that 28 (52%) patients had > 50% reduction of the largest lesions after TACE. Although there was no difference in overall survival between the two groups, subgroup analysis in the patients with tumors > 3 cm showed that those who had > 50% tumor reduction by TACE (19 of 35, 54%) had a significant better 5-year disease-free survival than patients whose tumor reduction was < 50%, or who did not receive TACE (71%, 29%, and 49%, respectively).

The concept of down-staging advanced HCC with LRT to make patients transplant candidates have evolved in the last decade. Otto *et al*[25] reported neo-adjuvant therapy by TACE for 34 patients within Milan criteria and 62 patients beyond Milan criteria. Thirty four (55%) patients beyond Milan criteria were listed upon successful downstaging by TACE with 3 median sessions of TACE. After median waiting time of 6 mo, 27 patients who were originally beyond MC underwent LT. The results showed that the initial tumor stage did not affect post-transplant recurrence, but sustained tumor response to TACE was associated with low recurrence rate. Five-year recurrence-free rate was 94.5% in patients (n = 39) who did not progress with TACE during the waiting time which was significantly better than 35.4% in patients (n = 11) who had responded initially but progressed prior to LT. The study demonstrated successful down-staging potential of TACE and indicated that tumor behavior during the waiting time can become a good surrogate marker of tumor biology. These findings were supported by several studies showing prolonged radiological response of tumor to neo-adjuvant therapy was associated with improved post-transplant outcomes[6,25,28].

With the advent of newer LRT, most centers have adopted multimodality approach for down-staging HCC. The University of California at San Francisco (UCSF) group reported their experience in multimodality neo-adjuvant therapy approach[6]. The group limited the inclusion criteria for down-staging and used the UCSF criteria (solitary tumor up to 6.5 cm, or up to 3 nodules with the largest being up to 4.5 cm and total a tumor diameter up to 8 cm) as a transplant eligible criteria. Neo-adjuvant LRT using TACE, RFA, and resection successfully down-staged 43 out of 62 (71%) enrolled patients. Thirty-five patients underwent LT after median treatment sessions of 1.25 and median waiting time of 8.2 mo. Recurrence free survival after LT was 92% at 2 years.

Another study of multimodality approach from Bologna Italy showed similar results[8]. The neo-adjuvant LRTs used were TACE, RFA, percutaneous ethanol injection, and resection. Their LT criteria after down-staging was Milan criteria with AFP ⩽ 400 ng/mL. The down-staging to Milan criteria was achieved in 32 (67%) patients, and all of the 32 patients underwent LT after median waiting time of 6 mo. Recurrence free survival after LT was 71% at 3 years.

Although many studies reported successful down staging using various approaches, most of these are uncontrolled observational studies. However, two prospective studies did demonstrate similar post-transplant survival in HCC patients who were successfully down staged compared to those patients who initially met the criteria for LT. Those studies potentially justifies the strategy of transplanting high risk patients following down-staging in the setting of organ shortage[10,12]. However large randomized trials are still lacking and more studies with longer follow up that can assess the post-transplant tumor recurrence are needed to confirm the current practice of down-staging advanced HCC prior to liver transplant.

LT CRITERIA FOR ADVANCED HCC AFTER DOWN-STAGING

Morphological tumor size and number

It is recently recognized that there are other variables beyond Milan criteria which can predict favorable post-

Table 2 Studies of neo-adjuvant therapy for down-staging hepatocellular carcinoma before liver transplant

Ref.	Year	*n*	LRT	Inclusion criteria for DS protocol	Successful DS criteria	Mandatory waiting time prior to LT (mo)	The role of AFP	DS rate	LT (patients)	Waiting time to LT (mo)	Patient survival after LT	Recurrence-free survival after LT
Transarterial therapy alone												
Otto *et al*[25]	2006	62	TACE	Beyond MC	30% decrease in size	No	NA	55%	27	5.9 (1.9-19.3)	73% at 5 yr	68% at 5 yr
Chapman *et al*[28]	2008	76	TACE	Beyond MC	MC	3-4	NA	24%	17	5.8 ± 3.5	94% at 5 yr	100%, 50% at 3, 5 yr
De Luna *et al*[32]	2009	27	TACI	Beyond MC	MC	No	Not significant	63%	15	10.9 (0.7-114.1)	79% at 3 yr	NA
Multimodal approach												
Yao *et al*[6]	2008	61	TACE, RFA, Resection	One lesion, 5-8 cm 2-3 lesions, 3-5 cm, total diameter ≤ 8 cm 4-5 lesions, ≤ 3 cm, total diameter ≤ 8 cm	MC for DDLT UCSF criteria for LDLT	3	AFP > 1000 ng/mL Predicts DS failure	71%	35	8.2 (3-25)	92% at 2 yr	92% at 2 yr
Ravaioli *et al*[8]	2008	48	TACE, RFA PEI, resection	One lesion, 5-6 cm 2 lesions 3-5 cm 3-5 lesions, ≤ 4 cm, total diameter ≤ 12 cm	MC and AFP ≤ 400 ng/mL	3	AFP ≤ 400 ng/mL, listing criteria AFP > 30 ng/mL, predictor of recurrence after LT	67%	32	6	NA	78%, 71% at 1, 3 yr
Barakat *et al*[44]	2010	32	TACE, RFA, TARE, resection	Beyond MC	MC	No	Failed *vs* successful DS 5670 ng/mL *vs* 799 ng/mL	56%	14	11.2 (4.4-22.6)	92%, 75% at 1, 2 yr	2 patients Recurrence

HCC: Hepatocellular carcinoma; LRT: Locoreginal therapy; DS: Down-stage; LT: Liver transplant; AFP: Alpha-fetoprotein; TACE: Transarterial chemoembolization; MC: Milan criteria; TACI: Transarterial chemo-infusion; RFA: Radiofrequency ablation; UCSF: University of California at San Francisco; PEI: Percutaneous ethanol injection; NA: Not available.

transplant outcomes. Several centers developed institutional LT criteria based on the outcome data. These outcome studies showed several predictors for post-transplant HCC recurrence that included tumor volume (size and number of the tumors), pathological findings (microvascular invasion, and poorly differentiation) and serum AFP levels[21,22,64]. Although the microvascular invasion is the strongest predictors for recurrence in most studies, it cannot be incorporated into the patient selection criteria as pathological information is not available before transplant. Therefore, most of the new proposed HCC criteria were created by extending Milan criteria[22,23,61]. Among the proposed LT criteria for HCC, only UCSF criteria has been validated from other centers, and widely accepted as expanded LT criteria for HCC.

Presence of vascular invasion and extrahepatic disease are still considered to be contraindications to LT[16]. To evaluate the response to neo-adjuvant therapy, EASL guidelines suggest that the treatment effect should be assessed based on the amount of viable tumor load, not just a reduction in overall tumor size[65]. Overall assessment should include the combined results of target lesions, non-target lesions, and new lesions based on modified Response Evaluation Criteria in Solid Tumors[66]. Three month interval reassessment of radiological image along with AFP sampling is widely accepted in clinical practice[67].

In terms of morphological criteria for down-staging of intermediate HCC, Milan criteria is the worldwide accepted LT criteria. However, UCSF criteria is also being used in some regions in US as well.

Tumor markers

There is the need to identify surrogate markers for tumor biology in addition to morphological tumor size and number to explore optimal criteria. Because of its association with pathological feature and tumor biology, tumor markers such as AFP and protein induced by vitamin K absence (PIVKA-Ⅱ) have gained attention. Several studies from Japan suggested that PIVKA-Ⅱ correlate well with microvascular invasion[20,68]. Positive and negative correlations of AFP with microvascular

invasion have been reported as well. AFP is recognized as predictive factor for post-transplant recurrence and should be included for the LT criteria after down-staging of advanced HCC[3].

Bologna group included AFP ≤ 400 ng/mL after down-stage as one of the criteria prior to LT[8]. This group of patients exhibited 3-years disease free survival equivalent to those meeting Milan criteria without down-staging (71% *vs* 71%). Several studies also showed a pre-operative AFP level > 1000 ng/mL to be a strong independent predictor of post-transplant tumor recurrence. Based on those findings US national conference on liver allocation recommended that for patients who had an initial AFP > 1000 ng/mL, successful down-staging should include a decrease to AFP levels < 500 ng/mL. Furthermore, all subsequent AFP levels must also be < 500 ng/mL prior to LT as well[3]. Merani *et al*[24] studied 6817 patients with HCC in SRTR data and validated those findings. According to their study, AFP down-staging to ≤ 400 ng/mL was associated with good survivals even if the initial value was > 1000 ng/mL. Only the pre-transplant AFP independently predicted post-transplant survival. Although there is no consensus in the cut-off value of AFP, reduction of AFP should be included as a criterion of successful downstage.

The concept of mandatory waiting time after LRTs

Currently there are no biomarkers that can predict or prognosticate HCC patients prior to LT other than AFP. Tumor behavior during the waiting time has been considered as a surrogate marker for tumor biology. During period of waiting time after down-stage, the tumor biology is allowed to become apparent by radiological study. This concept "ablate and wait" has recently gained popularity among transplant community[26].

Several studies demonstrated that sustained response to LRT during waiting time was associated with low post-transplant tumor recurrence. As described in above study by Otto *et al*[25] demonstrated that tumor recurrence was significantly higher in patients (n = 11) who progressed after initial response to TACE before LT compared to patients (n = 39) who maintained response. In the study from UCSF group, multimodality LRT down-staged 43 out of 62 (71%) enrolled patients[6]. The median waiting time from the fist LRT and LT was 8.2 mo. Although the waiting time is related to donor scarcity, this requisite time allows HCC to show its biology and about 30% of patients will drop out due to tumor progression. However, the patients who made it to LT had an excellent 2-year recurrence-free survival of 92%. Interestingly, explant histopathological examination revealed that none of the 35 patients who underwent LT had poorly differentiated grade tumors, and only one had microvascular invasion. This finding supported the hypothesis that the patients who sustained tumor respond over the waiting period have better tumor biology that likely to contribute to excellent post-transplant outcomes.

These studies support evidence that waiting time after down-staging helps exclude the high risk patients who have tumors with unfavorable biology in HCC. The period of mandate waiting time is debatable. The 3-mo observational period was accepted in US national conference on liver allocation[3]. However, some investigators claimed 6-mo observation is needed because the median waiting time of above mentioned studies are generally > 6 mo[26,62].

SHOULD WE TREAT PATIENTS WITHIN MILAN CRITERIA HCC?

The recent advance in LRT has significantly reduced major treatment-related complications thus preventing further drop out from the transplant list (2.5%-15%[9,31,69] to 0%-5%[10,28]). With respect to the benefit *vs* the risk of bridging therapy for patients within Milan criteria, the benefit for patients whose waiting time is longer than 6 mo certainly overweighs the risk from therapy related complications. The rate of drop-out due to tumor progression at 6 mo on the wait list is reported > 15%[70]. Studies on bridging therapy were summarized in Table 3. The median waiting time to LT in these studies ranges from 6 to 12.7 mo. Current evidences support the use of bridging therapy for those who is likely to wait 6 mo or more to LT[66].

In contrast, international consensus stated that there is no strong evidence for the need of neo-adjuvant treatments for HCC within MC if the expected waiting time for LT is shorter than 6 mo[16]. The statement is due to the paucity of the evidence in this area that includes data according to detailed classification of HCC within MC and the studies using more recent and tolerable bridging therapies.

Dropout rates are associated not only with waiting period but also with tumor characteristics. HCC within Milan criteria contains a heterogeneous group of HCC. Several investigators reported that patients with single tumors > 3 cm, 3 lesions, or high AFP have a higher risk of wait list dropout due to tumor progression[3,69]. A most recent study based on the Scientific Registry of Transplant Recipients by Toso *et al*[71] including 50000 LT candidates validated these findings. The study found that dropout risk of HCC patients was independently associated with MELD score, tumor size, and number, and AFP. The authors developed formula to calculate estimated drop-out rate based on these factors. The indication of LRT for high risk patients can be considered more aggressively.

Furthermore, in the clinical practice there is a commonly accepted attitude that most patients on the waiting list are treated with bridging therapies. This approach can be justified with extremely low complication rate from LRT reported by previous studies mainly using conventional TACE and RFA.

Another possible benefit from bridging therapy on the patients within Milan criteria is reduction in post-

Table 3 Studies of bridging therapy for hepatocellular carcinoma before liver transplant *n* (%)

Ref.	Treatment	Tumor stage (*n*)	Number of treatments	Exclusion for LT	Tumor progression	Waiting time to LT (mo)	Intention to treat survival	Transplanted patients	Patient survival after LT
Graziadei *et al*[9]	TACE	Within MC (48)	2.5 (1-8)	MC	0 (0)	6.0 (0.9-15)	94% at 5 yr	41 (85)	94% at 5 yr
Yao *et al*[69]	TACE, RFA, PEI, resection	Within MC (70)	3.1 (1-8)	UCSF	18 (26)	6.1	57% at 3 yr	38 (54)	NA
Hayashi *et al*[29]	TACE	Within MC (20)	?	MC	4 (20)	11.4 ± 9.8	61% at 5 yr	12 (60)	100% at 4 yr
Maddala *et al*[27]	TACE	Within MC (47), Beyond MC (7)	3 (1-4)	MC	6 (11)	7.0 (1-36)	61% at 5 yr	46 (85)	74% at 5 yr
Mazzaferro *et al*[33]	RFA	Within MC (40), Beyond MC (10)	1	MC	0 (0)	9.5 (2-47)	NA	50 (100)	83% at 3 yr
Lu *et al*[34]	RFA	Within MC (42), Beyond MC (10)	1.5	MC	3 (6)	12.7	74% at 3 yr	41 (79)	76% at 3 yr
Millonig *et al*[10]	TACE	Within MC (68)	2.7 ± 1.7	UCSF	2 (3)	9.0 (1.2-34)	70% at 5 yr	66 (97)	NA
De Luna *et al*[32]	TACI	Within MC (95)	1.8 ± 1.1	MC	6 (6)	11.4 (1.0-133)	85% at 3 yr	68 (72)	82.4% at 3 yr

HCC: Hepatocellular carcinoma; LT: Liver transplant; TACE: Transarterial chemoembolization; MC: Milan criteria; RFA: Radiofrequency ablation; PEI: Percutaneous ethanol injection; UCSF: University of California at San Francisco; TACI: Transarterial chemo-infusion; NA: Not available.

transplant HCC recurrence.

Historically pre-transplant TACE failed to show benefit in post-transplant recurrence. French multi-center study[72] compared 100 patients treated TACE with 100 matched non-treated patients. In both groups, 66 patients were within Milan criteria. With a mean waiting period of 4.2 mo and 1 TACE session, pre-LT TACE did not influence post-LT overall survival and disease-free survival. There were no differences in outcome of patients within Milan criteria either.

Contrarily, a recent Austrian cohort study appeared to show that the response to neo-adjuvant TACE was associated with better post-transplant survival in patients within Milan criteria[10]. The study included 68 patients within Milan criteria. A median waiting time was 9 mo and mean TACE sessions was 2.7. Two patients (2.9%) dropped off the list due to tumor progression. Repeated treatments resulted in pathological CR rate of 27% of all 106 transplanted patients including beyond Milan criteria. Patients with Milan criteria who had radiological CR and PR after TACE had better 1 year post-transplant survival than those with stable or progressive disease (89%, 94%, and 38%). The result of the study may advocate a period of tumor surveillance after LRT for patients within Milan criteria as well as those beyond Milan criteria before LT. However, tumor recurrence rate in Milan criteria patients is 7.6% (5 patients), and authors did not provide the tumor recurrence rate according to the response rate to TACE.

Therefore the data for bridging therapy for Milan criteria patients in order to reduce post-transplant HCC recurrence is lacking. But for preventing drop-out, there is strong evidence for the bridging therapy if waiting time is longer than 6 mo.

ROLE OF NEO-ADJUVANT THERAPY IN ADVANCED HCC BEFORE LDLT

In the context of organ shortage, LDLT has emerged as an attractive option for patients with advanced HCC in Western countries where DDLT prioritization is limited to those within Milan criteria. The use of living donor benefits other patients' chance of getting organs from shared organ pool. However, considering for the risk of complications or death of a healthy donor, international consensus group recommended that LDLT should be offered to patients who have an expected 5-year survival similar to patients receiving DDLT[16].

Accumulated experience of LDLT in USA led to the multi-center study comparing outcomes following LDLT and DDLT for HCC[73]. The study showed higher recurrence rate in LDLT due to advanced staged tumors in LDLT group. More importantly, a short observation time between LRT and LDLT might allow aggressive HCC to undergo LDLT. Considering a mandated observation time after LRT when LDLT was offered for advanced HCC to document response and a decline in AFP is suggested. The concept of mandated observation time before LDLT has not gained popularity in Eastern countries where live donor is the main source for transplant organs[4,60]. The most programs in Asia are likely to support LDLT even for patients with a dismal prognosis, to maximize individual patient benefit. Using this approach, Asian programs have expanded their LDLT criteria for advanced HCC with acceptable outcomes[60,61].

Kyoto university group reported the experience of 93 LDLT for HCC showing that patients with 1-2 pre-transplant treatments had significantly lower recurrence rates than those with > or = 3 treatments (9% *vs* 37%, $P = 0.04$). The higher recurrence rate in the latter group may just indicate biologically aggressive tumors requiring more treatment before LDLT.

It is difficult to establish general consensus in regards to the use of neo-adjuvant therapy before LDLT due to the differences in each program's approach to LDLT. Clear endpoints of neo-adjuvant therapy before LDLT for advanced HCC need to be set in each program including tumor volume and tumor markers to have satisfactory outcomes. It might be reasonable to have a man-

datory waiting time (*e.g.*, 3 mo) between LRT and LDLT for advanced HCC as well.

CONCLUSION

Conventional LRT are effective in down-staging intermediate staged HCC to fulfill Milan criteria for LT resulting in acceptable post-transplant outcomes. DEB-TACE, and TARE showed promising results in the treatment for advanced HCC over conventional TACE in terms of tolerability. In the current practice, these emerging modalities are being included in the multi-modality approach showing promising results. Bridging therapy should be considered with expected waiting time more than 6 mo, or those with high risk characteristics of HCC. Certain mandatory observation period after successful down-stage is important tool to unveil tumor biology, thus should be added before DDLT and may be considered before LDLT as well.

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