

Loco-regional therapies for patients with hepatocellular carcinoma awaiting liver transplantation: Selecting an optimal therapy

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Abstract

Hepatocellular carcinoma (HCC) is a common, increas-

ingly prevalent malignancy. For all but the smallest lesions, surgical removal of cancer *via* resection or liver transplantation (LT) is considered the most feasible pathway to cure. Resection - even with favorable survival - is associated with a fairly high rate of recurrence, perhaps since most HCCs occur in the setting of cirrhosis. LT offers the advantage of removing not only the cancer but the diseased liver from which the cancer has arisen, and LT outperforms resection for survival with selected patients. Since time waiting for LT is time during which HCC can progress, loco-regional therapy (LRT) is widely employed by transplant centers. The purpose of LRT is either to bridge patients to LT by preventing progression and waitlist dropout, or to downstage patients who slightly exceed standard eligibility criteria initially but can fall within it after treatment. Transarterial chemoembolization and radiofrequency ablation have been the most widely utilized LRTs to date, with favorable efficacy and safety as a bridge to LT (and for the former, as a downstaging modality). The list of potentially effective LRTs has expanded in recent years, and includes transarterial chemoembolization with drug-eluting beads, radioembolization and novel forms of extracorporeal therapy. Herein we appraise the various LRT modalities for HCC, and their potential roles in specific clinical scenarios in patients awaiting LT.

Key words: Liver transplantation; Loco-regional therapy; Transarterial chemoembolization; Radioembolization; Hepatocellular carcinoma

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Core tip: Hepatocellular carcinoma has increased in incidence in recent decades. Liver transplantation is an excellent therapy for carefully selected patients. Due to the risk of tumor progression while awaiting liver

transplantation, loco-regional therapy is frequently used in this setting. An expanding array of treatment options exist and are herein characterized, including descriptions of which modality may be ideal in various settings.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common human malignancy and the third leading cause of cancer-related death^[1,2]. Driven largely by the hepatitis C virus (HCV) epidemic, the age-adjusted incidence of HCC in developed nations has approximately tripled since the early 1970's^[3]. Cirrhosis is the major risk factor in HCC formation and is present in the vast majority of cases.

Therapy for HCC has evolved during recent decades. While some small HCCs may be fully eradicated with percutaneous ablation^[4], surgery with resection or liver transplantation (LT) is considered the only curative option in most situations. That cirrhosis is present in the majority of patients diagnosed with HCC may explain this, since localized ablation would not address the diseased non-cancerous liver which still harbors the potential for hepatocarcinogenesis.

Resection and LT both achieve favorable survival in selected patients with early-stage and/or unifocal HCC^[5,6]. However, a review of a large North American cohort (> 20000) of liver cancer patients using the Surveillance, Epidemiology and End Results 1973-2003 database showed a dramatically superior actuarial survival for LT compared to resection or ablation^[7]. Resection is associated with a relatively high rate of recurrence^[5], with 3-year recurrence frequency above 60% in some series^[8]. Recurrence of HCC following resection - at least in cirrhotic patients - is due to de-novo hepatocarcinogenesis in the diseased remnant liver and/or unseen micrometastases. The rationale for LT in the setting of HCC is that it removes not only the cancer but the diseased (and cancer-promoting) liver parenchyma surrounding the tumor(s).

EXPERIENCE WITH LT FOR HCC

Initial experience with LT for HCC as reported in early series was extremely poor^[9,10]. Such was the pessimism regarding LT for liver cancer that in many centers HCC was considered a contraindication to transplant. In this era there were no standardized transplant eligibility criteria based on tumor size or number, and imaging ability was limited compared to today. Thus

the poor outcomes were likely related to the inclusion of patients with large and/or multifocal tumors, with correspondingly high rates of HCC recurrence after LT. HCC recurrence itself is a leading cause of mortality in this patient population.

Despite the disappointing early experience, there was simultaneous awareness that patients who had small, incidental HCCs found at explant tended to have low rates of recurrence with favorable long-term survival after LT^[11]. This in turn led to consideration of LT in patients with limited tumor burden. In 1996 Mazzaferro published his landmark series demonstrating that patients whose pre-LT tumor burden was limited to a single lesion ≤ 5 cm, or 2 to 3 lesions each ≤ 3 cm, enjoyed excellent disease-free survival after LT (> 80% at 4 years)^[12]. These size parameters have become known as the "Milan criteria" and are widely endorsed as the most common eligibility criteria for LT among patients with HCC.

TUMOR PROGRESSION ON THE TRANSPLANT WAITING LIST

In the United States organ transplantation is regulated by the United Network for Organ Sharing (UNOS). By UNOS classification the Milan criteria include stage T1 (1 tumor < 2 cm) and stage T2 (1 tumor 2-5 cm or 2-3 tumors ≤ 3 cm). Current UNOS policy allows patients with Milan T2 to receive priority listing for LT^[13]. Historically, however, HCC patients pursuing LT still face reduced survival by intention-to-treat analysis^[14]. This is due to tumor progression while awaiting LT, resulting in waitlist dropout. For waiting times up to 1 year, historical dropout rates of 10%-30% are encountered, with 5-year survival reduced by as much as 20%^[14]. In some UNOS regions, expected waiting time for priority-listed HCC patients exceeds 1 year.

Neo-adjuvant loco-regional therapy (LRT) for HCC is widely utilized by transplant centers internationally. The specific types of LRT available for use have expanded in the last decade, and are discussed later in this manuscript. For patients meeting Milan criteria, the intent of LRT is to serve as bridging therapy to LT by preventing tumor progression and waitlist dropout. For another group of patients who exceed Milan criteria, but fall within expanded criteria allowing a cumulative total diameter for all lesions ≤ 8 cm, the intent of LRT is "downstaging". Successful downstaging implies that LRT has resulted in tumor shrinkage and/or devitalization (tumors no longer exhibit arterial phase enhancement on imaging), such that upon re-measuring the active tumor burden at some future time point after LRT, the patient falls within Milan criteria.

Advocates of these expanded downstaging criteria - particularly Yao and colleagues at the University of California San Francisco (UCSF) - have reported favorable outcomes for successfully downstaged patients, with a recent paper showing a 56.1% 5-year intention-

to-treat survival for 64 patients assigned to downstaging, not statistically different from a 63.3% 5-year intention-to-treat survival in 488 patients with Milan stage T2^[13]. However, expanded downstaging criteria have not been universally accepted and remain controversial in the face of already-present severe organ shortage.

LRT FOR HCC PATIENTS AWAITING TRANSPLANT

To date a post-transplant survival advantage for LRT prior to LT has not been definitively proven^[15,16]. However, given what is known about the risk of waitlist dropout, a randomized controlled trial comparing LRT to no LRT in patients awaiting transplant may be difficult to justify. An emerging concept is that tumor biology - as observed by imaging over time - is a more useful surrogate marker of tumor biology than size and number based on an initial imaging study. Patients with HCCs that display radiographic progression over relatively short time periods such as 3-6 mo - without LRT or despite it - are more likely to possess cancers that are inherently aggressive. Such patients are more likely to experience tumor recurrence and diminished survival after LT^[17].

Favorable response to LRT - whether used as bridging therapy for Milan criteria, or with downstaging intent for expanded criteria patients - has thus been proposed as a surrogate marker of more favorable tumor biology^[13,18-20]. In this paradigm, a mandatory waiting period of 3-6 mo after LRT is required before LT can be offered, in order to observe tumor response to LRT. Presumably, patients whose cancer progressed during the observation period - despite LRT - would not be offered LT. This strategy has been termed "ablate and wait"^[21]. The expanded downstaging criteria used and advocated by UCSF requires a minimum 3 mo waiting period after LRT before LT can occur^[13], and some UNOS regions (including Region 5 within which UCSF resides) impose a 6-mo delay of the assignment of priority points for listing of Milan stage T2 patients, in order to observe tumor behavior and response to LRT.

A number of different LRT options exist. Transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) have historically been the first and second most commonly utilized neo-adjuvant treatments before LT, respectively^[15]. TACE using drug-eluting beads (DEBs) - DEB-TACE - has become more widespread in recent years^[22]. Percutaneous ethanol ablation - once common for small tumors - and cryotherapy have declined markedly in use and are not further described here. Other forms of LRT include radioembolization with Yttrium-90 (Y-90), for which emerging literature suggests a favorable efficacy and tolerance^[23], and a novel mode of radiation therapy which may be effective as bridging therapy to transplant^[24]. The remainder of the manuscript appraises the types of LRT being used as neo-adjuvant therapy before LT, as well as

their respective efficacies and roles in various clinical situations.

INTRA-ARTERIAL CHEMOTHERAPY

Traditional TACE involves catheterization - as selectively as possible - of the artery branch(es) supplying the tumor(s) with blood, followed by the infusion of liquid chemotherapy agents into the branch(es). Specific chemotherapy agents differ across institutions, but often a mixture of doxorubicin, cisplatin and mitomycin-C is delivered. The liquid chemotherapy is often pre-mixed with ethiodized oil, which serves as both a drug-delivery vehicle as well as a radiopaque marker of where in the liver the mixture has been delivered^[25]. The oily nature of the emulsion itself contributes to embolization effect on small vessels, though transiently so. Many centers add embolic particles either to the oily emulsion or as a separate infusion immediately following release of the emulsion^[26]. Embolic agents include polyvinyl alcohol particles or Gelfoam. The duration of arterial occlusion is shorter with Gelfoam, with recannulization of flow occurring in about 2 wk. The intended duration of arterial occlusion is not permanent since this would interfere with future chemoembolization if it became clinically desirable. The combination of cytotoxic chemotherapy and embolization achieves varying degrees of tumor necrosis^[26,27], but achieving even complete necrosis has not necessarily been predictive of post-LT survival^[16].

The outcome of TACE must be assessed with two questions in mind. First, does TACE prior to LT improve survival after LT? And second, is TACE effective as a bridge to LT by preventing tumor progression and waitlist dropout. Both questions are problematic. As mentioned previously, there have been no large prospective trials comparing LRT to no-LRT in patients with HCC awaiting LT. And the evidence to date for pre-transplant TACE does not establish a clear post-transplant survival benefit. The waiting time to LT varies across regions, and a very short duration from TACE to LT does not allow sufficient time for observation of tumor behavior. This in turn will lead to some patients with biologically unfavorable tumors proceeding to LT, likely contributing to increased HCC recurrence and reduced survival. Those limitations notwithstanding, it does appear from a number of studies that TACE is associated with waitlist dropout rates of 3%-13%^[18,20,28,29], which is lower than expected based on historical data^[14] and supports TACE as an effective bridge to LT. TACE also has a favorable safety profile, and in the case of inoperable disease (non-transplant candidates), is associated with improved survival vs supportive care^[30].

DEB-TACE is similar to traditional TACE as an intra-arterial therapy for HCC administered selectively in the hepatic arterial circulation. The beads themselves are microspheres impregnated with a chemotherapeutic substance (most commonly doxorubicin), ranging in size from 100 to 700 μm . The amount of delivered doxorubicin is typically 100-150 mg/session^[22]. The

proposed advantage of DEB-TACE vs traditional TACE is a more concentrated delivery of chemotherapy in the targeted area, and for a longer duration, since traditional TACE results in a more transient drug concentration. This is because there is a delay from release of the oily therapeutic solution and the actual embolization in traditional TACE, causing some release into the systemic circulation (with systemic toxicities, and diminished activity at the intended tumoral site)^[31].

The safety of DEB-TACE has been validated in large studies as at least comparable to traditional TACE^[31], and the PRECISION-V study showed a statistically significant lower incidence of alopecia, degree of post-treatment aminotransferase elevation, and frequency of decreased left ventricular function with DEB-TACE vs conventional TACE^[22]. In clinical practice, since there is less induced arterial ischemia with DEB-TACE compared to conventional TACE, the former is an attractive consideration in patients with partially or completely thrombosed portal vein branches, since such patients may not tolerate a new, substantial arterial ischemia. For the same reason, many groups favor DEB-TACE for patients with worse liver function at baseline. In terms of efficacy and survival, there is insufficient data to claim that either TACE or DEB-TACE clearly outperforms the other^[22,31]. DEB-TACE has not been widely studied specifically for use as a bridge to transplant, though some published reports suggest its efficacy in this role^[32].

RADIOEMBOLIZATION

Transarterial radioembolization (TARE) has emerged as a viable strategy for solid liver tumors. The most commonly used form of TARE for HCC involves Y-90 microspheres delivered intra-arterially. Y-90 has a physical half-life of 64.2 h and decays to stable zirconium-90^[33]. A staging visceral angiography with injected technetium-99 is necessary to detect clinically relevant shunting to the gastrointestinal (GI) tract or lung, the latter assessed by measuring lung-shunt percentage on imaging^[34]. If shunts to the GI tract cannot be embolized (and closed), or if the lung-shunt fraction is elevated, Y-90 is not offered due to concerns about intestinal and pulmonary toxicity, respectively. If no such problems are encountered, Y-90 microspheres are delivered either to the right or left lobe, usually allowing at least 1 mo before treating the opposite side if bi-lobar disease is present, in order to monitor for toxicity.

Overall tolerance and safety appears comparable to TACE, although the amount of published experience with Y-90 is vastly less than with TACE. Due the hypervascularity of HCCs, radioactive microspheres theoretically flow preferentially - by a factor of 3 to 1^[35] - to tumors rather than hepatic parenchyma, limiting toxicity. Nonetheless, post-embolization syndrome following TARE - with nausea, abdominal pain and anorexia with or without fever - occurs with roughly the same frequency as with TACE, though severity may be

less^[36]. Some unique toxicities of Y-90 therapy must be appreciated. Radiation-induced liver disease (RILD) is a potentially serious sequela of TARE. RILD involves the emergence of varying degrees of liver decompensation with jaundice and ascites occurring 2-8 wk after treatment, with series suggesting a frequency of 4% to as much as 20%^[36,37]. The risk of RILD appears to increase significantly with repeated Y-90 administrations^[38]. Radiation-induced biliary stricturing is another potential consequence of TARE, though the incidence appears to be less than 10%^[39]. As with TACE, care must be taken to avoid inadvertent embolization of the cystic artery, which could cause gall bladder necrosis. Radiation induced pneumonitis and GI ulcerations are rare if standard precautions are undertaken^[36], but may occur with unrecognized shunting to lung or bowel.

Efficacy of radioembolization in terms of radiographic response and survival in non-operative candidates appears comparable or possibly superior to TACE^[23], acknowledging that the cumulative amount of experience with Y-90 is less. Its utility as a bridge to LT is similarly less defined, but selected series show that TARE is effective in this role^[34,40]. Lewandowski published a series comparing TACE (35 patients) to TARE (43 patients) for downstaging of HCC beyond Milan criteria, and reported successful downstaging to Milan T2 was superior with TARE (58% vs 31%, $P = 0.023$)^[41]. One theoretical concern with Y-90 as a bridge to LT is the risk of radioactivity affecting surgical or pathology team members handling the explanted organ. However the decay properties of Y-90 are such that unless LT happens within 4 wk of TARE, the risks should be trivial.

ABLATION THERAPY

Except for TACE, RFA has been the most widely utilized and reported LRT for patients awaiting LT. RFA involves the insertion of one or more narrow probes - under ultrasound or computed tomography guidance - into a target liver lesion, usually with the patient anesthetized. Occasionally more than one tumor is treated in a given session. The probes are connected to an alternating current that generates heat at their tip, causing thermal injury to tissue. Some technical limitations of RFA involve a relatively long time (16-18 min) to achieve adequate thermal injury to fully ablate a 3-4 cm lesion, as well as the potential loss of heat energy (and thus treatment effect) if large blood vessels are near the treatment zone. In such cases, the vessels act as heat sinks dissipating energy. In view of these limitations, some centers have begun to utilize microwave ablation (MWA). MWA achieves much more rapid heating with shorter treatment time, as well as a larger zone of ablation. However, neither RFA nor MWA is ideal for lesions high in the dome of the liver or near the gall bladder, due the risk of pulmonary insult or gall bladder necrosis, respectively.

Complications of ablation include abdominal pain and anorexia with or without fever, not necessarily different

from the symptoms of post-embolization syndrome. Serious bleeding is possible but uncommon (< 2%), as is the rate of abscess formation, portal vein thrombosis, thoracic injury, and severe liver decompensation^[42,43]. The risk of tumoral seeding by ablation probes (2%) and overall mortality (< 1%) is low, and seems comparable between RFA and MWA^[43-45].

For very small (≤ 3 cm) HCCs, it is recognized that RFA can achieve complete eradication and is viewed by many as equivalent in efficacy to resection for this scenario^[46,47]. Two large series published by Lu *et al.*^[48] and Mazzaferro *et al.*^[49] respectively, demonstrated the effectiveness of RFA as a bridge to LT, with very low dropout rates of 6% and 0%, respectively. A large Canadian study reported a higher rate of dropout with RFA (21%) as compared to an untreated cohort (12%), but this was in part driven by longer median waiting time to LT in the RFA cohort (9.5 mo vs 5 mo), as well as 9% of RFA-treated patients (vs 1% untreated) voluntarily seeking de-listing after achieving complete radiographic response^[50]. The role of RFA/MWA for downstaging - at least of larger diameter tumors - is limited in that ablation zones are not ideal to treat tumors > 3-4 cm.

NOVEL EXTRACORPORAL THERAPY

Stereotactic body radiation therapy (SBRT) has emerged as a treatment for solid liver and lung tumors, and is occasionally used for cancer in other sites such as the pancreas, prostate and kidney. SBRT involves highly confocal beams of energy delivered at a narrowly defined site. Prior to treatment, 4-dimensional imaging is used to map the target area as it moves during breathing. Occasionally gold seed fiducials are placed into the target tumor to assist with imaging. Whereas conventional external beam radiation - generally ineffective for HCC - delivers relatively small daily doses over the course of several weeks, SBRT can deliver a much larger dose of radiation per session - usually lasting 30-60 min - such that treatment is completed in 1-5 d. Due to the ability to deliver the radiation in a highly targeted and localized manner, SBRT may have advantages over ablation since it can be used to treat lesions high in the dome of the liver (sparing the lung), near the gall bladder (sparing it), or near large blood vessels (no heat sink effect).

SBRT has been studied in HCC both as a bridge to LT and for inoperable patients. O'Connor *et al.*^[24] reported in a small study that SBRT (used because patients were deemed ineligible for further standard LRT) was successful as a bridge to LT in 10/10 patients, with none experiencing HCC progression between SBRT and LT^[24]. Explant analysis from this series showed a 27% complete necrosis rate in treated tumors, with 75% of the incompletely necrotic tumors measuring smaller than pre-LT imaging size^[24]. In two sequential studies using SBRT in 102 patients with Child's class A liver disease and locally advanced HCC, Bujold *et*

al.^[51] reported a median survival of 17 mo^[51], which is substantially higher than the median survival of the cohort receiving placebo in the SHARP study of sorafenib, which also was restricted to patients with mostly preserved liver function^[52].

Toxicity from SBRT has been limited, and mostly grade 1 or 2 GI toxicity (nausea, vomiting, pain)^[24,53], though Bujold's study reported grade 3 toxicity in up to 30%^[51]. Rare GI ulcers have occurred following SBRT^[53]. The role of SBRT is still evolving, and studies comparing SBRT directly to other forms of LRT for bridging therapy to LT are in progress.

High-intensity focused ultrasound (HIFU) is a novel extracorporeal therapy that induces thermal injury to tumors using high frequency sound waves. Experience with HIFU is limited to date, but early experience with HCC patients has suggested a favorable radiographic response rate and safety profile^[54]. A recent pilot study from Hong Kong comparing TACE and HIFU as bridging therapy to LT showed comparable degrees of tumor necrosis for both modalities when assessed at explant^[55]. While more investigation is needed, the focused, extracorporeal nature of HIFU may permit its use in patients with Child-Pugh C liver disease. Reported side effects have included localized bruising and first-and second-degree skin burns on skin overlying treatment zones^[54].

CHOOSING THE OPTIMAL LRT FOR HCC IN THE PRE-TRANSPLANT SETTING

An ongoing difficulty for the transplant community is the lack of consensus regarding when/whether to use LRT for HCC prior to LT. There is further lack of consensus regarding which LRT to use for a given tumor. Even within each LRT category there is variation among institutions regarding the specifics of treatment. For example, "TACE" may involve different specific chemotherapeutic agents and/or embolic materials at different centers. And for small lesions, choice of TACE or ablation may come down to institution- or clinician-preference.

Despite these limitations, some general principles may assist decision-making. First, for Milan stage T2 HCC and preserved liver function, TACE has an excellent track record of safety and efficacy as a bridge to LT, with substantial lowering of dropout rates from historical standards^[14]. TACE is also effective as a downstaging modality for larger lesions^[13], though consideration for DEB-TACE is reasonable if there is portal venous thrombosis and/or decompensated liver function. Y-90 or TACE may be considered for larger (> 4 cm) tumors, the latter only if waiting time to LT is expected to exceed 1 mo.

Ablation (RFA/MWA) continues to be an effective bridge to LT for lesions < 3-4 cm, if the lesion is not located near the dome of the liver (lung), gall bladder or large vessels. For such lesions, ablation or TACE may

be equivalent in efficacy, though explant histological analysis suggests RFA has a higher rate of complete tumor necrosis for very small (< 3 cm) HCCs^[56]. For lesions 4–6 cm in sensitive areas such as the dome of the liver or near the gall bladder, SBRT appears to be a safe, targeted therapy with early success reported as a bridging therapy. Lesions these sizes are generally too large for successful ablation. SBRT and novel HIFU may also be compelling considerations for patients with greater liver decompensation, as such patients may not tolerate TACE or TARE. More study is needed and planned.

CONCLUSION

The incidence of HCC has substantially increased in many regions during the past 3–4 decades. For all but very small HCCs, surgery (resection or LT) is necessary for long-term survival or cure. As most HCCs occur in the setting of cirrhosis, resection leaves behind diseased (and presumably prone-to-cancer) tissue, and thus LT appears to strongly out-perform resection in actuarial survival.

Given the risk of tumor progression and waitlist dropout, LRT is routinely offered to patients on the transplant waiting list. TACE and RFA are the most widely studied modalities, and are effective as bridging therapy to LT in appropriate settings. TACE is also used for downstaging in patients whose initial tumor burdens exceed Milan criteria. Other forms of LRT include DEB-TACE, Y-90 and more recently, extracorporeal treatments such as SBRT. Each may have a “niche” role in the pre-transplant setting, and ongoing investigation will be critical in the development of widely accepted treatment paradigms to guide the use of LRT in waitlisted patients.

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