7

Locoregional Therapies for Bridging and Downstaging Hepatocellular Carcinoma Prior to Liver Transplant

Sandeep A. Ponniah • Andreas G. Zori • Roniel Cabrera

Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, FL, USA

Author for correspondence: Andreas G. Zori, Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, FL, USA.
Email: andreas.zori@medicine.ufl.edu

Doi: https://doi.org/10.36255/exonpublications.livercancer.2021.ch7

Abstract: Hepatocellular carcinoma is the most common primary liver malignancy and is a common indication for liver transplantation. To qualify for liver transplantation, the size and number of tumors must be within established criteria. The Milan criteria is the most well-established of these criteria, however there is evidence these criteria can be safely expanded without affecting outcomes. While awaiting liver transplantation, locoregional therapy can be used as bridging therapy to maintain the tumor burden within criteria. Locoregional therapy can also be used to decrease tumor burden within transplant criteria, a process called downstaging. For tumors <3 cm, thermal ablation—most commonly using a radio-frequency probe—is preferred when feasible and offers tumor control approaching that of resection. Larger or multifocal lesions are usually treated with either trans-arterial chemoembolization or yttrium-90 trans-arterial radioembolization. The choice between these two interventions is generally based on institutional preference as neither has demonstrated survival advantage in the transplant population. However, single center trials show longer time to progression, improved downstaging success, and less microvascular invasion in patients treated

In: *Liver Cancer*. Sergi CM. (Editor). Exon Publications, Brisbane, Australia.
ISBN: 978-0-6450017-2-3; Doi: https://doi.org/10.36255/exonpublications.livercancer.2021

with trans-arterial radioembolization. More recently stereotactic body radiation therapy has demonstrated efficacy in patients who are not candidates for other locoregional therapy or have progressed despite prior locoregional therapy.

Keywords: bridging therapy; downstaging; locoregional therapy; Milan criteria; transarterial chemoembolization

INTRODUCTION

Therapies for hepatocellular carcinoma (HCC) have evolved over the last several decades, but liver transplantation remains the only curative option in patients who are not candidates for resection. Liver transplantation allows for the cure of both the tumor and any underlying chronic liver disease. However, more than 70% of patients present with advanced disease that does not meet the criteria for transplantation (1). The first and most widely accepted criteria for liver transplantation in patients with HCC are the "Milan criteria", developed by Mazzaferro *et al.* (2). The Milan criteria include stage T1 (1 lesion <2 cm) and stage T2 (1 lesion 2–5 cm or up to 3 lesions ≤3 cm), tumors without vascular invasion, lymph node involvement, or extrahepatic metastases (3). When these criteria are met, four-year survival after transplant is >80% with recurrence rates below 15% (2). In the United States, the United Network for Organ Sharing (UNOS) affords patients who meet stage T2 disease Model for End-Stage Liver Disease (MELD) "exception points" due to poor survival associated with HCC that is not accounted for in standard MELD scoring system. Although the amount of HCC exception points has varied over time and by country, the current standard exception criteria adopted by UNOS assigns points equal to the mean MELD at transplant minus 3 of all liver transplants recipients (except status 1A/1B, living donor, donation after cardiac death donor and donors more than 500 miles from recipient hospital) in the last 180 days within 250 nautical miles of the listing center. Patients who do not meet the Milan criteria (greater than stage T2) can be eligible for liver transplantation if they receive locoregional therapies that reduce their tumor burden and maintain it within Milan criteria for 6 months. Lesions that are eligible for downstaging beyond Milan criteria are discussed in the following sections.

EXPANDED TRANSPLANT CRITERIA

A growing body of literature supports that the Milan criteria can be safely expanded to allow patients with more advanced disease access to liver transplantation, and under the right circumstances, they have comparable outcomes to patients that meet the Milan criteria. As such, modifications to the Milan criteria have been collectively termed "expanded criteria." In 2001, Yao *et al.* (4) from the University of California, San Francisco (UCSF), published a study with expanded criteria termed the "UCSF criteria": 1 lesion ≤6.5 cm or up to 3 lesions with the largest lesion ≤4.5 cm, with a total diameter of 8 cm (Table 1). In this study, patients had 1- and 5-year survival rates that were 90% and 75.2% respectively. In 2007, this

TABLE 1 Selection Criteria for Liver Transplantation

Milan criteria

- Most common eligibility criteria for LT among patients with HCC
- Single lesion ≤5 cm, or up to 3 lesions each ≤3 cm
- No evidence of extra-hepatic metastases or vascular invasion

Expanded criteria

- UCSF: Single lesion ≤6.5 cm or ≤3 lesions with the largest being ≤4.5 cm and a total diameter ≤8 cm
- Up-to-7: 7 cm as the sum of the size of the largest tumor and the number of tumors. No vascular invasion.
- Toronto criteria: Any tumor size or number. All lesions require a liver biopsy and must NOT show poor differentiation. No extra-hepatic metastasis, venous/biliary thrombosis OR cancer related symptoms.

UNOS Criteria for Downstaging

- Single lesion >5 cm but ≤8 cm
- 2-3 lesions each ≤5 cm with total diameter of all lesions ≤8 cm
- 4-5 lesions each ≤3 cm with total diameter of all lesions ≤8 cm

HCC, hepatocellular carcinoma; LT, liver transplant; MC, Milan Criteria; UCSF, University of California in San Francisco

same group from UCSF published a prospective study that showed a 5 year survival rate of 81%, which was similar to Milan criteria but with the added benefit of being able to transplant an additional 5–20% of patients initially not included by Milan criteria (5). Several studies have validated UCSF criteria having similar rates of survival compared to the Milan criteria (6).

In 2009, Mazzaferro *et al*. (7) described the Up-to-Seven criteria, where the sum of the total number of lesions and size in centimeters (cm) of the largest lesion can be up to 7 if vascular invasion and metastases are absent. In the initial study of over 1,500 patients, 5-year survival rates in patients that met Up-to-Seven criteria were similar (71.2%) to those that met the Milan criteria (73.3%) (7). This lead to the creation of the "Metro Ticket Calculator", which provides 3- and 5-year overall survival probabilities based on characteristics of HCC lesions (8). In 2016, the Toronto criteria was proposed, which do not include size or tumor number restrictions, but based candidacy on absence of extrahepatic disease, venous thrombi, cancer-related symptoms, and high-risk features on biopsy. In validating this criteria, patients transplanted outside MC (with the majority being beyond UCSF criteria but within Toronto criteria), had 5-year survival rates that were not statistically different to those within MC (68% vs 78%) (9). Other transplant centers outside the USA and Canada such as in Italy, England, Japan, Australia, New Zealand, and China have similar "expanded" criteria, and have shown comparable outcomes to the Milan criteria. Although individual centers may elect to transplant patients outside of Milan criteria, in the United States, tumor burden must be brought within the Milan criteria with locoregional therapy to qualify for standard MELD points, which is discussed in more detail in the downstaging section.

Bridging therapy

Once listed for transplant, HCC patients may experience long waiting times and growth of tumor beyond the Milan criteria, putting them at risk for dropout from the waiting list. Waiting times often exceed 1 year and can be as long as 2 years (10). Dropout rates while awaiting liver transplantation have been noted to be 25% at 6 months, 38% at 12 months and up to 55.1% at 18 months (11). Bridging therapy is locoregional therapy administered to patients on the liver transplantation waitlist to prevent tumor progression and decrease dropout rates, acting as a "bridge" until a suitable donor is obtained. Use of bridging therapy has steadily increased and is now used for most patients. Patients derive more benefit from locoregional therapy as the expected liver transplant list increases (12). Recommendations from the 2010 International Consensus Conference and EASL/EORTC Clinical Practice Guidelines suggest bridging therapy for all patients with HCC within the Milan criteria, with wait times >6 months for liver transplantation (13). In those meeting criteria for the Milan criteria, bridging therapy has decreased waitlist dropout to 0–10% (12). Risk factors responsible for an increased risk of dropout include tumors >3 cm or multifocal disease, serum AFP >200 ng/ml, waitlist time >6 months, and poor response to bridging therapy (12). The data on survival benefit is discussed later in this chapter.

Downstaging

"Downstaging" involves treating tumors outside of the Milan criteria with locoregional therapy to decrease tumor burden, allowing for application of standard MELD exceptions and ultimately liver transplantation. UCSF first proposed a downstaging protocol in 2005 where lesions outside the Milan criteria were eligible for downstaging. Lesions included were: 1 lesion >5 cm and ≤8 cm, 2–3 lesions each ≤5 cm or 4–5 lesions each ≤3 cm with a total diameter ≤8 cm. In a study from this group between 2002 and 2012 (14), survival at 5 years post liver transplantation in patients outside the Milan criteria but who were successfully down staged was identical to the Milan criteria control group (78%). Similarly in 2018, in a more recent multi-center study from this same group, 5-year post liver transplant survival in down staged patients was excellent at 80% (14). Based on these results, UNOS adopted the UCSF inclusion criteria for downstaging (UNOS-DS) above and in 2019 finalized the policy verbiage to clearly outline this criterion. Consequently, patients that are initially outside the Milan criteria but meet UNOS-DS receive automatic approval for MELD exception if they remain within the Milan criteria after locoregional therapy. Candidates that are outside UNOS-DS who receive downstaging locoregional therapies to the Milan criteria must be referred to the National Liver Review Board (NLRB) for consideration for MELD exception.

The options for locoregional therapies in downstaging are discussed in detail below. The decision on optimal locoregional therapy is contingent on multiple factors, but the Barcelona Clinic Liver Cancer (BCLC) staging system is often used to help make this decision (8). BCLC staging factors tumor burden, liver function and patient performance status to stratify patients by risk. Downstaging patients often have advanced stage disease and based on BCLS, trans-arterial chemoembolization (TACE) is most utilized followed by trans-arterial radioembolization and ablation (15).

Tumor biology

Over time, the focus of liver transplantation guidelines has shifted beyond tumor size and number to tumor biology and behavior (16). As a result, UNOS currently requires a 6-month waiting period prior to granting MELD exception points. This allows for observation of the tumor to ensure that it does not have aggressive biology which rapidly progresses to metastasis and can significantly increase the chances of post-transplant recurrence. Downstaging is similarly helpful in assessing tumor biology, in that tumors which cannot be brought within transplant criteria with locoregional therapy confer a poor prognosis. Conversely, tumors outside of the Milan criteria that respond to downstaging protocols have been noted with favorable histological changes, including a lack of microvascular invasion, low tumor grading, and lack of satellite lesions (17) which are similarly seen in patients within the Milan criteria. While histological data, such as degree of differentiation and microvascular invasion, is helpful in predicting tumor behavior and stratifying risk, it is often not available in pre-transplant settings since in most cases biopsy is not necessary to make the diagnosis of HCC. Therefore, there is significant interest in identifying serum markers which can classify tumor biology non-invasively.

Serum alpha-fetoprotein (AFP) has been studied extensively as a serum marker for HCC, and combined with tumor burden prognosticates HCC better than tumor burden alone (18–20). Absolute AFP >1,000 ng/ml is a strong predictor of vascular invasion and tumor recurrence. Patients with AFP >1,000 ng/ml had higher 5-year recurrence rates (53%) compared to patients with AFP 100–1,000 ng/ml (26.8%) and <100 ng/ml (16.2%) (21).

AFP levels have now been adopted by UNOS as a marker for exclusion for liver transplantation. Patients within the Milan criteria applying for MELD exception must have an AFP ≤1,000 ng/ml. Patients >1,000 ng/ml can still be granted standard MELD exception points provided they undergo LRT with drop of AFP <500 ng/ml and remain within this range. If AFP >500 ng/ml after LRT, a review must be filed with the NLRB.

LOCOREGIONAL THERAPIES

In this section, we discuss the most commonly used locoregional therapies in bridging and downstaging prior to transplant; TACE, radioembolization with yttrium-90 (Y-90), thermal ablative therapy and stereotactic body radiation therapy (Table 2). Factors that affect decision-making when formulating an optimal treatment strategy include tumor stage, performance status, tumor location, severity of liver disease, organ availability and tumor biology/behavior (22).

Trans-arterial chemoembolization

TACE is one of the most commonly used bridging therapies and involves intra-arterial administration of a chemotherapeutic agent, usually doxorubicin, mitomycin and/or cisplatin followed by an embolizing agent. Lipiodol, an oily radiopaque marker used as an emulsifying agent, is coupled to the

TABLE 2 Overview of Locoregional Therapies

Therapy	Mechanism	Primary Application	Complications	Advantages	Limitations
cTACE	Embolic ischemia augmented by emulsified chemotherapy	Larger (>3 cm) tumors Tumors <3 cm not amenable to resection/ablation	PES Liver failure GI ulcers Liver abscess Renal dysfunction	Studied extensively can be repeated	More systemic toxicity than DEB-TACE. Technical variability and non-standardized protocols Cannot be used with PVT
DEB-TACE	Embolic ischemia augmented by chemotherapeutic drug eluting beads.	Larger (>3 cm) tumors Tumors <3 cm not amenable to resection/ablation	Similar to cTACE	More controlled and sustained drug delivery than cTACE	More costly than cTACE. Cannot be used with PVT
TARE	Radiation induced cell death from Y-90 microspheres, minimal embolic effect	Larger (>3 cm) tumors Tumors <3 cm not amenable to resection/ablation	RILD Radiation induced pneumonitis Biliary stricturing Enteritis	Safe in PVT Slower TTP than TACE Outpatient procedure	Requires pre treatment mapping angiography More costly than TACE Requires higher level of expertise
Thermal Ablation (RFA)	High frequency alternating currents induce thermal injury and necrosis	Smaller (<3 cm) tumors, ≤3 nodules Improved outcomes combined with TACE for tumors 3-5 cm	Thermal injury to adjacent organs. Liver capsule rupture. Risk of peritoneal seeding treating peripheral tumors	Similar outcomes as surgical resection for tumors <3 cm (curative) Excellent safety profile	Heat sink effect. Limited efficacy in tumors >3 cm
SBRT	Multiple nonparallel radiation beams delivered in high-dose radiation fractions	Larger (>3 cm) tumors Tumors <3 cm not amenable to resection/ablation	Few: nausea, vomiting, GI ulcers (rare)	Alternative BT for patients with decompensated liver disease that are not LT candidates or failed other LRTs. Can treat lesions near adjacent organs, unlike ablation No heat sink effect Spares liver from RILD unlike TARE	Few comparative studies with other LRTs

BT, bridging therapy; cTACE, conventional TACE; LRT, locoregional therapy; LT, liver transplant; OS, overall survival; PES, post embolization syndrome; PVT, portal vein thrombosis; RFA, radiofrequency ablation; TTP, time to progression; RILD, radiation induced liver injury

chemotherapeutic agent and used as a carrier to deliver the drug to the tumor. Induction of ischemia and tumor necrosis through embolization of the tumor's microcirculation is the primary mode of tumor killing, which is then augmented by the chemotherapeutic agent (23). Trans-arterial embolization can also be done without a chemotherapeutic component, termed bland embolization, however this is performed less commonly. Currently, TACE using drug-eluting beads (DEB-TACE) has become more commonly used than conventional TACE, and as such in some literature the term TACE is used interchangeably with DEB-TACE. DEB-TACE involves the injection of embolization beads that are loaded with cytotoxic chemotherapeutic agents to target a tumor. Contrary to conventional TACE where there is concern of systemic exposure, drug-eluting beads release the chemotherapeutic in a controlled and sustained manner, minimizing systemic toxicity and improving drug delivery to the tumor (24). Both forms of TACE are used for treating larger (>3 cm) HCC without vascular invasion or extrahepatic spread where the patient has preserved liver function. Damage to normal liver parenchyma from arterial embolization is usually mitigated by the liver's dual blood supply from the portal vein and the hepatic artery. However, recurrent treatment with TACE increases risk of complications and some centers recommend no more than 3–4 treatments times a year (1).

The most common complication of TACE, occurring in approximately 50% of patients, is post-embolization syndrome (25). This occurs less frequently in patients treated with DEB-TACE than TACE. Post-embolization syndrome consists of a constellation of right upper quadrant pain, nausea, fever, fatigue, elevated liver enzymes, bilirubin and mild to moderate ileus. Typically, symptoms last 3–4 days and self-resolve in 7–10 days. Because this occurs frequently, in most centers patients are observed as inpatients following TACE. Despite most chemotherapy being localized to liver, other systemic complications include nausea, vomiting and very rarely bone marrow suppression.

Although serious complications of TACE remain uncommon, liver failure can occur as a result of ischemic damage. In a meta-analysis (26), liver failure was seen in 7.5% of patients with HCC treated with TACE. However, liver decompensation occurs most often in patients who had impaired liver function prior to TACE treatment; therefore, patient selection is critical to reduce the risk of decompensation. Other complications of TACE include gastroduodenal ulcers (3–5%), hepatic abscesses (2%), bile duct injury including strictures (0.5–2%) and renal dysfunction (2%). Rare but fatal complications include pulmonary and cerebral lipiodol embolization. Overall, mortality rates from TACE are low at less than 1%, with rates between 2–3% in patients with large tumors that develop tumor lysis syndrome (26). Small prospective studies and a meta-analysis have compared traditional TACE to DEB-TACE in the past and have suggested lower rates of complications with similar tumor control in the latter (27–30). In the PRECISION-V study (31), the largest comparative randomized controlled trial between both, DEB-TACE showed less hepatotoxicity, better tumor response, and lower doxorubicin related adverse effects compared to conventional TACE (in patients with Child-Pugh B, ECOG1, bilobar disease and recurrent disease). In the same study, less post procedural pain was noted with DEB-TACE. By contrast, two retrospective studies (32, 33) showed a higher risk of liver and biliary injuries with DEB-TACE than conventional TACE. While the results are favorable, there still exists some heterogeneity when comparing conventional TACE to DEB-TACE.

Overall TACE therapies are safe in most patients. Absolute contraindications for TACE therapies include decompensated cirrhosis (Child-Turcorrte-Pugh B score >8), compromised portal vein flow or thrombus, extensive tumor in both lobes of the liver, and renal failure. Several other relative contraindications exist and include but are not limited to: serum bilirubin >2mg/dl, lactate dehydrogenase >425 U/L, AST >100 units/L, tumor burden >50% of the liver, severe comorbidities, and untreated esophageal varices with bleeding risk. The ideal population for TACE therapies is asymptomatic patients with solitary or few HCC tumors, well compensated liver disease, and without metastatic disease or vascular invasion.

The use of TACE is not standardized and varies in protocol and type of embolic and chemotherapeutic agent use. Few randomized studies compare TACE to supportive care alone, however two landmark studies by Lo *et al.* (34) and Llovet *et al.* (35) show a clear survival benefit in TACE compared with supportive treatment. One-year survival rates were 57% (34) and 82% (35) compared to 32% and 63% in the control groups respectively. Mean survival was significantly longer with TACE (28.6 months) compared to supportive care (17.9 months; P = 0.009) (35). Additionally, in a recent systemic review (25) including 10,000 patients, TACE showed response rates in >50% of patients, with 1 year survival rates >70%. Current European Association for the Study of the Liver (EASL) guidelines support TACE with strong recommendation, citing high quality evidence. When comparing TACE to transcatheter arterial radioembolization (TARE [discussed below]), TACE is supported by a much greater number of trials, while TARE is largely supported by single-center studies with variable patient cohorts (36). While studies comparing TACE with TARE report no difference in overall survival, a single treatment with TACE is significantly less expensive than TARE (36).

Several favorable studies have advocated the use of TACE as effective bridging therapy. Lower dropout rates (3–13%) have been noted by several studies compared to historical data (3). In one of the most favorable studies by Graziadei *et al.* (37), no patient experienced tumor progression following locoregional therapy with TACE. Five-year survival rates after liver transplantation were high at 93% and tumor recurrence rates were notably low (2%) despite long waiting times prior to liver transplantation (mean of 178 days). While these studies show positive results, other studies (38–40) are less favorable and show no benefit in post liver transplantation survival or tumor recurrence.

Downstaging using TACE has been shown to be effective, however success rates have been variable in the literature. In the first ever study on locoregional therapy in 1997, 62% of patients outside of MC were down staged with improved 5-year survival when compared to patients who could not be down staged with TACE or did not receive TACE (1). Other studies have shown a similar favorable role of TACE in downstaging patients to MC, however results remain inconsistent with success rates ranging from 24% (41) to 90% (42).

Despite continued improvement in technique and patient selection, there continues to be debate regarding the ideal patient population, tumor burden and tumor biology for TACE in the treatment of HCC.

Transcatheter arterial radioembolization

TARE with Yttrium-90 glass microspheres induces extensive tumor necrosis with a favorable safety profile. Y-90 is a beta-emitting radioisotope of Yttrium that is

attached to a bead and injected into the hepatic artery, designed to emit radiation over a very small distance within the liver (2.5 mm). Y-90 undergoes beta decay and irradiates the nearby tumor causing cell death. In comparison to TACE, this procedure provides therapeutic effect through radiation instead of embolization. This results in reduced toxicity and damage to the liver parenchyma and can be used safely in patients with portal vein thrombosis (43, 44). The half-life of Y-90 is 2.67 days, and almost all radiation is delivered to the tumor within 2 weeks after treatment. TARE has been used for bridging, downstaging, as a palliative treatment for advanced disease, and as adjuvant therapy for surgically resected HCC (45, 46).

Before the use of TARE, visceral angiography mapping with technetium-99 and SPECT-CT is required to detect shunts to the GI tract or lung. If shunts cannot be reduced to less than 20% of the hepatic artery blood flow or less than 30 Gy radiation dose absorbed to the lungs via embolization or other means, there is a high risk of toxicity and TARE should not be performed. Contraindications are similar to TACE, however, unlike TACE, main portal vein thrombosis or obstruction is not a contraindication (47). TARE is also safe in patients with prior transjugular intrahepatic portosystemic shunt (48). Overall tolerance and safety are comparable to TACE, despite fewer published studies involving TARE. However, post-embolization syndrome is less common and tends to be less severe when it does occur (49). Complications unique to TARE include radiation-induced liver disease (RILD), radiation-induced biliary stricture, radiation-induced pneumonitis, and radiation induced enteritis. The frequency and risk factors for each have not been well studied and are listed in only a few studies. RILD is considered to be a serious event, with two studies (50, 51) suggesting rates between 4% and 20%, and presents as jaundice, ascites, and manifestations of liver decompensation 2–8 weeks after treatment. The risk of RILD increases with repeated Y-90 administrations (51). Radiation-induced biliary stricturing is a less common adverse effect of TARE occurring in less than 10% of patients (52). The frequency of these complications has decreased with improvement in technique and increased experience. As with TACE, proceduralists must be cautioned against inadvertent embolization of the cystic artery to prevent gallbladder necrosis. Radiation-induced pneumonitis and enteritis may occur if shunts to the gastrointestinal tract or lung are detected on pre-procedural evaluation, but rarely occur if standard precautions are followed. Lastly, a theoretical concern with Y-90 used as a bridge includes the risk of radiation exposure to the surgical or pathology team handling the explanted liver, but considering its short half-life, this only seems to be a consideration if liver transplantation is performed within 4 weeks of TARE (3).

Because there are limited head-to-head comparisons between TACE and TARE, there is no consensus regarding when/if TARE should be chosen over TACE. However, TARE has been used increasingly due to a number of favorable studies. Lewandowski *et al.* (53) compared TARE to TACE in T3 staged HCC down staged to T2 which showed a significantly better response (61% vs 37%) and slower time to progression (33.3 months vs 18.2 months). TARE-based bridging protocols have also been associated with fewer pre-transplant locoregional therapy and had lower rates of microvascular invasion in the explanted liver, which is associated with risk of post-transplant HCC recurrence. Salem *et al.* (54) performed randomized controlled trials (RCTs) comparing TARE to TACE (PREMIERE trial) in 179

patients and reported a significantly longer time to progression in TARE than with TACE. The complication rate was also lower in the TARE group. Ettore *et al.* (55) performed TARE in a small cohort of patients (22) with the majority being outside the Milan criteria, and successfully bridged all patients and down staged 79% of patients outside Milan criteria. More recently, the TRACE trial (56) compared Y-90 to DEB-TACE and included patients with BCLC A/B, ECOG 1 and segmental portal vein thrombosis. This study showed superior results in the Y-90 group with slower time to progression, improved survival, and comparable safety profiles between Y-90 and DEB-TACE. While these results are favorable, few current studies overall have noted a difference in survival between TARE and TACE. Other limitations to several favorable TARE trials include single centered studies, small cohorts of patients, inherent physician biases and heterogeneity in results and reporting. Lastly, TARE is more costly than TACE and may preclude its use at some institutions (36).

Overall, TARE is likely to be used preferentially where there is higher level of expertise, familiarity with the procedure, in those with infiltrative tumors, portal vein invasion, larger tumors (>2 segments) and those with progression of tumor despite use of TACE.

Thermal ablation

Multiple ablative techniques including radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation use directly applied thermal energy to induce tumor necrosis. RFA is the most commonly used and most widely studied of these interventions and therefore the focus of discussion for this section. RFA involves the insertion of narrow probes under imaging guidance, either ultrasound or computed tomography, into a targeted liver lesion. The probes can be inserted percutaneously, usually by an interventional radiologist or laparoscopically by a surgeon. High-frequency alternating currents move from the electrode to the lesion, creating a frictional pattern of ion movement which induces heating and necrosis to the target lesion (57). Tumor cells die as the tissue becomes heated above 60 degrees Celsius. The ablated area consists of the tumor plus 5–10 mm boundary of nearby liver parenchyma (58). While there is no absolute tumor size for RFA, most reported favorable outcomes to suggest smaller tumors <3 cm (59, 60), less than or equal to 3 nodules, and without major vascular or biliary structures near the target lesions.

Limitations of RFA involve the duration of treatment and the risk of thermal injury to nearby anatomical structures. RFA typically takes 16–18 mins to ablate a 3–4 cm lesion and there is a risk of dissipating heat energy to nearby blood vessels (>3 mm) termed the “heat sink effect”; the “cooler” vascular flow near the lesion may absorb heat resulting in incomplete tumor necrosis in the target lesion.

Additionally, RFA is not suitable for lesions near certain anatomical structures, namely the dome of the liver, the gallbladder and the biliary tree (60). There is also a risk of liver capsule rupture (~2%) and resulting peritoneal seeding when treating peripheral tumors (3). Overall, the major complication rate ranges from 2.4–13.1%, but RFA is still superior to surgical resection (13). Livraghi *et al.* (61), in 218 patients with small and early HCC, showed no perioperative mortality in RFA with lower than previously suggested rates of major complications (1.8%).

Analysis of 5 large series (59) showed major complications to be as low as 4.6% and mention RFA to be quite safe. Other complications are listed but are relatively uncommon, such as abscess formation, portal vein thrombosis, thoracic injury, liver decompensation, and bleeding. As in TACE/TARE, post-procedural abdominal pain similar to post-embolization syndrome is also a consideration.

Overall, RFA is an effective LRT for bridging therapy to prevent dropout and is recommended in small early HCC < or equal to 3 cm (13), with less favorable results in larger tumors. Large studies such as by Lu *et al.* (62) and Mazzaferro *et al.* (63) have shown dropout rates as low as 0–6% when RFA is used as bridging therapy. In larger tumors >3 cm, combination treatments as a bridge to liver transplantation have shown promise. In a review of 7 RCTs (62), a combination of RFA and TACE was superior to RFA alone and showed a significant survival advantage. More recent studies (64, 65) have also shown improved outcomes with combination treatment than RFA alone when used as a bridge to liver transplantation, especially in larger tumors between 3–5 cm.

RFA is more limited in downstaging, as these tumors are outside MC and often >3–4 cm. The mechanism in MWA is similar to RFA and is favored at some centers as it offers more rapid heating, shorter treatment time and larger ablative zones without an observed heat sink effect. Cryotherapy has also shown favorable results in bridging locoregional therapy for small HCC lesions, but is not widely adopted and has inherent limitations.

Stereotactic body radiation therapy

Stereotactic body radiation therapy (SBRT) is a more recently adopted treatment modality for bridging in HCC and for inoperable patients. SBRT involves directing multiple nonparallel radiation beams at narrow target sites through single or few high-dose radiation fractions. It is an alternative for patients with decompensated liver disease that may not be candidates for other locoregional therapies (12). Although HCC is a particularly radiosensitive tumor, care must be taken to deliver as little radiation to the surrounding parenchyma as possible to reduce the risk of toxicity and decompensation. Before SBRT, 4-dimensional imaging is used to map the target site. Contrary to conventional external beam, which delivers small doses of radiation over several weeks, SBRT delivers very large doses of radiation per session and can be completed in 1–5 days. A variety of dosing and fractionation protocols have been used, with doses ranging from 24–60 Gy over 3–6 fractions (65). Sessions typically last 30–60 mins. Compared to ablative therapy, SBRT is advantageous in that it can treat lesions near the dome of the liver sparing lung parenchyma, near the gallbladder, and near large vessels (3). There is no concern about the heat sink effect. SBRT can spare large portions of normal liver tissue from RILD. The adverse effects of SBRT are limited and mostly nausea, vomiting, abdominal pain, and rarely GI ulcers have been noted (3).

Few studies have compared SBRT to other forms of locoregional therapy, but results have been favorable, especially when used as a neoadjuvant treatment. The first study in 2009 (66) showed that SBRT was both safe and effective in those awaiting liver transplantation that could not tolerate TACE, RFA, and percutaneous ethanol injection. A larger study (65) corroborated these results and found SBRT to be both safe and effective in patients with Child A/B liver cirrhosis and lesions ≤6 cm. More recently, Sapisochin *et al.* (67) compared SBRT to TACE or

RFA as a bridging therapy in 379 patients meeting Toronto extended criteria. They found similar 5-year survival and dropout rates across all three modalities. A prospective study by Lee *et al.* (68) evaluated SBRT in decompensated cirrhosis with Child-Pugh B or C cirrhosis. Patients had either already completed TACE prior to SBRT or had TACE in combination with SBRT. This study showed favorable results as the Child-Pugh class remained stable in 30%, and even improved in 22% of patients, and was associated with an overall improvement in survival. Other studies (69–71), mostly retrospective in nature, all show comparable outcomes in local control of disease. These studies suggest that SBRT can be used safely as bridging therapy when other modalities have failed or are not applicable. Additionally, SBRT may offer advantages in patients with liver dysfunction who may not tolerate TACE or RFA (67). Overall, SBRT has now emerged as an effective LRT for patients with advanced disease with minimal toxicity.

CONCLUSION

Bridging therapy is now the standard of care to prevent waitlist dropout and decrease HCC recurrence post-transplant. There are no prospective RCTs comparing locoregional therapy modalities before liver transplantation, therefore no single bridging modality is recommended over another (13). The literature remains difficult to analyze due to non-standardized treatment protocols and heterogeneous patient populations. Recently, Kulik *et al.* compared 18 studies (72) and found that bridging locoregional therapy had no significant impact on survival rate or HCC recurrence post-transplant. Several studies were found to have imprecision regarding inclusion criteria, as some patients were within the Milan criteria, outside the Milan criteria, or undefined (11). The lack of randomized studies and potentially biased patient selection in these studies should also be considered; patients who received locoregional therapy, when compared to those who did not, likely had more risk factors such as advanced tumors, aggressive tumor biology, and longer wait times (72). Overall, bridging locoregional therapy is safe and effective. The type of locoregional therapy selected is based on liver function, size, the number of tumors, and institutional experience. Ablation is the preferred modality for smaller tumors with a size ≤3 cm; the type of ablation is expertise-dependent, but RFA is frequently used. Larger lesions are typically treated with TACE or Y-90 TARE based on institutional experience and/or preference. SBRT is a novel approach and has shown promising outcomes for those with liver dysfunction, failed other locoregional therapies, or for those who are no longer liver transplant candidates.

Like bridging therapy, there remains no consensus on optimal downstaging strategy. Several factors result in largely varying success rates (~25–90%) (11) as numerous inconsistencies in the current literature make data interpretation difficult. Firstly, the definition of downstaging is poorly defined amongst studies. None of the present studies were randomized controlled trials (11). Some studies define downstaging as the reduction of tumors to the Milan criteria, others base downstaging on the complete absence of tumors, and few use explant pathology to defined success (11). Secondly, there are inconsistencies in locoregional therapy selection, varying tumor burden before locoregional therapy, and differing

criteria to access radiographic response (72). Lastly, there is no universal definition for the waiting period following downstaging to determine efficacy and timing for liver transplantation (11). Despite these inconsistencies, there is optimism in tumor downstaging prior to LT. The recent adoption of UNOS-DS as inclusion criteria and focus on tumor biology rather than tumor burden alone has increased access to liver transplantation.

Since no single bridging or downstaging modality is advocated over another, expert preference often leads to individualized therapy. Additional research on expanded transplant criteria and organ allocation models would be of benefit. Further trials studying to define optimal waiting times after downstaging and standardizing study variables (demographics, treatment protocols, etc.) would minimize confounding factors to allow for a more accurate data interpretation.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this chapter.

Copyright and permission statement: The authors confirm that the materials included in this chapter do not violate copyright laws. Where relevant, appropriate permissions have been obtained from the original copyright holder(s), and all original sources have been appropriately acknowledged or referenced.

REFERENCES

1. Bryce K, Tsochatzis EA. Downstaging for hepatocellular cancer: harm or benefit. Transl Gastroenterol Hepatol. 2017;2:106. https://doi.org/10.21037/tgh.2017.11.18
2. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996 Mar 14;334(11):693–9. https://doi.org/10.1056/NEJM199603143341104
3. Byrne TJ, Rakela J. Loco-regional therapies for patients with hepatocellular carcinoma awaiting liver transplantation: Selecting an optimal therapy. World J Transplant. 2016;6(2):306–13. https://doi.org/10.5500/wjt.v6.i2.306
4. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology. 2001;33(6):1394–403. https://doi.org/10.1053/jhep.2001.24563
5. Yao FY, Xiao L, Bass NM, Kerlan R, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging. Am J Transplant. 2007;7(11):2587–96. https://doi.org/10.1111/j.1600-6143.2007.01965.x
6. Abdelfattah MR, Elsiesy H, Al-Manea H, Broering DC. Liver transplantation for hepatocellular carcinoma within the Milan criteria versus the University of California San Francisco criteria: a comparative study. Eur J Gastroenterol Hepatol. 2018;30(4):398–403. https://doi.org/10.1097/MEG.0000000000001044
7. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol. 2009;10(1):35–43. https://doi.org/10.1016/S1470-2045(08)70284-5
8. Lingiah VA, Niazi M, Olivo R, Paterno F, Guarrera JV, Pyrsopoulos NT. Liver Transplantation Beyond Milan Criteria. J Clin Transl Hepatol. 2020;8(1):69–75. https://doi.org/10.14218/JCTH.2019.00050

9. Sapisochin G, Goldaracena N, Laurence JM, Dib M, Barbas A, Ghanekar A, et al. The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: A prospective validation study. Hepatology. 2016 12;64(6):2077–88. https://doi.org/10.1002/hep.28643
10. Trieu JA, Bilal M, Hmoud B. Factors associated with waiting time on the liver transplant list: an analysis of the United Network for Organ Sharing (UNOS) database. Ann Gastroenterol. 2018;31(1):84–9. https://doi.org/10.20524/aog.2017.0217
11. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018 01;67(1):358–80. https://doi.org/10.1002/hep.29086
12. Coletta M, Nicolini D, Benedetti Cacciaguerra A, Mazzocato S, Rossi R, Vivarelli M. Bridging patients with hepatocellular cancer waiting for liver transplant: all the patients are the same. Transl Gastroenterol Hepatol. 2017;2:78. https://doi.org/10.21037/tgh.2017.09.01
13. Oligane HC, Close ON, Xing M, Kim HS. Bridging locoregional therapy: Longitudinal trends and outcomes in patients with hepatocellular carcinoma. Transplant Rev (Orlando). 2017;31(2):136–43. https://doi.org/10.1016/j.trre.2017.01.004
14. Mehta N, Dodge JL, Grab JD, Yao FY. National Experience on Down-Staging of Hepatocellular Carcinoma Before Liver Transplant: Influence of Tumor Burden, Alpha-Fetoprotein, and Wait Time. Hepatology. 2020;71(3):943–54. https://doi.org/10.1002/hep.30879
15. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68(2):723–50. https://doi.org/10.1002/hep.29913
16. Mehta N, Yao FY. What Are the Optimal Liver Transplantation Criteria for Hepatocellular Carcinoma. Clin Liver Dis (Hoboken). 2019;13(1):20–5. https://doi.org/10.1002/cld.793
17. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul JL, et al. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182–236.
18. Halazun KJ, Tabrizian P, Najjar M, Florman S, Schwartz M, Michelassi F, et al. Is it Time to Abandon the Milan Criteria?: Results of a Bicoastal US Collaboration to Redefine Hepatocellular Carcinoma Liver Transplantation Selection Policies. Ann Surg. 2018;268(4):690–9. https://doi.org/10.1097/SLA.0000000000002964
19. Giard JM, Mehta N, Dodge JL, Roberts JP, Yao FY. Alpha-Fetoprotein Slope >7.5 ng/mL per Month Predicts Microvascular Invasion and Tumor Recurrence After Liver Transplantation for Hepatocellular Carcinoma. Transplantation. 2018;102(5):816–22. https://doi.org/10.1097/TP.0000000000002094
20. Mehta N, Dodge JL, Roberts JP, Hirose R, Yao FY. Alpha-Fetoprotein Decrease from >1,000 to <500 ng/mL in Patients with Hepatocellular Carcinoma Leads to Improved Posttransplant Outcomes. Hepatology. 2019;69(3):1193–205. https://doi.org/10.1002/hep.30413
21. Hameed B, Mehta N, Sapisochin G, Roberts JP, Yao FY. Alpha-fetoprotein level >1000 ng/mL as an exclusion criterion for liver transplantation in patients with hepatocellular carcinoma meeting the Milan criteria. Liver Transpl. 2014;20(8):945–51. https://doi.org/10.1002/lt.23904
22. Mehta N. Hepatocellular Carcinoma-How to Determine Therapeutic Options. Hepatol Commun. 2020;4(3):342–54. https://doi.org/10.1002/hep4.1481
23. Raoul JL, Forner A, Bolondi L, Cheung TT, Kloeckner R, de Baere T. Updated use of TACE for hepatocellular carcinoma treatment: How and when to use it based on clinical evidence. Cancer Treat Rev. 2019;72:28–36. https://doi.org/10.1016/j.ctrv.2018.11.002
24. Thuluvath PJ, To C, Amjad W. Role of Locoregional Therapies in Patients With Hepatocellular Cancer Awaiting Liver Transplantation. Am J Gastroenterol. 2021;116(1):57–67. https://doi.org/10.14309/ajg.0000000000000999
25. Lencioni R, de Baere T, Soulen MC, Rilling WS, Geschwind JF. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: A systematic review of efficacy and safety data. Hepatology. 2016 07;64(1):106–16. https://doi.org/10.1002/hep.28453
26. Marelli L, Stigliano R, Triantos C, Senzolo M, Cholongitas E, Davies N, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. Cardiovasc Intervent Radiol. 2007;30(1):6–25. https://doi.org/10.1007/s00270-006-0062-3

27. van Malenstein H, Maleux G, Vandecaveye V, Heye S, Laleman W, van Pelt J, et al. A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. Onkologie. 2011;34(7):368–76. https://doi.org/10.1159/000329602
28. Gao S, Yang Z, Zheng Z, Yao J, Deng M, Xie H, et al. Doxorubicin-eluting bead versus conventional TACE for unresectable hepatocellular carcinoma: a meta-analysis. Hepatogastroenterology. 2013;60(124):813–20.
29. Prajapati HJ, Dhanasekaran R, El-Rayes BF, Kauh JS, Maithel SK, Chen Z, et al. Safety and efficacy of doxorubicin drug-eluting bead transarterial chemoembolization in patients with advanced hepatocellular carcinoma. J Vasc Interv Radiol. 2013;24(3):307–15. https://doi.org/10.1016/j.jvir.2012.11.026
30. Golfieri R, Giampalma E, Renzulli M, Cioni R, Bargellini I, Bartolozzi C, et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer. 2014;111(2):255–64. https://doi.org/10.1038/bjc.2014.199
31. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol. 2010;33(1):41–52. https://doi.org/10.1007/s00270-009-9711-7
32. Guiu B, Deschamps F, Aho S, Munck F, Dromain C, Boige V, et al. Liver/biliary injuries following chemoembolisation of endocrine tumours and hepatocellular carcinoma: lipiodol vs. drug-eluting beads. J Hepatol. 2012;56(3):609–17. https://doi.org/10.1016/j.jhep.2011.09.012
33. Monier A, Guiu B, Duran R, Aho S, Bize P, Deltenre P, et al. Liver and biliary damages following transarterial chemoembolization of hepatocellular carcinoma: comparison between drug-eluting beads and lipiodol emulsion. Eur Radiol. 2017;27(4):1431–9. https://doi.org/10.1007/s00330-016-4488-y
34. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. 2002;35(5):1164–71. https://doi.org/10.1053/jhep.2002.33156
35. Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002;359(9319):1734–9. https://doi.org/10.1016/S0140-6736(02)08649-X
36. Skef W, Agarwal M, Mikolajczyk AE. Position 1: Transarterial Chemoembolization Should Be the Primary Locoregional Therapy for Unrespectable Hepatocelluar Carcinoma. Clin Liver Dis (Hoboken). 2020;15(2):71–3. https://doi.org/10.1002/cld.909
37. Graziadei IW, Sandmueller H, Waldenberger P, Koenigsrainer A, Nachbaur K, Jaschke W, et al. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. Liver Transpl. 2003;9(6):557–63. https://doi.org/10.1053/jlts.2003.50106
38. Cabrera R, Dhanasekaran R, Caridi J, Clark V, Morelli G, Soldevila-Pico C, et al. Impact of transarterial therapy in hepatitis C-related hepatocellular carcinoma on long-term outcomes after liver transplantation. Am J Clin Oncol. 2012;35(4):345–50. https://doi.org/10.1097/COC.0b013e31821631f6
39. Decaens T, Roudot-Thoraval F, Bresson-Hadni S, Meyer C, Gugenheim J, Durand F, et al. Impact of pretransplantation transarterial chemoembolization on survival and recurrence after liver transplantation for hepatocellular carcinoma. Liver Transpl. 2005;11(7):767–75. https://doi.org/10.1002/lt.20418
40. Porrett PM, Peterman H, Rosen M, Sonnad S, Soulen M, Markmann JF, et al. Lack of benefit of pre-transplant locoregional hepatic therapy for hepatocellular cancer in the current MELD era. Liver Transpl. 2006;12(4):665–73. https://doi.org/10.1002/lt.20636
41. Chapman WC, Majella Doyle MB, Stuart JE, Vachharajani N, Crippin JS, Anderson CD, et al. Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. Ann Surg. 2008;248(4):617–25. https://doi.org/10.1097/SLA.0b013e31818a07d4
42. Ravaioli M, Grazi GL, Piscaglia F, Trevisani F, Cescon M, Ercolani G, et al. Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. Am J Transplant. 2008;8(12):2547–57. https://doi.org/10.1111/j.1600-6143.2008.02409.x

43. Sato K, Lewandowski RJ, Bui JT, Omary R, Hunter RD, Kulik L, et al. Treatment of unresectable primary and metastatic liver cancer with yttrium-90 microspheres (TheraSphere): assessment of hepatic arterial embolization. Cardiovasc Intervent Radiol. 2006;29(4):522–9. https://doi.org/10.1007/s00270-005-0171-4
44. Salem R, Thurston KG. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: Technical and methodologic considerations. J Vasc Interv Radiol. 2006;17(8):1251–78. https://doi.org/10.1097/01.RVI.0000233785.75257.9A
45. Tohme S, Sukato D, Chen HW, Amesur N, Zajko AB, Humar A, et al. Yttrium-90 radioembolization as a bridge to liver transplantation: a single-institution experience. J Vasc Interv Radiol. 2013;24(11):1632–8. https://doi.org/10.1016/j.jvir.2013.07.026
46. Kulik LM, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B, Ryu RK, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology. 2008;47(1):71–81. https://doi.org/10.1002/hep.21980
47. Kennedy A, Nag S, Salem R, Murthy R, McEwan AJ, Nutting C, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys. 2007;68(1):13–23. https://doi.org/10.1016/j.ijrobp.2006.11.060
48. Donahue LA, Kulik L, Baker T, Ganger DR, Gupta R, Memon K, et al. Yttrium-90 radioembolization for the treatment of unresectable hepatocellular carcinoma in patients with transjugular intrahepatic portosystemic shunts. J Vasc Interv Radiol. 2013;24(1):74–80. https://doi.org/10.1016/j.jvir.2012.09.030
49. Riaz A, Awais R, Salem R. Side effects of yttrium-90 radioembolization. Front Oncol. 2014;4:198. https://doi.org/10.3389/fonc.2014.00198
50. Sangro B, Gil-Alzugaray B, Rodriguez J, Sola I, Martinez-Cuesta A, Viudez A, et al. Liver disease induced by radioembolization of liver tumors: description and possible risk factors. Cancer. 2008;112(7):1538–46. https://doi.org/10.1002/cncr.23339
51. Lam MG, Louie JD, Iagaru AH, Goris ML, Sze DY. Safety of repeated yttrium-90 radioembolization. Cardiovasc Intervent Radiol. 2013;36(5):1320–8. https://doi.org/10.1007/s00270-013-0547-9
52. Ng SS, Yu SC, Lai PB, Lau WY. Biliary complications associated with selective internal radiation (SIR) therapy for unresectable liver malignancies. Dig Dis Sci. 2008;53(10):2813–7. https://doi.org/10.1007/s10620-008-0222-1
53. Lewandowski RJ, Kulik LM, Riaz A, Senthilnathan S, Mulcahy MF, Ryu RK, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant. 2009;9(8):1920–8. https://doi.org/10.1111/j.1600-6143.2009.02695.x
54. Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, et al. Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. Gastroenterology. 2016;151(6):1155–63. https://doi.org/10.1053/j.gastro.2016.08.029
55. Ettorre GM, Levi Sandri GB, Laurenzi A, Colasanti M, Meniconi RL, Lionetti R, et al. Yttrium-90 Radioembolization for Hepatocellular Carcinoma Prior to Liver Transplantation. World J Surg. 2017;41(1):241–9. https://doi.org/10.1007/s00268-016-3682-z
56. Seinstra BA, Defreyne L, Lambert B, Lam MG, Verkooijen HM, van Erpecum KJ, et al. Transarterial radioembolization versus chemoembolization for the treatment of hepatocellular carcinoma (TRACE): study protocol for a randomized controlled trial. Trials. 2012;13:144. https://doi.org/10.1186/1745-6215-13-144
57. McGahan JP, Brock JM, Tesluk H, Gu WZ, Schneider P, Browning PD. Hepatic ablation with use of radio-frequency electrocautery in the animal model. J Vasc Interv Radiol. 1992;3(2):291–7. https://doi.org/10.1016/S1051-0443(92)72028-4
58. Makary MS, Khandpur U, Cloyd JM, Mumtaz K, Dowell JD. Locoregional Therapy Approaches for Hepatocellular Carcinoma: Recent Advances and Management Strategies. Cancers (Basel). 2020;12(7):E1914. https://doi.org/10.3390/cancers12071914
59. Pompili M, Francica G, Ponziani FR, Iezzi R, Avolio AW. Bridging and downstaging treatments for hepatocellular carcinoma in patients on the waiting list for liver transplantation. World J Gastroenterol. 2013;19(43):7515–30.

60. Head HW, Dodd GD, Dalrymple NC, Prasad SR, El-Merhi FM, Freckleton MW, et al. Percutaneous radiofrequency ablation of hepatic tumors against the diaphragm: frequency of diaphragmatic injury. Radiology. 2007;243(3):877–84. https://doi.org/10.1148/radiol.2433060157
61. Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice. Hepatology. 2008;47(1):82–9. https://doi.org/10.1002/hep.21933
62. Lu Z, Wen F, Guo Q, Liang H, Mao X, Sun H. Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: a meta-analysis of randomized-controlled trials. Eur J Gastroenterol Hepatol. 2013;25(2):187–94. https://doi.org/10.1097/MEG.0b013e32835a0a07
63. Mazzaferro V, Battiston C, Perrone S, Pulvirenti A, Regalia E, Romito R, et al. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. Ann Surg. 2004;240(5):900–9. https://doi.org/10.1097/01.sla.0000143301.56154.95
64. Chu HH, Kim JH, Yoon HK, Ko HK, Gwon DI, Kim PN, et al. Chemoembolization Combined with Radiofrequency Ablation for Medium-Sized Hepatocellular Carcinoma: A Propensity-Score Analysis. J Vasc Interv Radiol. 2019;30(10):1533–43. https://doi.org/10.1016/j.jvir.2019.06.006
65. Andolino DL, Johnson CS, Maluccio M, Kwo P, Tector AJ, Zook J, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2011;81(4):e447–53. https://doi.org/10.1016/j.ijrobp.2011.04.011
66. Sandroussi C, Dawson LA, Lee M, Guindi M, Fischer S, Ghanekar A, et al. Radiotherapy as a bridge to liver transplantation for hepatocellular carcinoma. Transpl Int. 2010;23(3):299–306. https://doi.org/10.1111/j.1432-2277.2009.00980.x
67. Sapisochin G, Barry A, Doherty M, Fischer S, Goldaracena N, Rosales R, et al. Stereotactic body radiotherapy vs. TACE or RFA as a bridge to transplant in patients with hepatocellular carcinoma. An intention-to-treat analysis. J Hepatol. 2017;67(1):92–9. https://doi.org/10.1016/j.jhep.2017.02.022
68. Lee P, Ma Y, Zacharias I, Bozorgzadeh A, Wilson S, Foley K, et al. Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma in Patients With Child-Pugh B or C Cirrhosis. Adv Radiat Oncol. 2020;5(5):889–96. https://doi.org/10.1016/j.adro.2020.01.009
69. Wahl DR, Stenmark MH, Tao Y, Pollom EL, Caoili EM, Lawrence TS, et al. Outcomes After Stereotactic Body Radiotherapy or Radiofrequency Ablation for Hepatocellular Carcinoma. J Clin Oncol. 2016 Feb 10;34(5):452–9. https://doi.org/10.1200/JCO.2015.61.4925
70. Kim N, Kim HJ, Won JY, Kim DY, Han KH, Jung I, et al. Retrospective analysis of stereotactic body radiation therapy efficacy over radiofrequency ablation for hepatocellular carcinoma. Radiother Oncol. 2019;131:81–7. https://doi.org/10.1016/j.radonc.2018.12.013
71. Sapir E, Tao Y, Schipper MJ, Bazzi L, Novelli PM, Devlin P, et al. Stereotactic Body Radiation Therapy as an Alternative to Transarterial Chemoembolization for Hepatocellular Carcinoma. Int J Radiat Oncol Biol Phys. 2018;100(1):122–30. https://doi.org/10.1016/j.ijrobp.2017.09.001
72. Kulik L, Heimbach JK, Zaiem F, Almasri J, Prokop LJ, Wang Z, et al. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis. Hepatology. 2018;67(1):381–400. https://doi.org/10.1002/hep.29485