Role of interventional radiology in the management of hepatocellular carcinoma: current status

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Contributions: (I) Conception and design: All authors; (II) Administrative support: DC Madoff; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: The treatment of patients with hepatocellular carcinoma requires a careful balance of adequate oncologic control and the preservation of both liver function and performance status. Over the last few decades, the emerging field of interventional oncology has introduced a variety of minimally invasive, safe and effective therapies, expanding the armament of available treatment options. The Barcelona Clinic Liver Cancer staging system is the most widely adopted treatment classification which aims to match patients with the therapies that will yield the best outcomes based on these factors. Radiofrequency ablation has been recommended by this system for patients with very early stage disease and trans-arterial chemoembolization has been recommended as the gold standard therapy for patients with intermediate grade disease. Technical innovation brings newer ablative and embolotherapy techniques into practice, while clinical innovation continues to expand the indications of these treatments outside of the formal paradigm. This article will provide an overview of the varied interventional procedures being used in clinical practice and will review how they can be used to cure very early and early stage disease, to facilitate surgical resection, to bridge or downstage tumors for liver transplantation, and extend survival as palliative interventions in patients with intermediate or advanced disease.

Keywords: Hepatocellular carcinoma (HCC); ablation; embolization

Introduction

Surgery is considered the most effective chance at cure for appropriately selected patients with hepatocellular carcinoma (HCC); however, most patients are not surgical candidates at the time of presentation (1). For these patients, accurate prognostication is critically important for making treatment decisions that best balance oncologic control while maintaining their performance status. Multiple staging systems have been proposed to facilitate appropriate treatment allocation and are based on varied combinations of factors, such as, the extent of tumor burden, liver function, and performance status. The Barcelona Clinic Liver Cancer system (BCLC) (2) is currently the most widely accepted of these staging systems and is endorsed by multiple international multidisciplinary liver disease societies. The system stratifies patients into five grades (0, A, B, C, D) and appropriates treatment options accordingly. Interventional therapies, specifically radiofrequency ablation (RFA) and trans-arterial chemoembolization (TACE), are recommended by the BCLC for stage 0 and stage B patients, respectively. As technical and clinical innovation continue to outpace large randomized controlled trials, interventional therapies have

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expanded outside of these formal indications and can benefit carefully selected patients across multiple disease stages, especially at centers of excellence with multidisciplinary tumor boards. For the purposes of this article, interventional therapies used in the treatment of HCC are broadly classified as either ablative or embolotherapy. A brief overview of the different treatments comprising these two categories is first provided to familiarize the reader with these procedures and is then followed by a review of how these therapies fit into the evolving HCC treatment paradigm.

Overview of interventional oncology treatment modalities

Ablative techniques

Ablative therapies are minimally invasive procedures performed using a percutaneous, laparoscopic, or open surgical approach, and can be used for curative or palliative tumor treatment. As a review of interventional techniques, this article will focus on the percutaneous applications of ablation. Generally, ablative therapies can be categorized as thermal or non-thermal techniques. Other than cryoablation, most thermal techniques use different methods to heat tissues to temperatures greater than 60 ℃, causing instantaneous and irreversible damage to proteins resulting in coagulative necrosis (3). Besides the entire tumor, a margin of approximately 0.5–1 cm should also be included during ablation to control any adjacent microscopic disease (4,5).

RFA is the most ubiquitous and well-studied percutaneous thermal therapy for hepatic tumors and is included in multiple societal guidelines for the treatment of HCC (6,7). In RFA, a generator creates alternating high frequency RF waves (460–480 kHz) to agitate ions and disperse heat centrifugally from a needle-shaped electrode into surrounding tissues. This technique requires the application of a grounding pad to the patient's skin. The amount of energy delivered is based on Ohm's law and inversely relates to tissue impedance, which has multiple practical implications. For example, at temperatures greater than 105 ℃, the vaporization and carbonization of tissues occurs, increasing local impedance and limiting energy transfer to target tissues. This results in unexpected alterations to the size, shape, and homogeneity of the ablation zone, potentially inhibiting complete coverage of the tumor and margin with tumoricidal temperatures. Strategies to decrease this effect are used, such as, internally

cooled probes which maintain a lower temperature around the needle tip, however, the ablation size, temperature and speed remains limited. Impedance is also the basis of heat-sink effect. Current follows the path of least resistance and flowing blood or bile in adjacent structures draws charge away from the tumor, limiting the amount of heat delivered to target tissue (8).

RFA can be performed using a monopolar system, consisting of a single grounding pad and needle-shaped electrode which is inserted centrally into the tumor. This approach is generally used to treat tumors up to ~3 cm with a single probe. Monopolar systems are also used in an overlapping fashion to treat larger tumors; however, this approach can be fraught with issues, with effective ablation relying on the accuracy of probe positioning to ensure complete tumor coverage. Some experts advocate for using multipolar systems to treat larger tumors (9), which use pairs of electrodes placed around the periphery of a tumor, delivering heat concentrically to create an ablation zone centrally between the electrodes.

The success of RFA as an effective and low morbidity tumor treatment has paved the way for a wide array of other thermal technologies to be used in HCC treatment, many of which have demonstrated potential in early studies and may offer advantages, but currently remain less well-established at this time. These modalities will be described in the following paragraphs and are listed in *Table 1*.

Microwave ablation (MWA) emits electromagnetic radiation from an antenna probe for tumor therapy, typically using frequencies of either 915 MHz or 2.45 GH. High energy concentration is created around the probe tip, oscillating water molecules to generate heat from friction within the tissues. The excitation of water molecules happens across a larger radius compared to RFA, thus causing a more immediate and homogenous heating. Since MWA relies less on passive tissue heat conduction, MWA zones are also less susceptible to heat sink effects. Char and vaporization is also of less consequence because of this physical property of microwaves. The penetration depth of microwaves is dependent on the frequency used, with the 915 MHz probes yielding larger ablation zones, however, lower energy density (10). It is important to recognize there are stark differences between the ablation zones created by different microwave systems, especially first-generation microwave probes which produced smaller, suboptimal ablation zones. Newer, second generation MWA systems are capable of generating hotter, larger ablation zones (can be greater than 5 cm) at a faster rate than RFA

Table 1 Overview of interventional therapies

Technique	Mechanism	Pros	Cons
RFA	High frequency currents disperse → friction of molecules in tissue & heat → coagulative necrosis	Well-studied with curative outcomes in small tumors, excellent safety profile	Size and heat of ablation zone are limited by charring effect & heat sink, needs grounding pad
MWA	High frequency oscillating electromagnetic field → rapid realignment of polar molecules increasing kinetic energy/heat → coagulative necrosis	Produces higher temperatures faster than RFA, not limited by char or heat sink, no grounding pad, larger, consistent ablation zones, may be effective for larger tumors	Higher power requires caution and diligent monitoring; insufficient evidence to claim superior outcomes to RFA
Cryo	High pressure gas passed into larger volume at needle tip → rapid cooling in tissues. Cool-thaw cycles result in intracellular & intravascular ice resulting in cell death	Ice ball is visualized under CT and US facilitating accurate targeting	Subject to heat sink, possible risk of increased major complications
Laser	Laser light is applied to target tissue using fiberoptic applicators	MRI compatible allows intraprocedural temperature monitoring	Requires arrays of applicators for larger ablation zones, increasing procedural complexity and cost
HIFU	Absorption of high-intensity acoustic waves → cell death through thermal mechanism & mechanical cavitation injury	Truly non-invasive	limited penetrance for deep tumors, scatter causes complications, limited by respiration & coagulation/vapor formation
PEI	Cellular dehydration, protein denaturation and chemical sclerosis of small tumor vessels to cause coagulative necrosis	Cheap, fast, not affected by heat sink, lower rate of complications than thermal ablation	Less oncologic control than thermal ablation, frequently requires repeat injections
IRE	High voltage repetitive pulses which induce pore formation in the cell membrane resulting in apoptosis	Not affected by heat sink and it leaves extracellular matrix intact → less collateral damage to adjacent vessels or biliary ducts	Anesthesia for muscle blockade & ECG-gating, cumbersome with multiple probes in parallel, delayed imaging changes
Radiation segmentectomy	Selective intra-arterial radiotherapy with Y90 using doses over 190 Gy to treat 2 or fewer segments	Potentially "curative" modality that can be used to treat lesions which are unresectable and non-ablatable	More data needed, possibly less complete tumor necrosis compared contemporary ablation data
TAE	Induction of ischemic necrosis by occlusion of terminal arterioles using permanent microparticles	Cheap, no chemo side effects	More severe post-embolic syndrome
cTACE	Intra-arterial delivery of high dose chemotherapy & ischemic effects from embolization	Well-studied technique, resulting in improved survival outcomes, can be repeated as needed	Technical heterogeneity and inconsistency, more systemic toxicity than DEB-TACE
DEB-TACE	Similar to cTACE high dose intra-arterial chemo, & ischemia from particle embolization	More sustained tumor drug delivery, more standardized and reproduceable	More expensive than cTACE
TARE	Selective administration of high-energy, low penetration Y90 radiotherapy	Possibly better time to progression & tumor control vs TACE, fewer Rxs needed, minimal post-embo syndrome, discharged same day, can induce FLR hypertrophy for surgery	Requires mapping procedure, more expensive, more resource intensive

RFA, radiofrequency ablation; MIWA, microwave ablation; IRE, irreversible electroporation; DEB, drug-eluting beads; TACE, trans-arterial chemoembolization; TARE, trans-arterial radioembolization.

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technology (11,12), leading to increasing adoption amongst interventionalists.

Cryoablation (Cryo) is a thermal ablation technique that uses the rapid expansion of gas in the distal tip of a probe to cause rapid cooling to temperatures as low as –140 ℃, dependent on the gas used and probe design (13). Temperatures less than –40 ℃ are cytotoxic and rapid freeze/thaw cycles are used to create intracellular and intravascular ice crystals that lead to cell death. Cryoablation has not been widely used for hepatic tumor ablation because of a higher complication rate compared to RFA in older studies including hemorrhage, biliary injury, and "cryoshock", a severe systemic reaction specific to cryotherapy that is characterized by massive cytokine release and multi-organ failure (14). That said, some authors are now reporting reasonably low complication rates with newer probes resulting in comparable outcomes to RFA (15,16).

High-intensity frequency ultrasound (HIFU) is a non-invasive technique, performed using MRI guidance, to precisely aim multiple ultrasound waves at a 3-dimensional focal point. This focal point typically measures in the range of 1 to 5 mm in diameter and 10 to 50 mm in length, depending on the source's parameters. HIFU causes local sound pressure which is absorbed and converted to heat causing coagulative necrosis from a combination of hyperthermia and acoustic cavitation in target tissue, while sparing adjacent parenchyma and structures (17). Zhang et al. treated 39 patients with HCC tumors within 1 cm of main hepatic blood vessels with no major blood vessel injury observed in any subject (18). Morbidity from the procedure is also well tolerated in patients with cirrhosis. Complications have been in observed in about 13% of patients, mostly skin or subcutaneous tissue injuries (19). A limiting drawback of HIFU is the complex set-up required. This procedure often requires general anesthesia to render patients immobile and control their respiration, while the patient is positioned prone in a water bath to remove the air between the transducer and target area.

Laser ablation is an alternative thermal ablation technique, far less investigated than RFA or MWA, which uses thin optical fibers to transmit intense light (range, 600–1,000 nm) that is scattered and absorbed by the tissues and converted into heat to cause coagulative necrosis. The lasers have limited energy penetration, which can be altered by adjusting the frequency, and creates smaller ablation zones than other electromagnetic techniques (20). It also does not penetrate well through charred tissue. Multiple applicators can be used to develop larger ablation zones.

An advantage of using optical fibers is that they can be well visualized on MRI, and the absence of metal also produces less steak artifact on CT.

Non-thermal techniques include chemical ablation and irreversible electroporation (IRE). Both techniques are most useful for treating tumors adjacent to vascular structures or central biliary ducts, since they are not limited by heat sink. Chemical ablation is the percutaneous injection of chemicals directly into a tumor, most commonly absolute ethanol, which causes cellular dehydration and protein denaturation resulting in tumor necrosis (21). Reasonable diffusion of the chemical throughout the tumor is often achieved, however, repeat injections are required to complete the ablations. The technique is inexpensive, safe and, reasonably effective but has been demonstrated to be inferior to thermal ablation for most cases and is therefore not widely practiced. IRE is a newer, non-thermal technique using multiple probes aligned in parallel to deliver short, repetitive, high voltage electrical pulses to the tissue to damage cell membranes and cause apoptosis, while largely preserving the extracellular matrix (22). Since IRE does not rely on thermal effects, its purported advantage is that it is less likely to damage adjacent structures and can be used to treat tumors adjacent to central bile ducts or vascular structures. Kingham et al. showed no increase in recurrence when treating perivascular tumors (23). IRE requires unique considerations related to its electrical interference, affecting the cardiac rhythm causing arrhythmias and also muscle contractions. These side effects can be mostly mitigated by using cardiac gating and paralytic agents. IRE has mostly been used to treat locally advanced pancreatic cancer and the HCC data is limited, with relatively worse local control compared to thermal ablation. Additionally, it is technically cumbersome requiring the parallel placement of multiple probes, with slight deviations in alignment possibly resulting in failed treatment. Currently, it is best used in small, unresectable, hepatic tumors that are also unsuitable for thermal ablation because of neighboring vital structures.

Embolotherapy techniques

Primary hepatocellular cancers almost exclusively receive their blood supply from the hepatic arterial system, while normal liver parenchyma is mostly supplied by the portal vein (24). Trans-arterial chemoembolization (TACE), a procedure formally included in the BCLC staging system for patients with stage B intermediate disease, leverages this difference in blood flow to deliver highly targeted

treatment. Multiple variations of this procedure exist and are generally defined by two principles. First, that selective administration of therapeutics into the hepatic artery should improve drug tumor bioavailability and limit systemic exposure to unwanted effects (25). Second, that embolization of the tumor-specific blood supply using small particles will induce ischemic necrosis and also prevent the washout of any co-delivered therapeutic. The mechanism of cell death from TACE is somewhat unclear and is some combination of ischemic necrosis and/or chemotherapeutic cytotoxicity.

The two most common methods of TACE are conventional TACE (cTACE) or TACE using drug-eluting beads (DEB-TACE). cTACE is most commonly performed by creating an oily emulsion with ethiodized oil and chemotherapy (26). Ethiodized oil is radiopaque, allowing the operator to visualize the emulsion during therapeutic delivery, and also provides some embolic properties. This is mixed with either a single agent or combination of chemotherapeutics, most commonly doxorubicin, epirubicin, cisplatin or miriplatin. After infusion of the emulsion, additional embolic material is injected ranging from gelfoam to microspheres. In general, TACE procedures should be performed as superselective (i.e., segmental, subsegmental) as safely feasible and can be repeated either on schedule or when residual or recurrent disease is identified.

DEB-TACE has gained favor amongst some interventionalists after pharmacokinetic studies have shown cTACE may expose patients to similar systemic doses of chemotherapy as intravenous infusion (27). This is thought to be related to delays between emulsion administration and embolic injection. DEB-TACE uses hydrogel beads which can be loaded with doxorubicin using an ion-exchange mechanism, providing simultaneous embolization and drug delivery. The doxorubicin is more slowly released from the beads, resulting in decreased systemic doses compared to cTACE, despite higher doses of chemotherapy (28,29). The recommended doses range from 75 to 150 mg of doxorubicin depending on the extent of disease (30). Another perceived advantage of DEB-TACE, is the technical standardization relative to cTACE since there is less inter-operator variability and more repeatability. When performing DEB-TACE, small beads are preferred when safely possible (standard size: 100–300 um).

Trans-arterial embolization (TAE) or "Bland" embolization is performed only using embolic particles, causing terminal arterial vessel blockade and inducing ischemic necrosis (25). Historically, gelatin sponge autologous blood clot, cyanoacrylate glue, polyvinyl alcohol and microspheres were administered selectively, however, modern techniques now aim to deliver carefully calibrated 50 or 40–120 um microspheres as superselective as safely possible (31). Repeat embolization can be performed as needed for persistent viable tumor or new lesions.

Trans-arterial radioembolization (TARE) or selective internal radiation therapy (SIRT) is the trans-arterial delivery of microspheres containing yttrium-90 (Y90). Y90 is a beta-emitter with a half-life of 64.2 hrs and mean and maximal tissue penetration of 2.5 and 10 mm. The radioisotope is delivered using one of two FDA-approved methods for intra-arterial delivery, either resin microspheres bound to Y90 (SIR-sphere; Sirtex Medical) which are approved for the treatment of colorectal metastases or glass microspheres with Y90 embedded within (Therasphere; BTG Corporation) which are approved for treating HCC. Theraspheres have an average diameter of 20–30 μm and an average specific activity of 2,500 Bq/sphere, in comparison to SIR-spheres, which have an average diameter of 20–60 μm and an average specific activity of 50 Bq/sphere, so many more SIR-spheres are required to deliver the same prescribed radiation dose. This particle difference contributes to a minimal embolic effect noted with glass microspheres versus the moderate embolic effect when using resin microspheres, which can result in angiographic stasis when administered (32). Although the technical parameters of both Y90 vehicles differ, retrospective data shows comparable safety and efficacy in the treatment of HCC, while no randomized controlled trials have been performed to assess for clinical superiority between either technique. Mapping angiography is performed as a separate procedure prior to TARE to evaluate for collateral flow to enteric and other non-target organs, as well as, to calculate a lung shunt fraction. Standard treatment is usually delivered in a segmental, lobar or bilobar fashion. Radiation segmentectomy (RS) is a similar technique except higher doses of radiation are delivered in a more selective fashion, to achieve "ablative" radiation doses to a tumor. Usually 2 segments or less are targeted and a threshold dose of at least 190 Gy is used, which has been confirmed using pathologic correlation from explanted livers (33).

The role of interventional oncology in the management of HCC

The treatment modalities described above are useful

primary and adjunctive therapies in the treatment and palliation of HCC. The rest of this article will provide an overview of how these therapies are utilized in the management of HCC, organized by indications across disease stages. This information is summarized in *Table 2*.

Curative interventional therapy for very early or early stage disease

Ablation

Surgery is the most widely accepted primary intervention for very early or early stage HCC; specifically, the anatomical resection of tumors in patients without significant underlying liver disease and liver transplantation for patients with abnormal liver function (6,7). RFA is recommended as a curative therapy in patients precluded from surgical intervention with 2 or 3 nodules less than 3 cm or with a solitary tumor. This recommendation is based on a large body of data showing oncologic and survival outcomes comparable to resection, at least for tumors less than 3 cm in diameter. An example case is provided in *Figure 1*.

Multiple, randomized prospective studies have compared radiofrequency ablation to surgical resection (SR) for very early or early HCC in patients who were surgical candidates. Chen *et al.* (34) prospectively randomized 180 patients with solitary HCC smaller than 5 cm to surgery or RFA. There was no significant difference in overall or disease-specific survival at 1-, 2-, 3-, or 4-yr survival with 29 months average follow-up and no difference in sub-group analysis separating tumors by size (<3 or 3.1–5 cm). SR group had longer hospital stays and more post-op complications. Lü *et al.* (35) randomized 105 patients with early stage HCC listed for transplantation to surgery or thermal ablation and showed no significant difference in overall or disease-free survival at 1, 2, or 3 years with shorter hospital stays in the ablation group. Feng *et al.* (36) randomized 168 patients with solitary HCC to surgery or RFA, but the patients were informed of their treatment group prior to consent. No significant difference was found in overall or recurrence-free survival at 1-, 2-, or 3-year. Fang *et al.* (37) randomized 120 patients with solitary or multiple small HCC (<3 cm) to surgery or RFA and found no significant difference in overall and disease-free survival at 1, 2, and 3 years with mean follow-up of 40 months. The incidence of post-operative complications (27% *vs.* 5%) and hospital stay (11.8 *vs.* 4.3) were significantly higher in the SR group. Ng *et al.* (83)

randomized 218 patients with early stage HCC to either RFA or SR. RFA was performed percutaneously in 45% cases, the rest were laparoscopic or open. There was no significant difference in overall survival at 1-, 2-, 5-, and 10-yr survival with median follow-up of 93 months, however, there was a trend towards poorer disease-free survival in RFA starting 2 years post treatment in the RFA group. In subgroup analysis, no significant difference in overall survival or disease-free survival when limited to very early stage HCC or all solitary tumors. RFA group had less blood loss, shorter procedure times, shorter hospital stays and less post-operative complications. Lee *et al.* (84) randomly assigned 68 patients with solitary tumors 2–4 cm in size to SR or RFA. This study also showed no significant difference in 3- and 5-yr overall survival rates with median follow-up of 64 months. Intra-hepatic local recurrence was more frequent when more repeat treatments were required in the RFA group, but the rate of distant intra-hepatic and extra-hepatic recurrences remained similar.

Only one RCT has shown inferior overall survival with RFA compared to SR. Huang *et al.* (85) randomized 230 patients within Milan criteria to SR or RFA and concluded that overall survival and tumor recurrence rates were significantly better with resection. Their subgroup analysis by tumor size and multifocality, also showed surgery was significantly superior. The adverse events and length of hospitalization were significantly longer with resection. This study has been criticized for flawed methodology (86,87). First, the authors used a single monopolar electrode and performed sequential overlapping ablations under ultrasound guidance, which has been suggested to be suboptimal for achieving complete ablation of tumor and safety margin, especially for tumors measuring 3–5 cm (88). Also, the loss to follow-up rate for the SR group was much higher than with RFA (15.7% *vs.* 6.1%), possibly inflating the SR group's survival outcomes, considering their overall survival rate is among the highest published. Additionally, multiple patients with benign disease were treated, raising questions regarding their available imaging staging accuracy.

A recent Cochrane meta-analysis by Majumdar *et al.* included four of these clinical trials evaluating RFA *vs.* SR for very early and early stage HCC including 574 surgically eligible patients with reported outcomes (38). Their analysis showed no difference in overall mortality at maximal follow-up. Cancer-related mortality was significantly lower in the surgery group; however, this outcome was only reported in the Huang trial. Serious adverse events (11.3 per 100 *vs.* 1.6 per 100 participants) and total adverse

Table 2 Interventional therapies and the BCLC staging system for HCC

BCLC stage	Technique	Role	References
Stage 0 & stage A			
Curative therapy for very early and select early stage tumors	Thermal ablation	Curative therapy with similar long-term survival outcomes to surgery	(33-45)
	PEI	Less effective than thermal ablation for most situations, no heat sink	
	Radiation segmentectomy	Comparable survival and tumor control outcomes for tumors <5 cm, currently used in patients who are not candidates for surgery or ablation	
Stage A			
Planned surgical lobectomy	TACE + PVE	Useful for expected insufficient FLR, treats tumor to bridge to resection while inducing FLR hypertrophy to reduce post-op liver failure	(46-50)
	Radiation lobectomy (TARE)	Treats tumor to maintain surgical candidacy & induces FLR hypertrophy, although less and slower than PVE	
Bridge to transplant	Thermal ablation, PEI, TACE, TARE	Aims to keep patients within treatment criteria while awaiting organ allocation to prevent drop-off transplant list, improves outcomes in patients who dropout	(51-59)
Stage B			
Downstage to transplant	Thermal ablation, PEI, TACE, TARE	Decrease number and size of lesions to try and fit patients within transplant criteria, can indicate favorable histology for transplant	(59-61)
Local disease control	TACE, TARE	Increase progression-free and overall survival; insufficient evidence to suggest superiority of TAE, cTACE, DEB-TACE, TARE	(62-74)
Stage C			
Local disease control	TACE, TARE	Increased progression-free and overall survival, can be used in select patients with PVTT, possibly useful alternatives and/or adjuvants to sorafenib	(75-82)

HCC, hepatocellular carcinoma; TACE, trans-arterial chemoembolization; TARE, trans-arterial radioembolization; FLR, future liver remnant; PVE, portal vein embolization.

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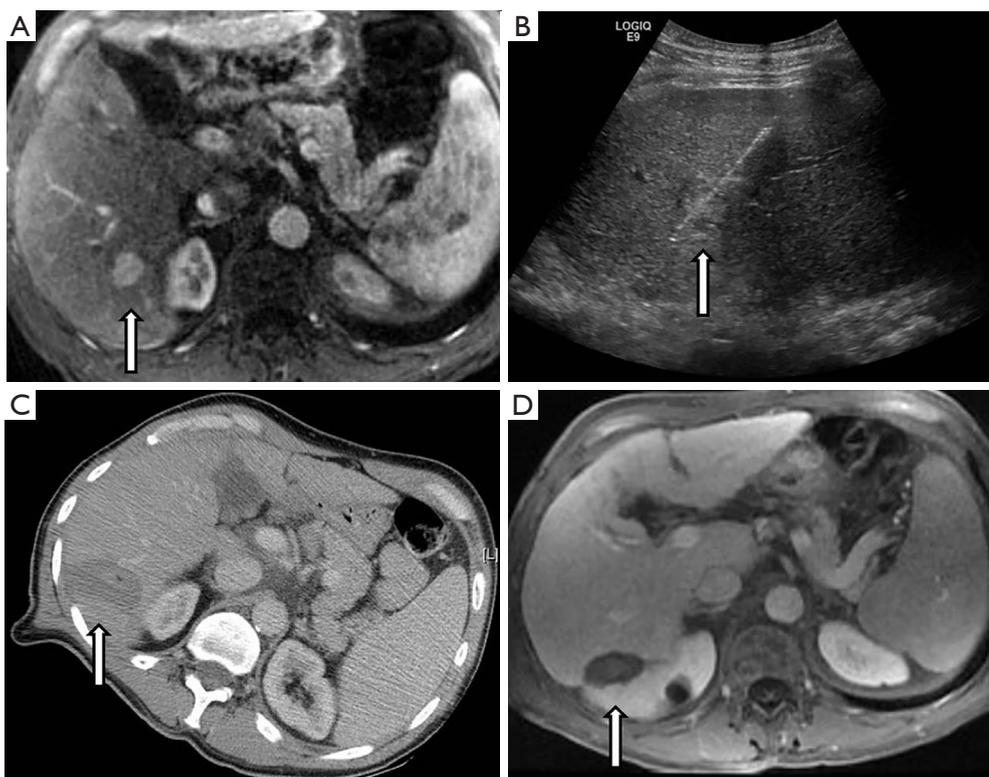
Figure 1 Thermal ablation of very early stage HCC. (A) MRI Liver shows a 2 cm HCC nodule in segment 6 (arrow); (B) intraprocedural ultrasound shows the echogenic tumor with the microwave probe within it (arrow); (C) final CT images from the ablation showing a hypodensity corresponding to the ablation zone with a foci of air within it (arrow); (D) MRI liver at 2.5 years shows no enhancement within the ablation zone (arrow), consistent with a complete response. HCC, hepatocellular carcinoma.

events were significantly higher in the surgery group. Three trials reported an additional mean 8.42 days longer hospital stay in the surgery group. There were lower intrahepatic and distant recurrence rates in the surgery group, however, without an impact on overall survival.

Mironov *et al.* (39) analyzed data from the population-based cancer registry SEER database, including 920 patients with T1 disease and found no significant difference in overall or tumor-free survival for up to 5 years, when comparing thermal ablation to SR for tumors <4 cm. Tumors from 4.1–5 cm benefited from surgery with improved overall and disease-specific survival. Considering the inherent selection bias within this dataset with sicker patients likely receiving thermal ablation. This study supports equivalence in oncologic control of thermal ablation to surgical resection for tumors <4 cm using a larger, "real-life" dataset.

Overall, it appears there is consensus that either surgery or thermal ablation should be performed in patients with very early or early stage HCC. The majority of data evaluating RFA and surgery as a primary treatment in surgical candidates shows no significant difference in overall mortality, however, mixed results from multiple studies suggest possibly higher intra-hepatic recurrence rates with ablation, leaving resection as the treatment of choice in low-risk patients. Further trials comparing surgery and thermal ablation are required to determine the relative benefits and harms of these treatments.

Comparison of ablative techniques

Although chemical ablation was the seminal ablative technique, thermal ablation has demonstrated superiority in RCT's (40-43) and meta-analyses (38,89) and should be favored in the majority of ablation candidates. Shen *et al.* performed a meta-analysis including four RCTs with 766 patients that showed RFA has significantly better 3-year overall survival and lower recurrence rates for small HCC's compared to chemical ablation. The perceived

downside is that RFA has more complications and is more expensive. Majumdar compared fourteen clinical trials, with 2,533 participants, evaluating non-surgical interventions in patient's ineligible for surgery. Overall survival at maximal follow-up was reported in ten trials including 1,417 participants, showing superiority of RFA compared to chemical ablation with mortality highest in percutaneous acetic acid injection (HR 1.77) and in percutaneous ethanol injection (HR 1.49) and no difference in adverse events. In the five trials reporting cancer-related mortality at maximal follow-up, RFA was significantly higher *vs.* PEI (16.8% *vs.* 8.6%).

Thermal ablation is favored in most scenarios, however, there is no consensus regarding which thermal technique to select. The body of evidence comparing thermal techniques consists mostly of heterogenous, poor-quality studies and the rapid pace of innovation limits the extrapolation of old data to new techniques. Specifically, newer microwave probes have been drastically improved compared to older microwave systems, and are gaining interest because of faster heating times, limited char/vaporization or heat sink effects, and higher, more-tumoricidal temperatures compared to RFA. For example, a retrospective cohort of 452 HCC patients with 163 HCC nodules within 5 mm of a major vascular structure, showed no difference in technical effectiveness, tumor progression rates or 1-, 3-, 5-yr cumulative survival rates when treating the perivascular lesions, demonstrating no difference related to heat sink effect (90). With regards to complications, a large retrospective cohort (91) demonstrated MWA has a comparable safety profile to RFA, with 2.6% of the 1,136 patients treated having major complications.

The improved heating parameters and comparable safety profile to RFA have influenced increased clinical adoption of MWA, although, there is still a paucity of data demonstrating clinical superiority to RFA. A meta-analysis by Facciorusso *et al.* (92) included seven comparative studies of 774 patients, evaluating RFA and MWA in mostly very early or early stage HCC. Six studies were retrospective and there was a single RCT (93). This showed an increased non-significant trend towards increased complete response with MWA (OR 1.12, P=0.67) no difference in local recurrence, and a non-significant trend towards increased overall survival with RFA (OR 0.95, P=0.85). When limiting the analysis to the three studies that enrolled larger tumor sizes, MWA significantly outperformed RFA (OR 0.46, P=0.02). There was also a non-significant trend towards increased rates of major complication with MWA, which may explain the increased survival trend with RFA. This study compared

these two modalities using the highest quality evidence available, however, the included studies were mostly performed prior to significant improvements in MWA technology. The data from older studies is only applicable to the systems evaluated and cannot be extrapolated to all MWA. Newer comparative studies are needed to better evaluate the risk benefit profiles of improved MWA systems and RFA.

Cryoablation is less used because of a perceived higher complication rate and decreased efficacy compared to RFA, based on studies with first-generation cryoprobes (94). Recently, Wang *et al.* (16) randomized 360 HCC patient with 1 or 2 nodules <5 cm to RFA or Cryo and showed comparable results to RFA ,with a trend towards better local recurrence rates for cryo. There was no difference in the rate of complete necrosis after 1 treatment (95.6% RFA *vs.* 98.3% cryo) and no difference in overall survival at 3- and 5-yr (66%, 38% *vs.* 67%, 40%). There was a mildly increased local recurrence rate at 3-yr. Interestingly, they rate of major adverse events was the same (4%), contradicting data from first generation cryoablation techniques.

Laser ablation, albeit less studied, has been shown to have a comparable safety and efficacy profile to RFA in retrospective studies, as well as in an RCT. Di Costanzo *et al.* (95) randomized 140 patients to receive RFA or LA in a non-inferiority trial and demonstrated no significant difference in radiologic response, time to local progression and overall survival endpoints.

There are currently no comparative studies evaluating IRE. There has been a demonstration of efficacy by pathologic evaluation at explant showing complete necrosis in 5 of 6 patients with small HCC and preservation of the bile ducts within treated areas (96). Also, a retrospective study evaluated IRE in 58 patients with 75 small HCC tumors not amenable to surgery or ablation. The 1-yr overall progression free survival was 70%, in nodules that would have otherwise not been treated. No biliary complications were noted, however, a treatment related death occurred secondary to liver failure in a patient with Child Pugh B cirrhosis and a 4.5 cm HCC tumor (97).

Embolotherapy

Although no formal role for embolotherapy exists in very early or solitary early stage HCC, it may offer durable control in patients who are not candidates for surgery or ablation. A two-center study (33) evaluated radiation segmentectomy in 102 patients with solitary HCC <5 cm,

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that were not resection or ablation candidates. A small cohort of 3 patients had eventual LT and pathologic evaluation of the explanted livers showed 100% of tumors had at least 90% tumor necrosis with 52% demonstrating complete necrosis. Complete necrosis was significantly associated with a treatment dose of >190 Gy. The rate and median time to progression was 26% and 33.1 months and the survival data was comparable to existing ablation literature. No major adverse events occurred, only mild and transient adverse events. This procedure can be performed on an outpatient basis and there were no readmissions in their cohort. Although well tolerated, careful patient selection is paramount, as patients with cirrhosis and poor hepatic reserve, such as elevated bilirubin and low albumin levels related to liver failure are more likely to have a major adverse event (98). Another retrospective review (45) showed excellent long-term control in 70 patients treated with RS with no progression in 72% of patients and a median time to progression of 2.4 years. These studies support RS deserving further attention as a durable and possibly curative modality available to patients deemed high-risk for surgery or ablation.

There are also several retrospective studies (99,100) evaluating superselective cTACE in patients with solitary lesions smaller than 3 cm. Yang et al. used inverse probability weighting in a retrospective study to correct for patient selection biases between patients with single HCC <3 cm who received SR, RFA, or cTACE and found no significant difference in overall survival after correction, although TACE remained an independent risk factor for recurrence. Hsu et al. reviewed 185 patients with possibly resectable, early stage HCC, and Child Pugh A cirrhosis who chose either TACE or SR. There was no significant difference in overall survival at 1-, 3-, and 5-yr, however, recurrence-free survival was significantly decreased in the TACE group. Overall survival is comparable but considering the increased risk of recurrence, when TACE is used in patients who are high-risk for surgery or ablation, it requires more vigilant surveillance and re-treatment as needed.

Combined TACE + RFA

For solitary HCC smaller than 7 cm, combined TACE + RFA has been shown to have better outcomes than RFA alone. Peng et al. (44) randomized 189 patients with solitary HCC <7 cm to TACE + RFA or RFA alone and found better overall and recurrence-free survival. Additionally, a Bayesian network meta-analysis (101) found TACE + RFA to be the most effective strategy for early stage HCC with

highest ranked 1-, 3-, and 5-yr survival rates, ranking above RFA and SR. These results have led authors to compare RFA + TACE to surgical resection. A meta-analysis (102) combined four retrospective studies and showed comparable 1- and 3-yr overall survival and 1-yr progression free survival, however, 3-yr progression free survival was significantly lower for RFA + TACE.

Interventional therapy to facilitate surgical resection

Surgical resection affords patients with large tumors the best oncologic outcomes, however, the risk of postoperative liver failure excludes some patients with insufficient estimated future liver remnant (FLR). Portal vein embolization (PVE) effectively induces compensatory hypertrophy in the contralateral lobe to increase the FLR and reduce the risk of post-operative liver failure after major hepatic resections (46,103). Two trans-arterial techniques garnering interest for facilitating major hepatic resection in HCC patients with insufficient FLR are sequential TACE + PVE and Y90 radiation lobectomy.

For sequential TACE + PVE, cTACE or DEB-TACE are performed prior to PVE. Yoo et al. (47) retrospectively compared 71 patients who received TACE + PVE vs. 64 patients who received PVE alone to evaluate for differences in FLR hypertrophy and oncologic control. The combined treatment group had a significantly increased mean FLR percentage increase (7.3% vs. 5.8%), as well as, increased overall and recurrence-free survival. Ronot et al. (48) performed TACE + PVE in 54 patients of which 72% underwent right hepatectomy. Interestingly, BCLC stage did not significantly influence survival. Additionally, 8 out of 15 patients in the unresectable cohort underwent subsequent TACE, 6 of which were ipsilateral, without complication. Even though resection was not performed, prior TACE + PVE did not exclude these patients from safely receiving subsequent palliative therapy.

Radiation lobectomy may also have a pre-operative role for inducing FLR hypertrophy, considering multiple recent studies showed increased contralateral hypertrophy after TARE. For example, a series of 83 patients (104) with mixed tumors receiving lobar TARE, had a median FLR hypertrophy of 45%. Portal vein thrombosis was significantly associated in this group with FLR hypertrophy. Another non-comparative series of 13 patients (49), 10 with HCC, underwent right lobar (+ or – segment 4) TARE prior to SR and had a median percent FLR hypertrophy of 30% with 50–99% necrosis in 92% of the resected tumors.

In a retrospective, comparative cohort of 52 patients with mixed hepatic tumors matched for several variables known to influence FLR hypertrophy, RE resulted in a mean FLR volume increase of 29%, significantly less than the 61.5% mean FLR volume increase in the PVE arm (50).

Future studies comparing radiation lobectomy and TACE + PVE should be performed to assess efficacy in FLR hypertrophy and oncologic control but should also assess the peri-operative benefits of FLR hypertrophy induced by TARE. Since TARE and PVE induce hypertrophy by different mechanisms, it is unclear if the same perioperative benefits from PVE can be extrapolated to TARE as there may be additional unrealized effects.

Bridging/downstaging to transplant for early and intermediate stage HCC

Liver transplant is the recommended curative therapy for many patients with early stage HCC. In many regions, HCC patients are given exceptional status to bolster listing priority to limit patient dropout from progression of disease (105). Therefore, it is critical to estimate post-transplant survival and recurrence rates from a patient's pre-transplant presentation to help balance allocation for other transplant indications. From an oncologic perspective, pre-operative assessment of tumor burden, the largest tumor diameter and sum of total tumor diameters, is currently the most important consideration when determining candidacy for liver allocation (106,107). The Milan criteria (1 lesion <5 cm or 3 lesions <3 cm, with no evidence of extra-hepatic spread) is the gold standard transplant criteria for HCC (108). Those within Milan criteria have comparable survival outcomes to liver transplant patients without HCC (108,109). Expand selection criteria has been emphasized with the successful prospective validation of the UCSF criteria and additional proposed systems including the "Up-to-seven" model (110) and extended Toronto criteria (111). While awaiting organ availability, disease can progress beyond transplant criteria, rendering that person no longer a transplant candidate. Bridging therapy with interventional treatment aims to keep patients within transplant criteria. An example case is provided in *Figure 2*.

A multi-specialty, international consensus statement declared there is insignificant evidence to make a recommendation about bridging therapy for UNOS T1 disease (single HCC <2 cm). No existing studies compare T1 HCC patients who receive LRT to those who do not. A systematic review by Kulik *et al.* (112) compared a study (113) where T1 patients with cirrhosis received LRT and had a list drop-off rate of 5.3% with another study (114) including patients with T1 HCC and cirrhosis who did not receive LRT and had a dropout rate of 15.2% and 88% progressed to T2 HCC at 2.4 years.

It is currently recommended that patients with UNOS T2 disease (HCC 2–5 cm or up to 3 lesions <3 cm) should receive locoregional bridging therapy if their estimated wait time is six months or greater (115). In current practice, the difficulty of predicting the timing of organ allocation leaves most patients receiving locoregional bridging therapy.

Multiple large retrospective studies (51-53) have compared LRT + transplantation to transplantation alone showing significantly improved rates of recurrence and post-transplant survival in those receiving pre-transplant LRT. A variety and combination of ablation and embolotherapy have reported comparable safety and efficacy in the bridge to transplant setting (54-56). Additionally, it is useful to consider the effects of bridging/downstaging LRT on the listed patients who eventually dropout and never receive LT. A retrospective study (59) of 359 patients listed for LT within a 6.5-year period compared patients who received LRT to those who did not. LRT was associated with significantly improved survival in patients who were delisted (1,249.6 *vs.* 742.1 days,). Also, in the LT group, patients with tumor diameters >30 mm had significantly improved survival (1,949.4 *vs.* 1,694.8 days).

When a patient's disease progresses and surpasses regional transplant criteria, an evaluation for downstaging therapy is recommended. Downstaging is the use of neoadjuvant therapy in patients presenting with tumor burden exceeding transplant criteria to reduce their disease to within pre-defined transplant criteria. Up to 25–40% of HCC patients listed for LT belong to a UNOS T3 sub-group and are receiving exception points and downstaging LRT (116). Multiple centers have enriched their transplantable HCC cohort by leveraging LRT to downstage and transplant these patients with comparable results. Yao *et al.* (60) performed an intention to treat study comparing 118 patients outside Milan criteria receiving downstaging LRT to 488 patients with T2 disease on presentation. 64 patients were successfully downstaged and underwent LT. These patients had comparable post-transplant survival and recurrence rates compared to the T2 disease control cohort. The downstaging group had increased risk of dropout with risk factors including AFP >1,000 ng/mL or Child Pugh B or C.

Response to LRT does not just provide oncologic control
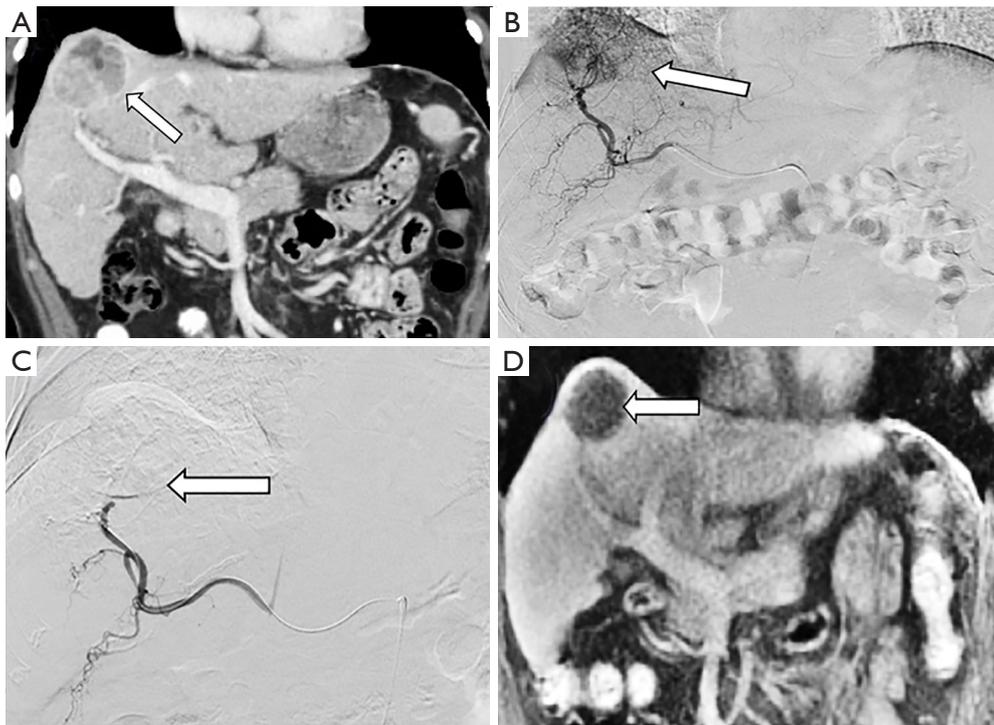
Figure 2 Bridge to transplantation for HCC & HCV cirrhosis with TAE. (A) CT shows an enhancing 4.8 cm segment 8 mass (arrow); (B) selective angiography reveals the hypervascular segment 8 mass (arrow); (C) repeat angiography after embolization with 40 micron microspheres shows no residual tumor enhancement with complete occlusion of the segment 8 branch (arrow); (D) CT scan 1 month after embolization shows decreased size and complete necrosis of the mass (arrow).

to improve dropout but also provides useful information regarding patients' tumor biology. Tumor response to LRT is associated with favorable tumor histology, and a tumor's response to LRT has become a selection tool to inform priority for transplant allocation to improve post-transplant survival and recurrence rates (61,117).

It is important that further research is performed to better evaluate the value of LRT for patients with different degrees of tumor burden and the effects on post-transplant mortality and recurrence. A meta-analysis aimed to evaluate bridging/downstaging LRT for patients with UNOS T1, T2 and T3 disease but was seriously limited given the high degree of selection bias in available studies. There was no significant data to evaluate the utility of LRT in T1 patients (112). Based on three retrospective studies (57,58,118) comparing T2 HCC patients receiving LRT or not, a non-significant reduction in dropout due to progression and all-cause dropout (RR: 0.32, 0.38) was shown in the LRT group.

There was no significant change in recurrence rates or post-transplantation survival. The type of locoregional therapy performed also had no significant impact on bridging success. An analysis of studies comparing downstaged and transplanted T3 patients to T2 patients who were transplanted was also performed and showed similar post-transplantation survival outcomes for both groups.

Palliative intervention for intermediate and advanced stage HCC

Patients with intermediate stage HCC who are not candidates for liver transplantation or resection can benefit from LRT. Embolotherapy has been included in HCC management guidelines since two seminal RCTS (62,63) and multiple meta-analyses (64,65) demonstrated a survival benefit for patients receiving TACE without curative options. A modern multi-institutional study from Asia (66) demonstrated a median survival of 3.1 years for intermediate

stage HCC patients treated with cTACE. Selecting the type of interventional therapy for intermediate HCC patients should be based on local expertise and preferences as there is insufficient evidence to recommend one technique over another.

For example, there is a paucity of data to support the use of chemoembolization over bland embolization. The RCT by Llovet *et al.* (62) was terminated when the survival benefit from TACE compared to supportive care was established. This trials smaller TAE arm also showed a trend towards improved survival but was not adequately powered at this trial endpoint. Additionally, there have been improvements in the selectivity which can be obtained with current microcatheters and in the embolic materials now delivered compared to the temporary gelfoam used in this trial. A meta-analysis of RCTs (67) did not find superiority of one technique over another and a recent RCT (68) compared TAE using modern small microspheres *vs.* DEB-TACE and showed no significant different in radiologic response, adverse events, or overall survival.

There is also insufficient data to support the use of DEB-TACE over cTACE or vice versa. The first RCT (69) comparing cTACE to DEB-TACE in stage B HCC patients (PRECISION V) showed no statistically significant difference between treatment arms. Subgroup analysis did show an improved radiologic response in patients with worse liver function, performance status, and recurrent or bilobar disease. No significant difference was confirmed in multiple follow-up meta-analyses (70,71). A recent retrospective study comparing DEB-TACE and cTACE in intermediate HCC patients challenged the safety of DEB-TACE purporting a higher risk of hepatobiliary complications (119). Regardless of TACE-type, patient selection is paramount. Patients with declining performance status (ECOG 2+) or decompensated cirrhosis are unlikely to benefit from TACE and are at increased risk of further hepatic decompensation.

Two pilot RCTs (72,73) compared radioembolization to chemoembolization in unresectable HCC with progression-free survival as the primary endpoint. Progression-free survival was similar in both studies, however, patients received TARE only once while TACE was performed on a 6-month basis. A larger single center observational cohort (74) compared TARE to TACE in unresectable, non-ablatable early HCC and intermediate stage HCC patients. The primary endpoint was time to progression and was significantly prolonged in TARE with no difference in the number of treatments (TARE 26 months *vs.* TACE 6.8 months). There was also no difference in overall survival

censored to transplant (TARE 18.6 months *vs.* TACE 17.7 months). Salem *et al.* (120) performed a prospective study with 56 patients which showed statistically significant improvements in quality of life factors and a trend for overall better quality of life using FACT-Hep scores. Additionally, a recent meta-analysis (121) showed statistically significant improved overall survival at 2 years but no difference at 1-, 3-, or 4-year. An example TARE case is shown in *Figure 3*.

For advanced stage HCC, BCLC guidelines recommend treatment with sorafenib, however, the role of embolotherapy continues to evolve. TARE has generated increasing interest after the completion of two RCTs (75,76). Both studies were designed to evaluate for superiority of TARE and failed to show significant differences in the primary outcome of overall survival, however, both showed significantly improved tumor response with TARE. Additionally, Chow *et al.* showed significantly improved progression free survival and time to progression in TARE over sorafenib. Vilgrain *et al.* showed significantly increased total and median adverse events in the sorafenib arm. Multiple additional trials are ongoing evaluating TARE head-to-head with sorafenib and also as adjuvant therapy.

TACE has also shown comparable safety and efficacy to sorafenib in patients with advanced stage HCC (77,78). For example, a small retrospective comparative study showed a non-statistically significant increased median survival in advanced stage HCC patients treated with TACE over sorafenib (79). However, RCT's combining TACE and sorafenib for unresectable HCC have yet to demonstrate significantly improved survival outcomes (80,122).

In carefully selected patients, embolotherapy can be used to obtain favorable outcomes in select HCC patients with portal vein thrombosis or macrovascular portal vein invasion. Considering its minimally embolic effect, TARE is the favored embolotherapy in patients with portal vein thrombosis. In an initial phase II study (81) evaluating TARE including 108 patients, 30 had PVT. Patients with lobar PVT in this study had a similar number of adverse events as patients with no PVT or branch PVT. Chemoembolization has also been reported with promising results in patients with macrovascular invasion, however, no controlled studies are available. A prospective study (82) of 164 patients with segmental or sub-segmental portal vein invasion were treated with cTACE or supportive care, based on multidisciplinary tumor board recommendations and patient preferences, and showed markedly improved 1- and 2-yr survival, 30.9%, 9.2%, and 3.8%, 0%, respectively.

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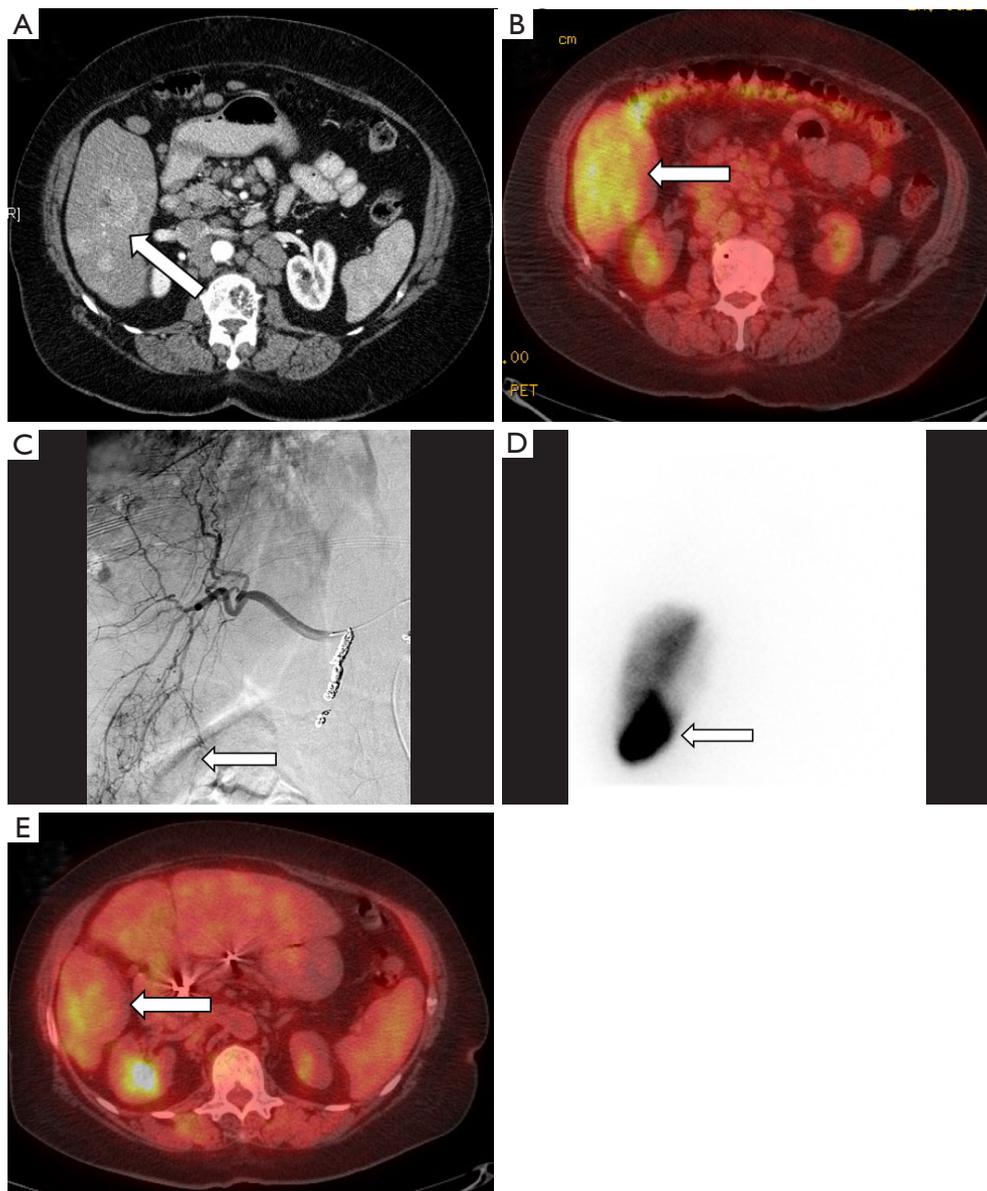
Figure 3 Unresectable right lobe HCC treated with TARE for local tumor control. (A) CT shows infiltrative enhancing tumor throughout the right hepatic lobe (arrow); (B) PET-CT shows tumors are hypermetabolic with marked FDG avidity (arrow); (C) angiography shows ill-defined tumor blush (arrow) in the right posterior lobe. Y90 glass microspheres were delivered through the microcatheter into the right hepatic artery; (D) Y90 Bremsstrahlung SPECT scan shows excellent localization of the therapy to the target tumors (arrow); (E) follow-up PET-CT three months later shows markedly reduced FDG-avidity in the right hepatic lobe after tumor treatment (arrow). HCC, hepatocellular carcinoma; TARE, trans-arterial radioembolization.

Conclusions

Interventional therapy plays an integral role throughout the different disease stages of HCC, beyond formal guidelines. These therapies are generally well tolerated and offer relatively low morbidity therapeutic options for palliation and cure. Ablation, embolization, and a combination of the two are also useful adjuncts to help bridge or downstage patients for surgical resection and liver transplantation. Future studies must aim to best identify which patients will

benefit most from these therapies at different stages, such as minimally invasive curative ablation in very early and early stage disease, as well as, which combinations of therapy can best extend survival in patients with intermediate or advanced disease.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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