

Embolic Locoregional Therapy for the Treatment of Hepatocellular Carcinoma

A general survey of embolization agents, characteristics, data, and applications.

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Hepatocellular carcinoma (HCC) is the fastest-growing cause of cancer-related death in the United States, with more than half a million new diagnoses per year worldwide.¹ Major risk factors for HCC include liver cirrhosis secondary to chronic hepatitis B and C infection, alcohol consumption, and increasingly nonalcoholic steatohepatitis. Transarterial embolization is an integral component of international treatment guidelines, such as the Barcelona Clinic Liver Cancer staging system,² and is a benchmark therapy within the expanding field of interventional oncology. From the initial autologous blood clot injections used in canine models of the previous century to current standard of care applications, embolization has demonstrated exponential clinical and technologic advancement.³ This article provides a survey of embolization for the treatment of HCC for oncologic clinicians.

HISTORY OF HCC EMBOLIZATION

Reports of transarterial chemoembolization (TACE) for HCC began emerging in the 1980s and initially described the transcatheter infusion of mitomycin or doxorubicin mixed with gelatin sponges, an example of what is now referred to as conventional TACE (cTACE).⁴ Embolic agents such as mitomycin-containing microcapsules made out of a water-insoluble ethyl cellulose shell were introduced shortly thereafter.⁵ Developments in embolization led to two subsequent landmark randomized controlled trials (RCTs) in 2002, which demonstrated a survival benefit to cTACE over best supportive care.^{6,7} Interestingly, the bland embolic arm of one trial did not show a survival benefit within the study period, a notion that has since been disputed.⁶ The role for HCC embolization continued to evolve with improvements in clinical experience and microcatheter and angiographic

technology, an understanding of arterial supply as a conduit for therapy, and the accumulation of extensive medical research. In current practice, HCC embolization requires specialty training in interventional radiology and a thorough understanding of interventional oncology to optimize treatment outcomes and promote standardization.

SPECTRUM OF HCC EMBOLIZATION

Bland Embolization

Embolic therapy is exemplified by the delivery of material that occupies the vascular space and exerts an effect on local tissues. This is represented in its most basic form by bland embolization, which treats a tumor by reducing blood supply and associated ischemia-induced necrosis. Bland embolization can be accomplished with various agents, including polyvinyl alcohol, trisacryl gelatin spheres (Embosphere microspheres, Merit Medical Systems, Inc.; Embozene microspheres, Varian Medical Systems), Gelfoam (Pfizer, Inc.), and iodinated sterile poppy seed oil (Lipiodol, Guerbet LLC), with each agent having unique properties and therapeutic advantages. Tumor-supplying vessels are typically 25 to 75 μm ; as such, particles sized 40 to 150 μm have been reported to result in a more distal embolization, which generates more severe ischemia while preserving flow through the parent branch.⁸ Larger particles, such as 500 to 700 μm , may be used when attempting to reduce arteriovenous shunts or when a less ischemic endpoint is desired.

Conventional Chemoembolization

Although an RCT and large retrospective studies have demonstrated similar response rates and overall survival when cTACE is compared with bland embolization, many interventionalists continue to use chemotherapy

given the stand-alone efficacy in numerous phase 3 TACE trials.⁹⁻¹¹ Internationally, cTACE is most commonly performed by mixing Lipiodol with a chemotherapeutic agent to create an emulsion that is retained in the neovasculature, extracellular space, portal venules, sinusoids, and peribiliary plexus of hepatic neoplasms, where it may also cause inflammation and chemical vasculitis.¹²⁻¹⁶ This is frequently followed by infusing an embolic agent until stasis is achieved in the tumor-supplying vessels. Multiple cytotoxic and cytostatic agents have been used individually or in combination, including anthracyclines (eg, doxorubicin, epirubicin), platinum-based agents (eg, cisplatin, oxaliplatin, lobaplatin), and DNA cross-linking antibiotics such as mitomycin C. The use of any one specific agent or combination is largely dependent on institutional and operator preference because there are no high-level data to support a particular drug regimen.

Drug-Eluting Bead/Embolic Chemoembolization

Drug-eluting bead TACE (DEB-TACE), more broadly referred to as drug-eluting embolic chemoembolization, was introduced in 2007 to decrease the toxicity of cTACE and enable a more sustained drug delivery after embolization. DEB-TACE particles elute chemotherapy over several weeks by diffusing up to 600 μm into adjacent tissue.¹⁷ This local deposition theoretically offers a 400% increase in tumor drug deposition while decreasing systemic drug levels when compared with cTACE.^{18,19} Multiple drug-eluting embolics are available, including DC/LC Beads (Boston Scientific Corporation), LifePearl (Terumo Europe), HepaSphere (Merit Medical Systems, Inc.), and Oncozene (Varian Medical Systems), and each have unique properties reported by the manufacturers. For example, LC Bead LUMI (Boston Scientific Corporation) has a covalently bonded iodine that improves radiopacity during embolization. Similar to bland embolization, studies have demonstrated that drug-eluting embolic particles of 100–300 μm are associated with increased survival, lower complications, and may have higher response rates compared to 300–500 μm and 500–700 μm particles.^{20,21} Additional particle properties, such as deformability and swell size, have not been as rigorously tested to clearly demonstrate treatment impact. Although initial studies suggested that DEB-TACE increased response in patients with more advanced disease with reduced toxicity when compared to cTACE, a meta-analysis of four RCTs and eight observational studies failed to support these findings.^{22,23}

Transarterial Ethanol Embolization

Embolization with cTACE and DEB-TACE frequently generates incomplete vascular occlusion with subsequent sublethal ischemic penumbra within the tumor. This is

the fundamental principle that prevents both therapies from offering reliable curative outcomes. Tumor progression is common secondary to reperfusion via vasogenic hormones, such as vascular endothelial growth factor (VEGF), and the promotion of aggressive biology by hypoxia-driven tumor gene expression.^{24,25} Agents with trans-sinusoidal deposition and chemical ablative properties, such as transarterial ethanol (TAE), have been suggested to improve on the inherent limitation of ischemic therapy alone. TAE is delivered in a wedged, superselective manner as a Lipiodol/ethanol mixture that infiltrates arterioles, sinusoidal spaces, peribiliary plexus, and tumor cells (Figure 1). Ethanol permeates adjacent tissues, resulting in cellular destruction irrespective of oxygen tension. This reproduces the fundamental mechanism of percutaneous ethanol injection, which has been considered curative for small HCCs. Pathologic outcomes of TAE have shown the formation of extensive coagulative necrosis and complete pathologic necrosis rates as high as 75%.²⁶ Several studies, including one RCT, have demonstrated improved radiographic response, time to progression (TTP), and pathologic necrosis compared with cTACE.²⁶⁻²⁸

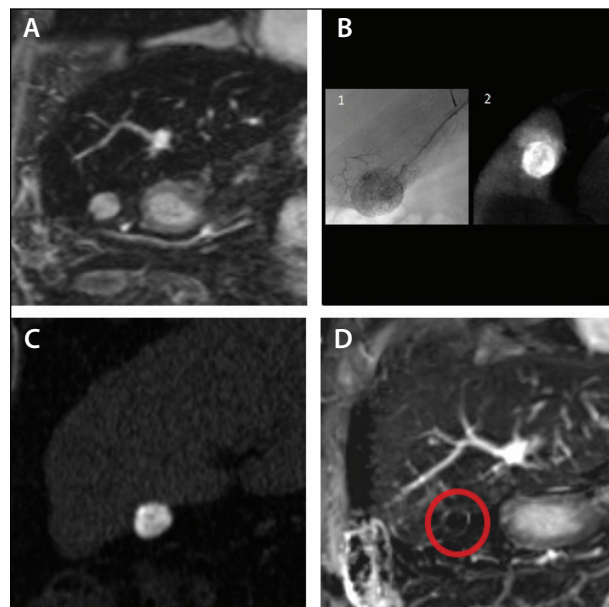


Figure 1. Contrast-enhanced MRI demonstrating a 1.8-cm hypervascular HCC in segment 4B (A). Wedged superselective TAE embolization was performed with coverage of the lesion and at-risk margin demonstrated by posttreatment fluoroscopy (1) and noncontrast cone-beam CT (2) (B). CT performed 214 days after treatment demonstrated retained Lipiodol within the lesion (C). Follow-up contrast-enhanced subtraction MRI 241 days after treatment demonstrated complete response, as assessed by modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria (red circle) (D).

Radioembolization

Transarterial radioembolization, also known as TARE, is the intra-arterial injection of yttrium-90 (Y-90)-containing microspheres that emit β particle radiation, which penetrate adjacent liver tissue with a range of 2 to 11 mm. This results in high-dose radiation, which in turn generates localized cell death through double-stranded DNA breaks and apoptosis, as opposed to ischemia. Currently, the two FDA-approved radioembolization products include glass microspheres (TheraSphere, Boston Scientific Corporation), which has a humanitarian device exemption for unresectable HCC, and resin microspheres (SIR-Spheres, Sirtex Medical Inc.), approved for unresectable colorectal cancer metastases with adjuvant intrahepatic artery floxuridine. Glass microspheres are composed of Y-90-containing aluminum and silicon dioxide glass and have greater specific activity (approximately 2,500 Bq) at calibration. Resin microspheres are made of a biocompatible resin with Y-90 bonded to the surface and have less specific activity (approximately 50 Bq) when compared with glass microspheres.

From the first reports of vascular brachytherapy for the treatment of liver malignancy in the early 1960s and iodine-131-containing Lipiodol to the current practice of personalized dosimetry, radioembolization has evolved into a versatile and indispensable therapy for the management of HCC.^{29,30} Benefits of radioembolization include the ability to ablate large volumes of tissue, such as devitalizing an entire lobe as a neoadjuvant to resection (known as a radiation lobectomy), treating tumor thrombus and infiltrative tumors requiring larger margins, and providing definitive ablative radiation to small HCCs (known as radiation segmentectomy) (Figure 2).³¹⁻³³ As opposed to external beam radiation therapy, repeat radioembolization treatments are not limited by the constraints of entry dose. Response to radioembolization is dose-dependent with a tumor partition threshold dose of 205 Gy or > 190 Gy for segmentectomy using the medical internal radiation dose model, or MIRD.^{32,34,35}

Retrospective studies of radiation segmentectomy have shown response and pathologic necrosis rates that may be akin to thermal ablation.³⁶ Although phase 3 data for locally advanced HCC did not show superiority over sorafenib using resin microspheres with body surface area dosimetry, long-term, single-center data have demonstrated outcomes comparable to established curative treatments for early stage disease in select patients.^{36,37} A recent phase 2 RCT abstract describing personalized dosimetry to achieve a threshold tumor dose of at least 205 Gy showed improved response and overall survival when compared to infusions of 120 (\pm 20) Gy and may explain the negative results of trials using nontailored dosimetry.³⁸ A phase 2

RCT comparing radioembolization to cTACE met its primary endpoint of superior TTP in favor of radioembolization (6.8 vs > 26 months).³⁹

Emerging Embolic Agents

As embolization has secured an indispensable role for the treatment of HCC, so has the interest in utilizing arterial supply as a means of therapeutic leverage for other agents. Preclinical models have utilized Lipiodol as a vector for sorafenib, viruses, naked DNA, Lipofectamine (Invitrogen) supplemented VEGF small interfering RNA, doxorubicin-loaded supramagnetic iron oxide nanoparticles, tumor necrosis factor, and antitumoral antibiotics such as lidamycin.¹⁵ Novel embolization agents have also been validated in clinical practice, such as iodine-131-labeled metuximab combined with cTACE, which demonstrated increased 1-year survival and TTP compared with cTACE alone.⁴⁰ Transarterially infused dendritic cells stimulated with *Streptococcus pyogenes* after TAE demonstrated prolonged recurrence-free survival compared with TAE alone.⁴¹ Intra-arterial infusion of rhenium-188 Lipiodol has demonstrated safety, efficacy, and cost-effect-

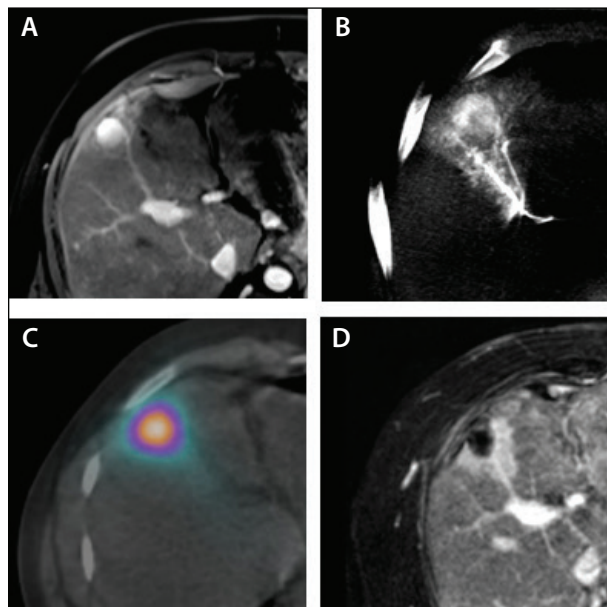


Figure 2. Contrast-enhanced MRI demonstrated a 2-cm hypervascular HCC abutting the gallbladder in a pretransplant patient (A). Contrast-enhanced cone-beam CT demonstrated a subsegmental angiosome encompassing the tumor and at-risk margin (B). Bremsstrahlung single-photon emission CT (SPECT)/CT demonstrated deposition of Y-90 within the target lesion and the margin (C). Contrast-enhanced MRI 96 days after treatment demonstrated mRECIST complete response (D). The patient underwent liver transplant 184 days after treatment with complete pathologic necrosis of the tumor in the explant.

tiveness in the treatment of HCC, and degradable starch microspheres have been combined with chemotherapy and Lipiodol in an effort to decrease postembolization syndrome.^{42,43} There are currently multiple ongoing clinical trials evaluating the intra-arterial injection of oncolytic viruses, chimeric antigen receptor T-cells, and lipid nanoparticles.⁴⁴ The intra-arterial infusion of mesenchymal stem cells with TACE demonstrated improved liver function when compared with TACE alone. Genetically modified stem cells expressing glypican-3 can redirect T-cells to glypican expressing HCC, resulting in antitumor activity, which may be another embolization strategy in the future.^{45,46}

Pressure-Assisted Embolization

Improvements in catheter technology have also contributed to progress in the field of HCC embolization. Pressurized delivery microcatheters have an expandable cone-shaped or compliant balloon occlusion tip, which minimizes reflux and allows for perfusion above interstitial

pressure. Pressurized delivery has been adopted for both TACE and Y-90 in addition to being used for the truncation of distal treatment angiosomes to reduce nontarget liver exposure during proximal infusions (Figure 3).⁴⁷⁻⁵¹ Balloon occlusion has been shown to be an independent factor for improved overall survival, radiographic tumor response, and increased drug concentrations within the targeted tumor during TACE.⁵²⁻⁵⁵ However, balloon occlusion can also result in overtreatment due to ischemia of both arterial and portal supply within large-volume embolizations and may decrease tumor conspicuity in certain instances.⁵⁶⁻⁵⁸ Pressure-assisted catheters are a valuable adjunctive tool during embolization but require an understanding of their potential hazards prior to use.⁵⁸⁻⁶⁰

GENERAL APPROACH TO HCC EMBOLIZATION

Successful HCC embolization requires appropriate patient selection, consideration of the oncologic intent, and knowledge of performance status, hepatic substrate, and both tumor biology and stage. The operator should have detailed knowledge of hepatic arterial anatomy, anatomic variations, and tumor neovascularization to correctly generate a care plan for the targeted HCC and margin. Selective treatment and use of cone-beam CT is associated with improved outcomes and should always be performed when possible.⁶¹⁻⁶³ When using bland or chemoembolic agents, a wedged position of the microcatheter as close to the tumor as possible is preferable to best saturate the tumor vasculature and overcome small collaterals, which may not be visible angiographically. The use of radioembolization necessitates experience with radiation activity and the effects of vascular and particle dynamics on dose distribution. The authors' institutional approach to radioembolization is detailed in a review article by Toskich and Liu.⁶⁴ Given the heterogeneity of HCC presentation, the interventionalist should be well versed with multiple embolization techniques, as operator experience has been shown to affect locoregional therapy success.^{65,66}

CONCLUSION

Modern-day embolization has grown substantially since its inception and forever changed the field of HCC treatment. Embolization has improved survival for HCC, which was previously a devastating diagnosis for many patients. There are plentiful embolization options, each with distinct characteristics and advantages that allow for individualized therapy of a very heterogeneous disease process. As novel agents are developed to adopt the benefits of transarterial delivery, embolization will likely continue to serve a major role in HCC locoregional therapy. ■

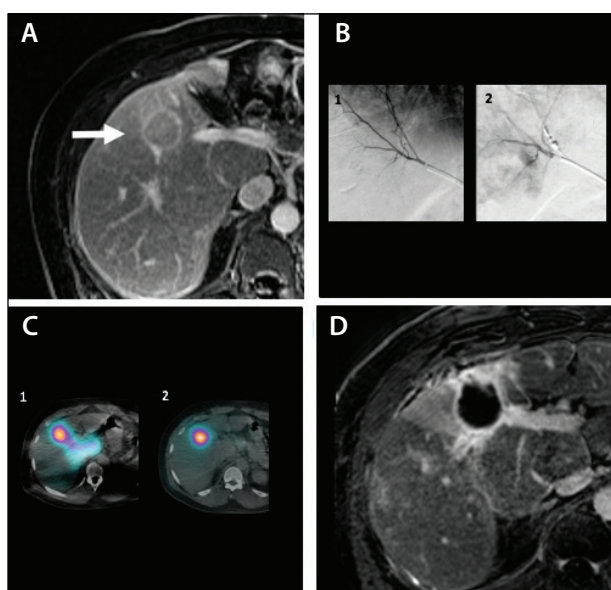


Figure 3. Contrast-enhanced MRI demonstrated a segment 5 HCC with washout (A, white arrow). Due to multiple small arterial feeders, selective delivery into the tumor was not possible and central delivery would unnecessarily treat uninvolved normal liver. Angiography before (1) and after (2) balloon occlusion and gelfoam embolization of the segment 8 and 1 arteries demonstrated improved preferential flow into the tumor and decreased flow into nontarget liver parenchyma (B). Bremsstrahlung SPECT/CT fusion before (1) and after (2) angiosome modulation demonstrated improved tumor dose conformality and sparing of normal liver (C). Contrast-enhanced MRI 125 days after treatment demonstrated mRECIST complete response (D).

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