

Interventional radiology therapies for liver cancer

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ABSTRACT

Hepatocellular carcinoma (HCC) is the fifth most frequently found primary malignant tumor in the world. Hepatic surgery and liver transplantation are considered optimal for the curative treatment of HCC. However, only 15-20% of HCCs may be surgically treated. Most of the surgically-non-eligible patients have to receive locoregional image-guided interventional treatments including intra-arterial and percutaneous ablative therapies. The goal of this paper is to review these interventional oncology approaches. Ablative therapeutic approaches include chemical therapies (such as ethanol or acetic acid injection), and thermal therapies (such as radiofrequency ablation, laser-induced thermotherapy, microwave ablation, cryoablation, and high-intensity focused ultrasound ablation). Catheter-based therapies include embolotherapy/chemotherapy-based treatments (such as transcatheter arterial chemoembolization, bland embolization, transcatheter arterial chemoinfusion, and chemoembolization with drug-eluting beads), and radiotherapy-based treatments (such as radioembolization with yttrium-90 and injection of iodine-131-labeled lipiodol). As a result of the technical development of locoregional approaches for HCC during the recent decades, the range of combined interventional therapies has been continuously extended. In this article, an evidence-based approach will be used to review the current role of interventional radiology therapies in the management of unresectable HCC.

Key words: Hepatocellular carcinoma; local ablative therapy; radioembolization; transarterial chemoembolization

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INTRODUCTION


Hepatocellular carcinoma (HCC) ranks the fifth in overall frequency and fourth in annual tumor mortality.^[1] Surgical treatments including hepatic resection and liver transplantation are considered the most effective treatments of HCC. However, less than 20% of HCC can be treated surgically because of multifocal diseases, proximity of the tumor to key vascular or biliary strictures precluding a margin-negative resection and inadequate functional hepatic reserve with cirrhosis.^[2-4] Usually,

patients with single small HCC (≤ 5 cm) or up to three lesions ≤ 3 cm are indicated for surgery.^[5,6] When surgery is precluded, interventional treatments can be used to improve the prognosis of the patients. Such therapies, which rely on imaging guidance for tumor targeting and response assessment, include various catheter-based and percutaneous ablative techniques. These minimally invasive therapies have been used mainly for palliation but have also increasingly been used with curative intent.

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This review outlines the current status of the most commonly used image-guided therapeutic approaches for the management of patients with HCC.

INTRA-ARTERIAL CATHETER-BASED THERAPIES

Embolotherapy/chemotherapy-based therapies

Transarterial chemoembolization

The radiological technique for tumor devascularization was developed in the 1970s.^[7] Now, it is the most widely used primary treatment for unresectable HCC. It is also the most extensively used therapy for patients on the waiting list for liver transplantation. Embolization agents, like gelatin, may be administered together with selective intra-arterial chemotherapy mixed with lipiodol (iodized oil). Doxorubicin, mitomycin, and cisplatin are commonly used anti-tumor drugs.^[8] The rationale of transarterial chemoembolization (TACE) is as follows: cytotoxic drugs achieve higher intra-tumoral concentrations when injected in the hepatic artery, and lipophilic or amphiphilic anticancer drugs, when mixed with lipiodol, are thought to be liberated progressively inside the tumor. Lipiodol, which destroys capillary beds and induces extensive necrosis in HCC with abundant blood supply, can be transported in a tumor and may remain for weeks or months, for which the absence of Kupffer cells would presumably be responsible.

Usually, lesions that are rich in arterial blood supply can be anticipated to undergo complete necrosis, while those that lack arterial blood supply have less iodine oil deposits and need other combinative therapies. The whole procedure can be repeated monthly or longer to achieve higher degree necrosis and avoid recurrence. However, the injection of cytotoxic drugs mixed with lipiodol but not followed by embolization has not shown any substantial anti-tumor effect, suggesting that ischemia plays a key role in tumor necrosis.^[9] Still, some authors reported that transcatheter arterial infusion chemotherapy had a better anti-tumor effect than TACE.^[10] With respect to the relationship between TACE and pulmonary metastasis, Lin *et al.*^[11] reported that TACE did not significantly increase the risk of pulmonary metastasis. Post-embolization syndrome including abdominal pain and fever is extremely frequent and fades in a few days. Complications related to aberrant arterial embolization, such as acute cholecystitis, stenosis of the biliary tract, acute pancreatitis, or gastroduodenal ulcerations have also been reported. The selection of candidates for TACE is a key point. The benefits of the procedure should not be offset by treatment-reduced liver function failure. Patients with preserved liver function and asymptomatic multinodular tumors without vascular invasion or extra-hepatic spread are indicated for TACE.^[8] Child-Pugh class C is considered a contraindication.^[12]

TACE achieves partial responses in 15-55% of patients and significantly delays tumor progression and vascular invasion.^[8,12-14] For HCC invading the portal venous system, TACE could be an effective treatment with the 1-, 3-, and 5-year survival rates of 42%, 11%, and 3%, respectively.^[15] Although an earlier study showed that TACE could not improve the survival of the patients,^[12] survival benefits were identified by two studies on chemoembolization.^[13,14] Overall, the effect may be considered modest.

Arterial bland embolization

Transcatheter arterial bland embolization, which simulates arterial ligation, induces tumor ischemia by disrupting the blood supply to the tumor. Advocates of this catheter-based therapy claim that bland embolization may be equally effective as TACE for palliative treatment of primary liver cancer.^[16] Despite a trend toward improved survival with TACE, no study to date has demonstrated a difference in survival between the two techniques.^[17] A randomized trial comparing embolization (without chemotherapy) vs. symptomatic treatment in patients with hepatitis C virus-related liver disease and Child-Pugh class A liver function failed to demonstrate a 2-year survival advantage.^[18]

Drug-eluting bead chemoembolization

Drug-eluting bead (DEB)-TACE is a drug delivery system that combines the local embolization of vasculature with the release of chemotherapy into adjacent tissue.^[19,20] It is intended for use in the treatment of hyper-vascular tumors such as HCC. Its administration is similar to that of conventional TACE. Beads are composed of biocompatible polymers such as polyvinyl alcohol (PVA) hydrogel that have been sulfonated to enable the binding of chemotherapy.^[21] The beads occlude vasculature, causing embolization, and the chemotherapy is delivered locally.^[22,23]

Like conventional TACE, DEB-TACE is considered a palliative option for unresectable HCC. DEB-TACE may also use as an adjunctive therapy for liver resection or as a bridge to liver transplantation, as well as before or after radiofrequency ablation (RFA).^[24-28] There are currently two types of microspheres available for drug loading: DC Bead microspheres (Biocompatibles, UK) and the recently introduced superabsorbent polymer (SAP) HepaSphere microspheres (BioSphere Medical, USA). Most of the literature involves the application of DC Bead microspheres. These microspheres are non-biodegradable PVA microspheres that are approved for the treatment of malignant hyper-vascular tumors and loading of doxorubicin. Precision Bead (Biocompatibles, UK) microspheres are the first factory-preloaded (doxorubicin 37.5 mg/vial) microspheres. They can be polymerized to formulate different-sized spheres,

ranging in maximum diameter from 100 to 900 μm . SAP HepaSphere microspheres (BioSphere Medical) are biocompatible, hydrophilic (absorbent), non-resorbable, and acrylic copolymer microspheres designed for hepatic arterial embolization with an ability to absorb fluids at up to 64 times their dry state volume. The expansion rate is dependent on the ionic concentration of its surrounding media. The size of dry particles ranges between 50 and 200 μm , corresponding to an expanded size range of 200 and 800 μm . The SAP microspheres can be loaded with doxorubicin or cisplatin for drug delivery during TACE.^[29] Initial *in vitro* and *in vivo* studies showed encouraging results, and these microspheres now have CE mark approval for TACE of HCC in combination with doxorubicin.

DEB-TACE appears to be a relatively safe procedure, with few long-term serious complications associated with its administration. Although symptoms of post-embolization syndromes, such as fever, nausea, vomiting, and abdominal pain appears to occur in most patients, these symptoms are associated with short hospital stays averaging 2.3 days among publications, which is significantly lower than conventional TACE procedures. The most frequent major complication associated with this procedure is liver abscess, which occurred in approximately 0.75-1.58% of publications. Other complications are infrequent, although some are quite severe. Overall mortality is potentially lower than the reported values (2.06-4.74%) because reported mortality rates include both procedure-related causes of death, such as sepsis and hepatic failure, and death secondary to progressive disease, cardiovascular disease, pulmonary embolism, and other causes. Patients selected for most of these studies are predisposed to comorbidities as a result of their diminished hepatic function and potentially other age or lifestyle-related conditions, which should be taken into consideration.^[30]

The current results show that DEB-TACE produces beneficial tumor response and has exceptionally low complication rates. The technique has the potential to become an effective alternative therapy or palliative measure in the treatment of HCC, but both delivery and data collection must be standardized in order to clarify efficacy. It is a safe alternative for the treatment of unresectable HCC but is unproven as an adjunctive treatment for other standard therapies such as resection and RFA. Further investigation is essential to better define its role as an adjunct in treating HCC.

Transcatheter arterial chemoinfusion

Transcatheter arterial chemoinfusion (TACI) is a catheter-based intra-arterial therapy that traps high concentrations of chemotherapeutic agents in tumor tissues followed by

minimal embolization.^[31] TACI with maximally selective catheterization and highly concentrated chemotherapy preparations minimizes the risk of hepatocellular ischemic and cytotoxic complications and maximizes chemotherapy delivered to tumor tissue. TACI with super selective catheterization, although labor intensive, has been shown to be safe. The eligibility criteria for TACI are similar to those for TACE. Portal venous thrombosis is not a contraindication. Caution should be exercised to avoid injecting large volumes (> 10 mL) of lipiodol. Moreover, patients with poor hepatic function and tumors with diameters of > 9 cm have a high risk of irreversible hepatic failure. A recent retrospective study by Kim *et al.*^[32] compared clinical outcomes of patients treated with TACE ($n = 49$) vs. TACI ($n = 61$) in HCC patients with major portal vein occlusion. The morbidity rate was similar for both TACE (6.1%) and TACI (6.5%) patients, and complications were adequately managed by medical treatment. Median survival for TACE was longer than for TACI (14.9 vs. 4.4 months, respectively, $P < 0.001$).

Radiotherapy-based therapies

Yttrium-90 radioembolization

Transarterial radioembolization (TARE) with intra-arterial injection of yttrium-90 microspheres (Y-90) is another form of hepatic arterial therapy that is available as glass (TheraSpheres; Theragenics Corp., Ottawa, Canada) or resin (Sirtex; Sirtex Medical, Wilmington, MA, USA) and can be delivered to single or multiple segments based on selective arterial cannulation. Its small size (20-60 μm) results in preferential trapping in the tumor capillary bed. These spheres can safely deliver up to 150 Gy of β radiation to induce tumor necrosis by radiation and microscopic embolization once they obstruct the tumor capillary bed. This limits radiation exposure to adjacent healthy tissue, given its half-life of 62 h and radius of action of up to 1 cm.^[33] Patient selection requires pre-treatment procedures, including an angiogram to perform prophylactic embolization in which variant anatomy is identified to avoid non-target delivery of Y-90, and a macro-aggregated albumin scan to confirm that hepatic artery-to-lung shunting is $< 16\%$ to prevent lung injury.^[34] An advantage of this treatment over TACE is its applicability in patients with portal vein thrombosis and potential complications caused by non-target delivery of Y-90 include gastrointestinal ulcerations, pancreatitis, pneumonitis, and cholecystitis.^[35] Salem *et al.*^[36] recently published a comprehensive study on the long-term outcomes after intra-arterial radiotherapy for unresectable HCC. In this study, 291 patients with HCC were treated with Y-90 as part of a single-center, prospective, longitudinal cohort study. Response rate and time to progression were determined by the World Health Organization (WHO) and

of control of large tumors. The effectiveness of RFA depends on thermal necrosis and blood flow through the tumor promotes heat loss and prevents proper heating of the tumor. A strategy of combining TACE with RFA by performing TACE before RFA treatment to reduce the heat-sink effect and increase the ablation volume of the tumor was recently evaluated in a randomized study.^[74] In this study, patients with tumors larger than 3 cm were randomized to TACE, RFA, and TACE-RFA. The combination modality was superior in median survival (TACE-RFA at 37 months, TACE at 24 months vs. RFA at 22 months) and rate of objective tumor response (TACE-RFA at 54%, TACE at 35% vs. RFA at 36%). The positive findings in this study represent initial evidence in support for the use of combining local regional modalities to improve outcomes in patients with unresectable tumors. Despite aggressive local treatments with this combinational strategy, recurrence, and distant metastasis continue to have a significant effect on the overall survival of patients with HCC. Therefore, studies that combine effective systemic treatment such as sorafenib with either TACE or RFA have the potential of further improving treatment outcomes. Although the combination of RFA and TACE is most commonly used, TACE has also been combined with interstitial laser photocoagulation, microwave coagulation, ethanol injection, or HIFU.^[73,75,76] On the other hand, the combination of TACE and immunotherapy or anti-angiogenesis therapy could also be an attractive field for future clinical application.

CONCLUSION

Image-guided transcatheter and ablative approaches currently play an important role in the management of patients with HCC, a role that is likely to grow even more given the rapid pace of evolution in these technologies. In selected patient populations, these approaches already offer survival rates that are comparable to that of surgery, with the added benefits of reduced morbidity and costs, improved quality of life and shortened recovery time. As the management of patients with HCC continues to evolve toward disease containment rather than a cure and locoregional targeted therapy rather than systemic approaches, image-guided techniques pose as perfectly suited methods for this direction. Results from clinical trials involving such approaches are increasingly promising, and the potential for improvement remains vast. As a result, these therapeutic approaches will undoubtedly positively impact the outcomes of patients with HCC.

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Conflicts of interest

There are no conflicts of interest.

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