cTACE: The Rebirth of Lipiodol?

Lipiodol-based cTACE remains the most well-studied transarterial therapy for hepatocellular carcinoma.

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Primary liver cancers are the sixth most common malignancy worldwide, with hepatocellular carcinoma (HCC) accounting for approximately 80% of primary liver cancers.[1] An estimated 700,000 new cases of HCC are diagnosed worldwide each year, with more than 600,000 deaths attributed to HCC.[2] The prevalence of HCC in the United States has more than tripled since the 1980s, with a current incidence rate of approximately 6 per 100,000.[3]

Several evidence-based algorithms have been created to manage patients with HCC, taking into account factors such as Child-Pugh score, number of tumors, tumor size, and vascular invasion. In the United States and Europe, the Barcelona Clinic Liver Cancer (BCLC) classification, which includes many of these criteria, is widely used.[4] Current treatments are categorized as curative or palliative, with the three potentially curative options being tumor resection, liver transplantation, or radiofrequency ablation. By the time of diagnosis, fewer than 30% of patients qualify for resection or transplant due to the multiplicity of lesions, background chronic liver disease, and other comorbidities.[5] For patients with unresectable HCC, adjuvant therapies such as transarterial chemoembolization (TACE) can play an important role.

Conventional TACE (cTACE) involves transcatheter arterial administration of one or several cytotoxic drugs mixed with Lipiodol (Guerbet LLC), which may or may not be followed by transient embolization of the tumor-feeding vessels with particulate embolic agents such as gelatin sponge and polyvinyl alcohol (PVA) particles. The rationale for the use of TACE for HCC is to target the blood supply of the liver tumor; healthy liver parenchyma receives three-quarters of its blood supply from the portal vein, whereas liver tumors have preferential blood supply, derived nearly exclusively from the hepatic artery.[6]

This article's title is actually a misnomer. Lipiodol has been in use since the early 1900s and was first used with TACE in the 1980s. cTACE with Lipiodol is still the standard of care for HCC throughout Asia and parts of Europe, as well as in many centers in the United States where it is widely used for BCLC stage B HCC. TACE with Lipiodol has been acknowledged in national guidelines by the Society of Interventional Radiology and is currently the gold standard for comparative studies involving various chemoembolization treatments for HCC, including drug-eluting bead transarterial chemoembolization (DEB-TACE), transarterial radioembolization (TARE) with yttrium-90 (Y-90), and bland transarterial embolization (TAE).[7]

EVOLUTION OF cTACE USING LIPIODOL

Lipiodol is a pale yellow/amber-colored, oil-based, radiopaque contrast agent consisting of iodine that is organically combined with ethyl esters of fatty acids of poppy seed oil. Lipiodol was first synthesized in 1901 by French pharmacist Marcel Guerbet.[8] The radiopaque properties were later discovered in 1921 by French radiologist Jean-Athanase Sicard.[9] Prior to the use of Lipiodol for TACE, its applications were vast and included myelography, bronchography, hysterosalpingography, lymphography, urethrography, and cystography.[6] The use of Lipiodol for chemoembolization of HCC as used today was first popularized by Japanese physician Toshimitsu Konno and colleagues during the 1980s.[10]

TACE with Lipiodol has been performed since the 1980s due to its unique properties, including its radiopacity, tumor-seeking ability, prolonged deposition within tumors, transient embolization, and its ability to deliver the cytotoxic drug (Figure 1). Two randomized trials demonstrated significant survival benefits for patients with unresectable HCC undergoing TACE, which led to its use

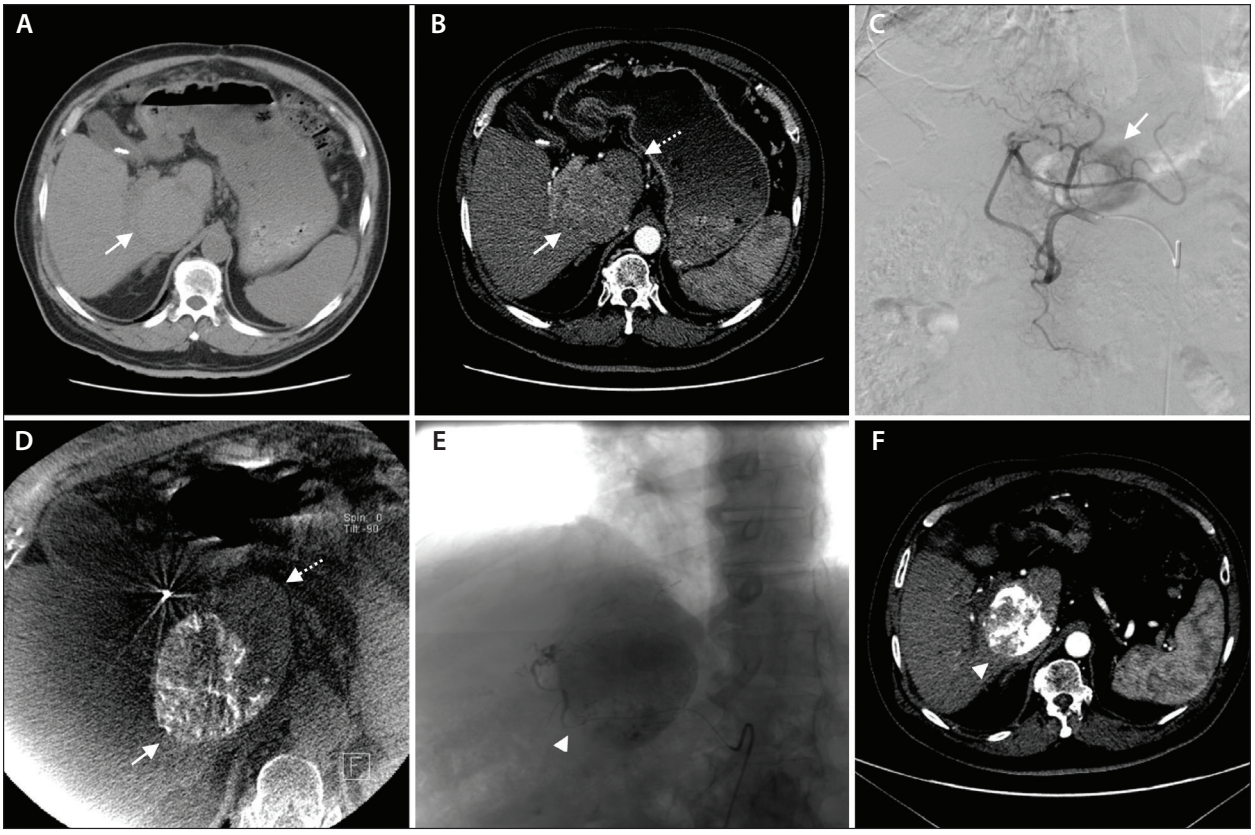

Figure 1. Preprocedural noncontrast (A) and contrast-enhanced (B) axial CT showing a partially enhancing lesion within the caudate lobe (solid white arrows). The nonenhancing hypodense anterior portion of the lesion is likely infarcted (dotted white arrow) (B). Selected celiac artery angiography demonstrates standard celiac anatomy with patent left gastric, splenic, and common hepatic arteries (C). Note the possible right hepatic lobe branches, secondary to the known replaced right hepatic artery. Tumor blush can be visualized, which corresponds to the caudate lobe lesion. Additionally, a cone-beam CT performed with the catheter positioned in the branch that appears to feed the caudate lobe confirms contrast filling the targeted caudate lobe lesion (solid white arrow) (D). The infarcted anterior portion of the lesion is again visualized (dotted white arrow) (D). A total of 20 mL of chemoembolic agent including doxorubicin, mitomycin, and Lipiodol is injected, followed by small aliquots of 100–300-µm Embosphere microspheres. The final angiogram demonstrates appropriate stasis with no further tumor blush seen. Lipiodol uptake in the tumor is present (arrowhead) (E). Follow-up CT at 1 week demonstrates Lipiodol deposition within the targeted caudate lobe lesion (arrowhead) (F).

as the standard of care.[11,12] Because of its radiopaque properties, Lipiodol-based TACE gives the operator the ability to visualize the delivery of the cytotoxic drug to the tumor in real-time through fluoroscopy. This not only allows for safe administration, but also provides visualization of tumor labeling on posttreatment CT.[13] Lipiodol has been used with TACE for decades, and its ability to seek and uptake within HCC has been widely documented and provides a basis for its use in TACE.

Mechanism of Action

The mechanisms for Lipiodol uptake within the tumor cells remain uncertain. Lipiodol is reported to have preferential flow to larger-diameter arterial branches at each bifurcation.[14] This is important because the highly vascular nature of HCC may give Lipiodol an increased selectivity for the tumor compared to background liver. There is increased uptake of Lipiodol by the tumor and endothelial cells of HCC, and the mechanism is thought to be secondary to a tumor cell membrane pump that absorbs the Lipiodol.[15,16] After intrahepatic arterial injection of Lipiodol, it passes through the terminal portal venules and into the sinusoids. The accumulation of Lipiodol produces sinusoidal congestion (dual arterial and portal transient embolization), which leads to adjacent inflammation and cell death. This effect is temporary, as passage of Lipiodol from the

sinusoids into the hepatic veins has been reported, but this still provides prolonged uptake within HCC.[9,17]

Another hypothesis is that the decreased prevalence of Kupffer cells within HCC prevents the breakdown of the iodinated lipid. This is based on changes seen in Kupffer cells after the administration of an iodinated lipid emulsion, suggesting activation of macrophages.[18] It has been reported that the long-term deposition of Lipiodol within tumor cells and accumulated macrophages surrounding the Lipiodol gradually decreased in HCC over time.[16] In this way, the macrophages and lymphatic system contribute to the clearance of Lipiodol.[19] Lack of a normal lymphatic system in HCC may contribute to the prolonged deposition of Lipiodol within tumor cells.

Cytotoxic Drug Delivery System

The goal of TACE is to provide local delivery of a cytotoxic drug while minimizing systemic toxicity and reducing drug concentrations in nontumor cells. Lipiodol has been the radiopaque oil of choice to carry cytotoxic drugs, and the mixture with various cytotoxic drugs has been shown to produce better pharmacokinetics, greater necrosis, and better long-term overall survival.[9] The majority of cytotoxic drugs are more soluble in water than Lipiodol, so emulsions are generally used. Depending on the volume of each liquid, oil in water (O/W: oil droplets dispersed in water) and water in oil (W/O: water droplets dispersed in oil) can be created. A standardized formula or technique for the combination of Lipiodol with the various cytotoxic drugs does not exist.[20] Variables such as specific cytotoxic drug used, the type of emulsions (O/W or W/O), as well as droplet sizes can potentially alter the effectiveness of TACE.

Various cytotoxic drugs have been used with TACE, including doxorubicin, cisplatin, mitomycin, epirubicin, streptozotocin, and idarubicin. A study by de Baere et al compared different Lipiodol and doxorubicin emulsions (small 10–40-µm and large 30–120-µm droplet W/O and O/W). The poorest embolic effect was noted with small droplets of O/W, while W/O emulsions achieved the greatest embolic effect.[14] A second study further demonstrated W/O emulsions were retained better in tumor cells than O/W emulsions.[21] A study in rats by Kan et al demonstrated that W/O emulsions have higher doxorubicin-carrying capacity as well as longer release times than O/W emulsions.[22] Although W/O emulsions may be superior to O/W, the many parameters involved in producing these emulsions, such as the water and Lipiodol volume ratio, pressure exerted on the liquids during preparation, the number of times the emulsions are mixed, and the effects the various cytotoxic drugs have on the emulsions, may not be consistently reproducible even if a standardized formula existed.

Many cytotoxic drugs can be used during TACE, either as a single drug or a combination of two or more. The most common group of anticancer drugs for single use is the anthracycline group, which includes doxorubicin and epirubicin. No consensus for a standardized concentration for any of these drugs exists, and concentrations are often operator/center dependent. Doxorubicin is often cited in the rate of 30 to 100 mg, while cisplatin ranges from 50 to 100 mg.[23] During an online questionnaire in August and September 2010, Society of Interventional Radiology members most commonly reported a chemotherapeutic regimen consisting of cisplatin (100 mg), doxorubicin (50 mg), and mitomycin C (10 mg) emulsified in Lipiodol (10 mL).[24] Which single or combination of cytotoxic drug should be used and the amount of each remains an active discussion. Cohort studies have demonstrated greater effectiveness of cisplatin over doxorubicin, while at least one other study did not demonstrate a difference when comparing cisplatin and epirubicin.[25,26] More recently, combined trials with systemic sorafenib and TACE have been performed with controversial results. A systematic review concluded that this combined therapy may be beneficial to patients with unresectable HCC in terms of time to progression but not in overall survival.[27] Further studies are needed before a consensus can be obtained; which parameters are the most effective and how best to utilize them will continue to be topics of discussion.

Superselective Therapy and C-Arm Cone-Beam CT

Cone-beam CT (CBCT) can provide useful information during cTACE, including improved three-dimensional road mapping of small feeding arteries. It can provide the anatomic detail necessary for superselective catheterization into more distal arterial tumor branches (Figure 1), which may improve the overall efficacy and safety of chemoembolization and suggests that routine use should be considered to best optimize patient care.[28,29] A retrospective Japanese study found that the use of C-arm CBCT during TACE provided accurate information that positively affected treatment by improving local progression-free and overall survival in patients with unresectable HCC.[30] Another study performed at Stanford University compared the short-term safety and efficacy of cTACE and DEB-TACE during superselective C-arm CBCT and found them to be equivalent.[31] The group further suggested that the continued use of meticulous superselective TACE using C-arm CBCT can increase therapeutic efficacy while limiting toxicity, possibly diminishing or nullifying advantages that DEB-TACE may offer.

TABLE 1. CHARACTERISTICS OF cTACE AND DEB-TACE			
	cTACE	DEB-TACE	Reference
Technical			
Real-time fluoroscopy-guided drug delivery	Yes	No	Kinugasa et al[42]
Tumor labeling on posttreatment CT	Yes	No	Lim et al[13]
Local release of anticancer drug	Fast	Slow	Namur et al[45]
Simultaneous local delivery of several therapies	Yes	No	Idee et al[9]
Selectivity for the tumor	Yes	Yes, (if < 300 µm)	de Baere et al[14,21]
Clinical			
Benefit on overall survival	Yes	Yes	Kloeckner et al[39]; Gao et al[40]; Hui et al[41]
Systemic release of anticancer drug	Moderate	Low	Lewis et al[32]
Risk of liver infarct and biloma	Low	High (if > 300 µm)	Guiu et al[43]
Cost	Low	High	Cucchetti et al[44]

Abbreviations: cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization.

cTACE VERSUS DEB-TACE IN THE MANAGEMENT OF HCC

DEB-TACE was first introduced to improve the overall outcome of TACE and to diminish its systemic side effects.[32] Using chemotherapy-preloaded embolic microspheres in DEB-TACE was thought to result in more targeted and extended exposure of HCC to the chemotherapeutic agent along with lower associated toxicity due to reduced systemic chemotherapy exposure.[33] Since the introduction of DEB-TACE, there have been multiple prospective and retrospective studies comparing the efficacy, toxicity, cost-effectiveness, and overall survival of the DEB-TACE versus cTACE as the standard clinical treatment for HCC patients with BCLC stage B disease.

A direct comparison of cTACE and DEB-TACE is challenging, if not impossible. There is no standardized treatment protocol for cTACE within published trials. Technical approach; number and type of delivered drugs; selected patient population in terms of tumor burden, liver function, and performance status; and outcome measures vary widely among studies, which makes study comparisons difficult.[34-36] The PRECISION V study, conducted at 19 European centers, is the largest prospective randomized trial comparing cTACE and DEB-TACE. Results from PRECISION V showed no significant difference in tumor response of HCC to cTACE and DEB-TACE. The systemic side effects of doxorubicin were lower with DEB-TACE and patients reported less pain.[37,38] Compared to cTACE, DEB-TACE was statistically more efficient in treating patients with Child-Pugh B, ECOG (Eastern Cooperative Oncology Group) grade 1, and bilobar or recurrent disease, demonstrating a higher objective response, defined as complete or partial response based on European Association for the Study of Liver Disease criteria.[37] Multiple meta-analyses have been performed evaluating cTACE and DEB-TACE. For example, a single-center, retrospective, nonrandomized study involving 674 patients evaluating overall survival found no significance difference between the two therapies.[39] Two meta-analyses that included 693 patients and 527 patients, respectively, concluded that the two therapies have similar efficacy.[40,41]

Table 1 summarizes the main features of cTACE and DEB-TACE.[9,13,14,21,32,39-45] Compared to Lipiodol, DEBs occlude more proximal branches, which has been attributed in part to their hydrophobic characteristics, unless small beads (< 300 µm) are used.[14,21] The hydrophobic characteristics of DEBs may also lead to incomplete and slower release of doxorubicin.[46] Lipiodol is unique in that it is an oily radiopaque material, allowing the operator to monitor the flow of embolic material and homogeneous Lipiodol uptake as well as tumoral blush at the time of administration.[42] In addition, Lipiodol embolizes more distally and deposits more selectively in the tumor, which can be verified on follow-up CT imaging.[10] Although systemic release of cytotoxic drug is lower with DEB-TACE, the risk of biloma and liver infarct has been shown to be nine times more common with DEB-TACE compared to cTACE.[43] This is important in selected HCC patients with longer life expectancies and in posttransplantation patients in which biliary damage secondary to DEB-TACE may endanger liver function in the long term. There is an ongoing debate about long-term cost-effectiveness of DEB-TACE compared to cTACE in selected patients with intermediate-stage HCC,[44] which can be further assessed in future studies.

TARE FOR HCC TREATMENT

TARE with Y-90 is a relatively new therapeutic modality for advanced unresectable HCC that is not amenable to TACE, diffuse or multifocal disease, or in HCC patients with portal vein thrombosis.[47,48] Y-90 is a pure β-emitting isotope that decays to zirconium-90 and has a half-life of 64.1 hours. TARE is an outpatient procedure, and postprocedure isolation precautions are not necessary because the emitted radiation penetrates surrounding liver tissue to an average depth of only 2.5 mm and a maximum depth of only 11 mm. Therefore, there is no expected radiation exposure to untreated individuals in contact with the patient. There is preferential flow of the embolic particles, and thus the radiation dose moves toward the hypervascular tumors.[49] SIR-Spheres (20–60-µm particles made of a biocompatible resin, Sirtex Medical Inc.) and TheraSpheres (20–30-µm glass particles, BTG International) are two available commercial products that can be used to deliver Y-90.

TARE has been reported to have at least comparable clinical outcomes to TACE in patients with HCC.[50] In a study of 179 patients with BCLC stage A or B HCC, Salem et al found that Y-90 radioembolization provided a significantly longer time to progression compared to cTACE. Additionally, Y-90 radioembolization provided better tumor control and therefore could potentially reduce dropout from transplant wait lists.[51] TARE is also reported to be superior to TACE in terms of quality of life, as patients undergoing TARE have shorter hospitalization times, fewer treatment sessions, and fewer visits to the hospital than those undergoing TACE.[35,52] The most common side effects of TARE are fatigue and elevated bilirubin.[53] More serious complications, including radiation pneumonitis, radiation cholecystitis, hepatic abscess, radiation-induced liver disease, and gastrointestinal ulceration, are infrequently seen.[53]

BLAND EMBOLIZATION FOR HCC TREATMENT

Although Lipiodol-based TACE remains the standard of care for patients with intermediate unresectable HCC, TAE is another alternative therapy. TAE involves using an embolizing agent (eg, PVA, Gelfoam [Pfizer, Inc.], acrylic copolymer gelatin particles, Embosphere microspheres [Merit Medical Systems, Inc.]) to occlude the blood supply to the tumor without the addition of a cytotoxic agent. Clear survival benefit of TACE over supportive care has been demonstrated through multiple trials, but convincing evidence establishing superiority over TAE is somewhat lacking. HCC is considered chemoresistant, and TAE may be better tolerated in patients with borderline liver function, leading some operators to prefer bland embolization.[54]

In a randomized trial that compared bland hepatic artery embolization using microspheres alone with chemoembolization using doxorubicin-eluting microspheres (DEB-TACE), using RECIST (Response Evaluation Criteria In Solid Tumors) to evaluate treatment response, no difference was found between the treatments.[55] A recent meta-analysis of six randomized controlled trials comparing TACE and TAE found that cTACE was not superior to TAE in HCC patients.[56] More data are needed, but in light of the lack of clear superiority of cTACE over TAE and given the higher cost of the cytotoxic drugs and possible better toleration, bland embolization may play an important role in the management of selected patients with unresectable HCC.

CLINICAL TRIALS INVOLVING cTACE

Clinical trials evaluating Lipiodol-based TACE continue. A simple search on the United States National Library of Medicine using the search terms TACE and Lipiodol produced 59 active, recruiting-enrolling, and recently completed trials.* These trials are occurring worldwide and include six studies in Europe, nine studies in North America, and 43 studies throughout Asia. The high number of trials in Asia indicates the long-term viability of Lipiodol and the continued use of cTACE as the standard of care for HCC in Asia. For example, in North America, one study is comparing cTACE with transarterial tirapazamine embolization, while another is comparing cTACE with proton beam radiotherapy for HCC. In Japan, an ongoing trial is comparing cTACE with stereotactic body radiation. Other trials are investigating TACE emulsion versus TACE suspension, TACE versus microsphere TACE, and adjuvant TACE, as well as others.

CONCLUSION

Lipiodol-based cTACE remains the most well-studied transarterial therapy for HCC. It continues to be used routinely in clinical practice and clinical studies. There is a role for DEB-TACE, TARE, and TAE in selected patients, and these treatments should be considered complementary rather than competitive to cTACE. ■

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