Chemoembolization and Radioembolization for Hepatocellular Carcinoma

RIAD SALEM and ROBERT J. LEWANDOWSKI
Section of Interventional Radiology, Division of Interventional Oncology, Department of Radiology, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, Illinois

This article has an accompanying continuing medical education activity on page e44. Learning Objective—At the end of this activity, the successful learner will be able to report the state of the science for embolic therapies in unresectable hepatocellular carcinoma.

Hepatocellular carcinoma (HCC) continues to represent a major worldwide problem. Although treatments such as resection, transplantation, and ablation may provide a chance for a cure, these options are often precluded because of advanced disease presentation. Palliative treatments include transarterial embolization and systemic therapies. This review will summarize the state of the science for embolic therapies in HCC (conventional and drug-eluting chemoembolization, radioembolization) as well as discuss related topics including HCC staging, assessment of response, and ongoing clinical trials.

Keywords: Hepatocellular Carcinoma; Chemoembolization; Radioembolization.

Hepatocellular carcinoma (HCC) is the sixth most common malignancy diagnosed worldwide. Its incidence is on the rise and has now become the third most common cause of cancer-related mortality. Late stage presentation, comorbidities, and limited donor availability enable only 10% of patients to receive curative therapies. According to the Barcelona Clinic Liver Cancer (BCLC) staging system, conventional transarterial chemoembolization (cTACE) represents the mainstay of treatment for intermediate BCLC B disease. This has now evolved into more controlled delivery of chemotherapy in the form of drug-eluting bead transarterial chemoembolization (DEB-TACE). Radioembolization, also an intra-arterial treatment, represents an alternate form of treatment for HCC patients with BCLC B disease. Rather than injecting chemotherapy, micron-sized nonembolic radioactive particles are injected in the hepatic artery. Studies have shown that radioembolization may also have a role in the treatment of patients with early (BCLC A) or advanced stage disease (BCLC C). This review article will focus on cTACE, DEB-TACE, and radioembolization, with special discussions on the practical aspects of each modality including scientific rationale, number of treatment sessions, adverse events, clinical outcomes, response assessment, and ongoing clinical trials.

Embolotherapy: Mechanism of Action
Arterial embolotherapies are based on the fact that whereas the normal hepatic parenchyma derives its blood supply primarily from the portal vein (75%), HCC derives all of its blood supply from the hepatic artery. Hence, although tumors grow in size, the hepatic arterial blood supply also hypertrophies. Capitalizing on this mechanism, hepatic arterial catheterization can be exploited to deliver a therapeutic (drug, radiation) in the hypertrophied vessels, eventually lodging near or within the target, depending on the size of the agent administered (Figure 1). In the case of cTACE, lipiodol is mixed with 1 or more chemotherapeutics (doxorubicin, cisplatin, mitomycin) and injected within the target vessel. Lipiodol acts as a delivery vehicle for the agents and ultimately lodges near the tumor. DEB-TACE, the evolution of cTACE, involves the loading of drug (doxorubicin) in drug-eluting microspheres; once injected near the tumor, a slow and controlled release of the drug results in antitumoral effects. Finally, with radioembolization, 30-μm-sized particles are injected and ultimately lodge within the tumor. A low dose-rate brachytherapy is applied to the tumor.

Abbreviations used in this paper: BCLC, Barcelona Clinic Liver Cancer; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; HCC, hepatocellular carcinoma; TTP, time-to-progression.

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Figure 1. (A) Schema depicting arterial blood supply to HCC. (B) Demonstration of mechanism of action of bland chemoembolization, drug-eluting beads, and radioembolization.
during the radioactive decay process. Although all 3 of these treatments appear to share similarities, there are distinct differences in patient selection, technique, patient monitoring, and complications. All have achieved encouraging clinical outcomes in terms of response, time-to-progression (TTP), and overall survival. Because of these outcomes, all are gaining acceptance for treating appropriately selected HCC patients.

Conventional Chemoembolization
cTACE is defined as the delivery of 1 or more chemotherapeutics directly to the tumor via hepatic arterial injection. This method has been in clinical practice since the 1980s and represents the mainstay of embolotherapy worldwide. Although controversial, the most commonly used drugs for cTACE include doxorubicin alone or in combination with mitomycin C and/or cisplatin. The triple-drug combination is the preferred method in the United States.

Patient Selection
cTACE is indicated in HCC patients with preserved performance status and liver function without vascular invasion or extrahepatic disease. In general, contraindications include intractable systemic infection, leukopenia (white blood cell count <1000/μL), cardiac/renal insufficiency (serum creatinine >2.0 mg/dL), hepatic encephalopathy, performance status >2, hepatofugal flow, and biliary obstruction.

Procedure
Once a patient has been deemed a candidate for cTACE, a thorough pretreatment preparation is required. Patients are typically admitted the morning of the procedure for hydration, antibiotics (optional), antiemetic, and narcotic loading. The procedure is performed by using a common femoral artery catheterization (same for DEB-TACE and radioembolization), and the lipiodol/chemotherapy emulsion is administered to the hepatic artery perfusing the tumor(s). The vehicle used for chemotherapy delivery is lipiodol, a poppy seed oil containing 38% iodine by weight. To obtain an embolic effect and prevent washout of the drug, 100–500 μm bland occlusive particles are subsequently injected. Lipiodol permits the drug to concentrate in the tumor and is retained for weeks; normal hepatocyte excretion is 7 days. Immediately after cTACE, a noncontrast computed tomography scan is obtained that demonstrates the proper location of the chemotherapy/lipiodol combination (Figure 2). The standard approach to cTACE is for repeated treatments at 2- to 4-month intervals, depending on the tumor burden and response.

Clinical Outcomes With Conventional Transarterial Chemoembolization
Lo and Llovet published 2 separate studies establishing the benefit of cTACE in patients in HCC. Both studies used repeated, fixed-interval (intention-to-treat) chemoembolization compared with best supportive care. They concluded that cTACE improved survival in patients with unresectable HCC. In a large phase 2 study, Takayasu et al published data from a large cohort study of 8510 HCC patients treated with cTACE that described liver function, alpha-fetoprotein, tumor size, number of lesions, and portal vein invasion as significant prognosticators of survival. These findings were later confirmed with a meta-analysis of 7 published randomized controlled trials concluding that cTACE is an effective palliative treatment modality for unresectable HCC. Lewandowski et al reported on a recent comprehensive imaging and long-term survival analysis in a cohort of 172 patients after cTACE. Median survival was significantly different between patients with BCLC stages A, B, and C disease (stage A, 40.0 months; B, 17.4 months; C, 6.3 months; P < .0001). The study concluded that chemoembolization was safe and effective in patients with HCC; however, TTP and survival were confounded by tumor biology and background cirrhosis. Most recently, Takayasu et al published another large cohort of 4966 HCC patients. As opposed to the series by Lewandowski et al, the recent Japanese study excluded patients with vascular invasion, extrahepatic metastases, and prior treatment. Applying these selection criteria, excellent results were achieved (median survival, 3.3 years), with Child–Pugh class, tumor number, size, alpha-fetoprotein, and des-gamma carboxy prothrombin levels being independent predictors of survival.

Adverse Events and Complications
Postembolization syndrome, manifest by pain, nausea and vomiting, is managed during the hospitalization (1–3 days). Other complications may include (1) biliary duct injury (up to 5.3%), (2) liver abscesses in patients after biliary interventions (stents, sphincterotomy), (3) duodenal or gastric ulcers from inadvertent deposition of the chemotherapeutic agents, (4) vascular injury such as spasm/dissection from repeated chemotherapy injection in the arterial system, and (5) tumor rupture (<1%).

Drug-eluting Bead Chemoembolization
The concept of DEB-TACE builds on the rationale for cTACE. Through a drug-loading process, the microspheres are able to absorb the chemotherapeutic agent. These unique properties permit release of drug in a controlled and sustained manner. This leads to a significant reduction of peak plasma concentration when compared with cTACE. The mechanism of drug elution is based on a strong drug-bead interaction that can be attributed to an ionic exchange process between anionic drug moieties and the hydrogel sulfonate or carboxyl counter ions.

Figure 2. (A) T1-weighted gadolinium-enhanced magnetic resonance imaging reveals a focal-enhancing mass in hepatic segment 7 (arrow). This mass demonstrated venous phase-contrast washout, meeting the guidelines for HCC. After discussion at multidiscipline tumor board, this nonoperative candidate underwent cTACE. (B) A noncontrast computed tomography scan performed immediately after cTACE revealed focal uptake of lipiodol within the targeted tumor (double arrows). There is some nontarget lipiodol uptake in the noncancerous hepatic parenchyma (arrowhead) adjacent to the tumor.
Patient Selection

In general, patients in the intermediate BCLC B category may be considered for DEB-TACE, provided they have preserved performance status and liver function. However, in accordance with clinical trials that have been completed with DEB-TACE, ideal patients should have HCC that can be isolated angiographically, such that selective (as opposed to lobar) injections can be performed. Similar to cTACE, the microspheres are infused slowly while the delivery to tumor is performed. Treatment guidelines for DEB-TACE recommend up to 4 treatments within 6 months to the entire treatment field.25

Clinical Outcomes With Drug-eluting Bead Transarterial Chemoembolization

There have been several studies reporting on pharmacokinetic rationale for DEB-TACE.22,26 The rationale is one of increased intratumoral retention and decreased bioavailability, translating into lower toxicity rates. In an early study, Lo et al reported a 63% response by using the modified Response Evaluation Criteria in Solid Tumors criteria. A recent randomized controlled trial on 212 patients comparing conventional TACE with DEB failed to show an improvement in response by using the more controlled drug-eluting methodology. However, in a subset analysis, more advanced patients were better able to tolerate DEB-TACE compared with cTACE.28 In a recent retrospective analysis, Dhanasekran et al concluded that transcatheter therapy with DEB-TACE offered a survival benefit over conventional chemoembolization in patients with unresectable HCC. There were fewer adverse events when compared with cTACE, further supporting the safety profile of DEB-TACE.

Varela et al reported on a small 27-patient series of DEB-TACE in HCC and Child–Pugh A cirrhosis. They demonstrated that response rate was 75% by computed tomography at 6 months, with systemic doxorubicin levels significantly lower than cTACE. One-year and 2-year survival rates were 92.5% and 88.9%, respectively, with a median follow-up of 27.6 months. They concluded that chemoembolization by using DEBs is an effective procedure with a favorable pharmacokinetic profile. The same group recently reported on a 104-patient cohort of patients treated with DEB-TACE. They reported a median survival of 48 months, challenging current thinking on the 20- to 22-month expected outcomes in intermediate BCLC B patients.31 The combination of sorafenib and DEB-TACE was also shown to be safe in a recent 35-patient cohort, resulting in a response rate of 58% by necrosis criteria.32

Recently, Malagari et al performed a prospective randomized trial comparing DEB-TACE with bland embolization. Although a partial imaging response to therapy was similar between the groups, TTP was longer in the DEB-TACE arm, establishing that the chemotherapy, along with embolization, plays an important role in the cytotoxic effects. The same group also expanded their analysis into a 173-patient cohort and a 5-year survival analysis. Outcomes replicated those reported by other investigators, with median survival exceeding 43 months.33 Clinical outcomes of cTACE and DEB-TACE are summarized in Table 1.

Complications

Recent studies, including a 237-patient cohort, have reported on the safety profile of DEB-TACE. Although the

Table 1. Outcomes of cTACE and DEB-TACE in HCC

<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose</th>
<th>Patients</th>
<th>Response rate (%)</th>
<th>TTP (mo)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takayasu et al.</td>
<td>Determine best indication for TACE and survival after TACE</td>
<td>172</td>
<td>49.66</td>
<td>7.9</td>
<td>1: 82%</td>
</tr>
<tr>
<td>Takayasu et al.</td>
<td>Analyze survival and TTP after TACE</td>
<td>8510</td>
<td>64</td>
<td>10.4</td>
<td>1: 47%</td>
</tr>
<tr>
<td>Lewandowski et al.</td>
<td>Compare response rate and TTP with DEB-TACE</td>
<td>108</td>
<td>22</td>
<td>9.4</td>
<td>1: 47%</td>
</tr>
<tr>
<td>Lammer et al.</td>
<td>Compare DEB-TACE with DEB-TACE</td>
<td>93</td>
<td>27</td>
<td>11.5</td>
<td>1: 47%</td>
</tr>
<tr>
<td>Malagari et al.</td>
<td>Compare DEB-TACE with bland embolization</td>
<td>41</td>
<td>73.1</td>
<td>10.6</td>
<td>1: 47%</td>
</tr>
<tr>
<td>Burrel et al.</td>
<td>Report on outcomes of patients treated with DEB-TACE</td>
<td>27</td>
<td>41.4</td>
<td>9.1</td>
<td>1: 93.6%</td>
</tr>
<tr>
<td>Malagari et al.</td>
<td>Report on outcomes of patients treated with DEB-TACE</td>
<td>104</td>
<td>58</td>
<td>1: 47%</td>
<td></td>
</tr>
<tr>
<td>Malagari et al.</td>
<td>Report on outcomes of patients treated with DEB-TACE</td>
<td>35</td>
<td>58</td>
<td>1: 47%</td>
<td></td>
</tr>
<tr>
<td>Pawlik et al.</td>
<td>Report on outcomes of patients treated with DEB-TACE</td>
<td>93</td>
<td>58</td>
<td>1: 47%</td>
<td></td>
</tr>
<tr>
<td>Takayasu et al.</td>
<td>Discern survival of selected patients treated with DEB-TACE</td>
<td>27</td>
<td>58</td>
<td>1: 47%</td>
<td></td>
</tr>
<tr>
<td>EASL CR: 23</td>
<td>Discern survival of selected patients treated with DEB-TACE</td>
<td>173</td>
<td>58</td>
<td>1: 47%</td>
<td></td>
</tr>
<tr>
<td>EASL PR: 48</td>
<td>Discern survival of selected patients treated with DEB-TACE</td>
<td>35</td>
<td>58</td>
<td>1: 47%</td>
<td></td>
</tr>
</tbody>
</table>

EASL, European Association for the Study of the Liver; WHO, World Health Organization.
systemic exposure is reduced with controlled release of drug in the tumor microenvironment, adverse events seen with DEB-TACE are similar to (but lower in frequency than) cTACE. These include pain, nausea, vascular injury, hepatic failure, abscess formation, and tumor rupture.35,36

Radioembolization

The technique of radioembolization involves the delivery of high-dose radiation via the hepatic arterial system. This is distinctly different from external beam radiation therapy, where dose limitations and hepatic radiosensitivity limit the amount that can be delivered to hepatic tissue before the development of radiation-induced liver disease (ascites, anicteric hepatomegaly, elevation of alkaline phosphatase).3,37,38 High-dose 30-μm-sized radioactive particles are delivered to the tumor at the segmental or lobar level. In contradistinction to cTACE/DEB-TACE, vessel occlusion is not the intent with radioembolization. Rather, the microspheres lodge without causing occlusion at the macroscopic level and emit beta radiation.40 Consequently, because vessel occlusion does not occur, hospitalization is not required. Patients are discharged 2–6 hours on the same day after radioembolization.

Patient Selection

As more experience with radioembolization has been garnered during the last decade, certain clinical observations have been made. First, although the concept of segmental injections in HCC is the standard for most embolotherapies, radioembolization, with an improved toxicity profile, appears to play a role in more advanced disease.40–42 This includes patients with performance status 1–2, multifocal disease with or without portal venous thrombosis. Because segmental injections are not mandated, lobar infusions treating larger territory of disease are routine.43 Second, whereas cTACE/DEB-TACE requires inpatient hospitalization, radioembolization has shifted the embolotherapy paradigm into one of outpatient therapies, translating to better quality of life.41,42 Finally, in contradistinction to routine, scheduled embolizations with cTACE/DEB-TACE, radioembolization patients receive 1 treatment, with follow-up sessions on an as-needed basis.

Clinical Outcomes With Radioembolization

Several large phase 2 studies have been published describing long-term outcomes with radioembolization. A 291-patient comprehensive cohort was the first to describe toxicity, imaging, and survival outcomes stratified by BCLC, United Network for Organ Sharing, tumor stage, and Child-Pugh.44 This study was also the first to describe TTP outcomes in granular detail, serving as background data for comparative studies. Subsequently, a 108-patient study from Germany validated these outcomes in advanced patients, confirming the reproducibility of this technique and equivalent outcomes to cTACE/DEB-TACE.45 A 325-patient study followed, further confirming long-term survival outcomes stratified by BCLC stages.46 Finally, most recently, a phase 2 study from the group in Italy described the role of radioembolization in intermediate/advanced patients. This last report served to launch a randomized phase 3 study comparing radioembolization with sorafenib.47

Although there has been no randomized study comparing radioembolization with chemoeombolization, a comparative effectiveness report described outcomes in a 245-patient cohort. The authors reported that adverse events, clinical toxicities, response rate, and TTP were improved with radioembolization when compared with cTACE. However, overall survival was no different, likely as a result of competing risks of death of HCC and cirrhosis. The study also challenged the concept of TTP being a surrogate of survival in HCC. On post hoc analyses, it was concluded that a sample size of >1000 patients would be required to establish survival equivalence between cTACE and radioembolization.40 The improvement in TTP was also confirmed by another comparative report that demonstrated that radioembolization outperformed cTACE in downstaging to transplantation (Figure 3).48 Finally, Kulik et al43 and Memon et al49 reported on the niche clinical application of radioembolization in portal venous thrombosis, reporting on the safety profile in this advanced patient population. The authors confirmed that radioembolization could be used in vascular invasion without the risk of ischemic hepatitis. These findings were recently further confirmed by the same group.49 Clinical outcomes of radioembolization are summarized in Table 2.

Complications

Adverse events from radioembolization are distinctly different from those from other embolotherapies. The dominant side effect is fatigue, with other adverse events including nontarget deposition of microspheres (possibly leading to ulcer formation), fibrosis/scarring of the liver parenchyma, and cholecystitis. Radiation-induced liver disease is rare when proper patient selection criteria are applied.38,50

Assessing Response After Embolotherapy

Assessing response to locoregional therapies can be complex. In contradistinction to systemic treatments in which all tumors are simultaneously exposed to the agent, this is not the case with embolotherapy. During the course of treatment with embolization, lesions are treated at different times at staged 4- to 6-week intervals. Hence, response is often assessed in the treated lesion, whereas untreated lesions are only incorporated once the entire treatment field has been completed.51 Although size criteria are the most common reporting standards, methods that use necrosis have been implemented to incorporate the mechanism of action of embolization. However, because of the lack of standardization of these methods, overall
tumor size reduction is still considered the gold standard. In 1979, the World Health Organization (bidimensional measurements) published guidance on the anatomic assessment of tumor response to therapy. This further evolved to the Response Evaluation Criteria in Solid Tumors guidelines (unidimensional measurements). The European Association for the Study of the Liver guideline was based on percent change in amount of enhancing tumoral tissue (necrosis). Recently, the modified Response Evaluation Criteria in Solid Tumors were published, formally recommending the concept of viable tumor tissue (arterial phase of contrast-enhanced imaging), and aimed to provide a common framework for the imaging response of clinical trials in HCC. The field of response assessment after local therapies is dynamic, with studies investigating the optimal number of target lesions, pathology correlates and scoring systems, patterns of disease progression, surrogates of survival, and biomarkers.

### Ongoing Trials

Research in embolotherapy continues to be a very active. Because cTACE and sorafenib have both been shown to provide a survival advantage, studies with radioembolization have been proposed to either compete against or combine with these other standards of care. Recently, the equivocal findings from a trial that used DEB-TACE/sorafenib were announced. This study was unable to definitively confirm a role for sorafenib in combination with embolization. Cooperative groups are also carrying out similar studies to further investigate the role of sorafenib in HCC patients undergoing embolization. There are also several ongoing trials comparing cTACE and radioembolization in randomized designs with TTP as the end point (incorporating quality of life, econometrics). Finally, there are other studies looking at the role of radioembolization in combination with or comparison to sorafenib in the advanced patient population. These trials are robust in their rationale, statistical design (international, multicenter, randomized phase III), and primary end points (survival). Final results of these seminal studies are expected within the next 3–5 years.

### Conclusions

Chemoembolization and radioembolization are transarterial locoregional therapies that have gained widespread recognition for the treatment of HCC. Although a randomized trial comparing cTACE and DEB-TACE did not reach its end point, there appears to be better tolerability in more advanced patients with DEB-TACE. Similarly, although a comparative effectiveness study of cTACE and radioembolization did not show a survival advantage, yttrium-90 radioembolization patients did exhibit lower toxicities and longer TTP. Currently enrolling studies combining these arterial locoregional therapies with targeted systemic therapies are underway. As the results of randomized studies of embolotherapy combined with systemic agents mature, the clinical indications and specific patients ideally suited for these palliative interventions will continue to be refined.

### References


