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# Transarterial Therapies for Hepatocellular Carcinoma

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## Introduction

Treatment of hepatocellular carcinoma (HCC) may include 1 or more surgical, locoregional or medical approaches (Table). Liver transplantation is the most likely to provide long-term survival and cure for HCC.[1] Thermal ablation (radiofrequency ablation and microwave ablation) is most effective when tumor diameter is $\leq$3 cm, although its efficacy and safety are occasionally limited by the anatomical location of the lesion. Most cases of HCC present at an advanced stage and are not amenable to liver transplantation, surgical resection or thermal ablation. Transarterial therapies (transarterial radioembolization using Y-90 [TARE-Y90] and transarterial chemoembolization [TACE]) are often used to provide palliation for patients with solitary and multifocal HCC. In certain instances, transarterial therapies may be used to downstage tumors so that patients may be considered for surgical therapy (transplantation or resection).

Both TARE-Y90 and TACE share the mechanism of therapy where the therapeutic agent is bound to microspheres (TARE-Y90), drug-eluting beads (drug-eluting beads transarterial chemoembolization [DEB TACE]), or combined with Ethiodol (conventional TACE [cTACE]) and infused into the hepatic artery branch that supplies the tumor. The agent preferentially flows to the tumors compared to the uninvolved hepatic parenchyma because of the relative hypervascular arterial supply of HCC as compared to the normal liver. Excellent tumor necrosis is provided by these transarterial therapies. However, despite the preferential flow to the tumor, there is still a degree of "collateral damage" to uninvolved liver following TARE-Y90 or TACE. As a result, these therapies may be poorly tolerated in patients with marginal pre-existing hepatic function. The cause of death in HCC patients is more likely to be due to liver failure than the direct consequences of HCC. Transarterial treatments of HCC provide effective tumor necrosis but have the potential to hasten the natural history of liver failure in patients with pre-existing marginal hepatic function.

Our goals in this article are to provide an overview of TACE and TARE-Y90, guidance on management of patients with HCC by transarterial therapies, and recommendations on performance of these procedures. This include, patient evaluation and selection, preprocedure imaging, medications, and embolic agent choice. We will also discuss procedural and technical considerations, complications, postprocedure care, follow-up, treatment assessment, and outcomes.

## Transarterial Chemoembolization

### Background

TACE has an integral role in the care of patients with HCC who have relatively preserved liver function, increasing patient survival when incorporated into the management of these patients.[2] TACE interrupts blood flow to the tumor and induces necrosis. However this may increase certain markers such as inducible factor 1$\alpha$ and both plasma and hepatic vascular endothelial growth factor that may encourage angiogenesis. Antiangiogenic agents can be combined with TACE to counteract a possible rise in vascular endothelial growth factor–mediated signaling and to target tumor that was not included in the treatment zone.[3]

cTACE using a chemotherapy agent in oil emulsion followed by an embolic agent such as gelfoam has been used for a long time. Subsequent development of embolic drug-eluting beads (DEB) has provided an attractive alternative to cTACE. Clinical studies have shown that DEB loaded with doxorubicin is safe with a superior pharmacokinetic profile and improved tolerability compared to cTACE. It has lower systemic drug levels and significantly reduced liver toxicity compared to cTACE.[4-6]

Evaluation of DEB TACE in a multicenter phase 2 randomized trial showed marked reduction in liver toxicity and drug-related adverse events as compared to cTACE with

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http://dx.doi.org/10.1053/j.ro.2016.02.005

**Table** Treatment Options for Hepatocellular Carcinoma

- Surgery
  - Transplantation
  - Resection
- Ablation
  - Radiofrequency ablation (RFA)
  - Microwave ablation (MWA)
  - Alcohol ablation
- Catheter-directed transarterial therapies
  - Transarterial radioembolization using Y-90 (TARE-Y90)
    - Y-90 glass microspheres (TheraSphere)
    - Y-90 resin microspheres (SIR-Spheres)
  - Transarterial chemoembolization (TACE)
    - Conventional TACE (cTACE) using Ethiodol emulsion with chemotherapy (Doxorubicin, Cisplatin, and Mitomycin C)
    - Drug-eluting beads (DEB TACE) (LC Beads, QuadraSphere) adsorbed to Doxorubicin
  - Bland microsphere embolization
- Chemotherapy
  - Anti-VEGF targeted agent (Sorafenib)
- Stereotactic body radiation therapy (SBRT)
- Supportive care

doxorubicin.[5] The DEB TACE group showed higher rates of complete response, objective response, and disease control compared with the cTACE group although $P = 0.11$. Patients with Child-Pugh B, Eastern Cooperative Oncology Group (ECOG) performance status of 1, bilobar disease, and recurrent disease showed a significant increase in objective response ($P = 0.038$) in the DEB TACE group. LC Beads were associated with improved tolerability and a significant reduction in serious liver toxicity ($P < 0.001$).

## Patient Evaluation and Selection

The criteria for using transarterial therapies, TACE and TARE-Y90, are similar. Patients receiving transarterial treatments for HCC should be seen in the interventional radiology (IR) clinic before the treatment to carefully evaluate the patients clinically. The treatment should be explained in detail to the patient and family members. Recent laboratory evaluation should be obtained including liver function tests (LFTs), platelet level, coagulation profile, renal function, and alpha fetoprotein (AFP). The diagnosis should be secured with diagnostic imaging, AFP elevation or histology. The patient should be discussed at the hospital multidisciplinary liver tumor board to set a goal regarding treatment. The goal may be palliation, downstaging or bridging to transplant or surgical resection, or an attempt at long-term control without surgery.

The patient performance status should be Eastern Cooperative Oncology Group (ECOG) 0-2, which means the patient is at least capable of self-care and is up and about approximately >50% of waking hours. There should be no significant extrahepatic metastatic disease. Life expectancy should be >3 months and the patient should not be in a hospice program. Adequate hepatic reserve is assessed by key parameters such as a total serum bilirubin <2 mg/dL and the absence of intractable ascites or uncontrolled hepatic encephalopathy. Transarterial therapies in the setting of more abnormal hepatic function may be employed to treat segmental or subsegmental regions, instead of the entire lobe. In this fashion, a focused hepatic transarterial therapy causes minimal "collateral damage" to the surrounding nonmalignant liver tissue.

The presence of biliary obstruction increases the risk of cholangitis and hepatic abscess following hepatic transarterial therapies. Most interventional radiologists do not treat patients with previous hepaticojejunostomy or existing endoscopic or percutaneous biliary stents. However, transarterial therapies may be performed with imaging evidence of mild intrahepatic biliary dilation and serum bilirubin levels <2 mg/dL.[7]

Branch or segmental portal vein thrombosis is not a contraindication to transarterial therapies.[8] However, main portal vein occlusion without adequate recanalization of portal venous flow is a strong reason to withhold these therapies.

## Imaging

Computed tomography (CT) or magnetic resonance imaging using a dedicated liver protocol is needed to evaluate tumor burden, extent of liver involvement, arterial anatomy, patency of the venous system, ascites, and extrahepatic disease.[9-12] Additional imaging of the chest can be obtained to rule out metastatic disease.

## Preprocedure Medications

For TACE, this should include antibiotics, antiemetics, and dexamethasone. The antibiotic (such as ciprofloxacin) should cover Gram-negative bacilli. At our institution for antiemetics, we have used parenteral Aprepitant before TACE to facilitate same-day discharge. Some operators add a gastric acid suppression agent such as famotidine. In the setting of chronic kidney disease, periprocedural intravenous hydration is used to reduce the risk of acute kidney injury. If the platelet count is less than 50,000 platelet transfusions are suggested at the time of arteriography. Fresh frozen plasma transfusions may be indicated with an elevated prothrombin time.

## Chemotherapy and Embolic Agent

The most popular chemotherapeutic agent for TACE of HCC is doxorubicin. The dose of doxorubicin is adjusted to body surface area and bilirubin level. The dose typically ranges from 25-100/$m^2$, to a maximum of 150 mg.[4]

In cTACE, the drug is usually mixed with 5-20 mL of Lipiodol. This can be followed by mechanical embolization of the feeding arteries with gelfoam to enhance cytotoxic effect by ischemia.[13] The end point is typically stasis in the second- or third-order branches of the lobar hepatic artery. Technique inconsistency of cTACE had always been a limitation that hindered it from being a standard oncology treatment for HCC. DEB TACE, as opposed to cTACE, provides consistency that makes it an acceptable standard of HCC treatment.[14] Unlike gelatin sponges, the particle size of DEB TACE is uniform. This makes it easier to predict the level of embolism and ensure a sustained embolic effect.[15]

In DEB TACE for patients with low tumor burden (HCC within Milan criteria: single tumor <5 cm or up to 3 tumors