Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

Description

Transcatheter arterial chemoembolization (TACE) of the liver is a proposed alternative to conventional systemic or intra-arterial chemotherapy and to various nonsurgical ablative techniques, to treat resectable and non-resectable tumors. TACE combines the infusion of chemotherapeutic drugs with particle embolization. Tumor ischemia secondary to the embolization raises the drug concentration compared with infusion alone, extending the retention of the chemotherapeutic agent and decreasing systemic toxicity. The liver is especially amenable to such an approach, given its distinct lobular anatomy, the existence of two independent blood supplies, and the ability of healthy hepatic tissue to grow and thus compensate for tissue mass lost during chemoembolization.

TACE is a minimally invasive procedure performed by interventional radiologists who inject highly concentrated doses of chemotherapeutic agents into the tumor tissues and to restrict tumor blood supply. The embolic agent(s) causes ischemia and necrosis.
of the tumor and slows anticancer drug washout. The most common anticancer drugs used in published TACE studies for hepatocellular carcinoma include doxorubicin (36%), followed by cisplatin (31%), epirubicin (12%), mitoxantrone (8%), and mitomycin C (8%).

The TACE procedure requires hospitalization for placement of a hepatic artery catheter and workup to establish eligibility for chemoembolization. Before the procedure, the patency of the portal vein must be demonstrated to ensure an adequate post-treatment hepatic blood supply. With the patient under local anesthesia and mild sedation, a superselective catheter is inserted via the femoral artery and threaded into the hepatic artery. Angiography is then performed to delineate the hepatic vasculature, followed by injection of the embolic chemotherapy mixture. Embolic material varies but may include a viscous collagen agent, polyvinyl alcohol particles, or ethiodized oil. Typically, only one lobe of the liver is treated during a single session, with subsequent embolization procedures scheduled five to six weeks later. In addition, because the embolized vessel recanalizes, chemoembolization can be repeated as many times as necessary.

TACE of the liver has been associated with potentially life-threatening toxicities and complications, including severe post-embolization syndrome, hepatic insufficiency, abscess, or infarction. TACE has been investigated to treat resectable, unresectable, and recurrent hepatocellular carcinoma, cholangiocarcinoma, liver metastases, and in the liver transplant setting. Treatment alternatives include resection when possible, chemotherapy administered systemically or by hepatic artery infusion. Hepatic artery infusion involves the continuous infusion of chemotherapy with an implanted pump, while TACE is administered episodically. Hepatic artery infusion does not involve the use of embolic material.

**OBJECTIVE**

The objective of this evidence review is to determine whether the use of transcatheter arterial chemoembolization improves the net health outcome in patients with various resectable and unresectable malignancies confined to or deriving from the liver.

**POLICY STATEMENT**

Transcatheter arterial chemoembolization of the liver may be considered medically necessary:

- to treat hepatocellular cancer that is unresectable but confined to the liver and not associated with portal vein thrombosis and liver function not characterized as Child-Pugh class C.
- as a bridge to transplant in patients with hepatocellular cancer where the intent is to prevent further tumor growth and to maintain a patient's candidacy for liver transplant (see Policy Guidelines section).
- to treat liver metastasis in symptomatic patients with metastatic neuroendocrine tumor whose symptoms persist despite systemic therapy and who are not candidates for surgical resection.
- to treat liver metastasis in patients with liver-dominant metastatic uveal melanoma.

Transcatheter arterial chemoembolization of the liver is considered investigational:

- as neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable.
- to treat unresectable cholangiocarcinoma.
- to treat liver metastases from any other tumors or to treat hepatocellular cancer that does not meet the criteria noted above, including recurrent hepatocellular carcinoma.
- to treat hepatocellular tumors prior to liver transplantation except as noted above.

**POLICY GUIDELINES**

When using transcatheter arterial chemoembolization of the liver as a bridge to transplantation to prevent further tumor growth, the patient candidate should have the following characteristics: a single tumor less than 5 cm or no more than 3 tumors each less than 3 cm in size, absence of extrahepatic disease or vascular invasion, and Child-Pugh class A or B.

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BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Chemoembolization for hepatic tumors is a medical procedure and, as such, is not subject to regulation by the U.S. Food and Drug Administration. However, the embolizing agents and drugs are subject to Food and Drug Administration approval.

RATIONALE

Summary of Evidence

Unresectable and Resectable HCC

For individuals who have unresectable hepatocellular carcinoma (HCC) confined to the liver and not associated with portal vein thrombosis who receive transcatheter arterial chemoembolization (TACE), the evidence includes several randomized controlled trials (RCTs), large observational studies, and systematic reviews. The relevant outcomes are overall survival (OS), disease-specific survival, quality of life (QOL), and treatment-related mortality and morbidity. Evidence from a limited number of RCTs has suggested that TACE offers a survival advantage compared with no therapy and survival with TACE is at least as good as with systemic chemotherapy. One systematic review has highlighted possible biases associated with these studies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome. For individuals who have resectable HCC who receive neoadjuvant or adjuvant TACE, the evidence includes several RCTs and systematic reviews. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. Studies have shown little to no difference in OS rates with neoadjuvant TACE compared with surgery alone. A meta-analysis found no significant improvements in survival or recurrence with preoperative TACE for resectable HCC. While both RCTs and the meta-analysis that evaluated TACE as adjuvant therapy to hepatic resection in HCC reported positive results, the quality of individual studies and the methodologic issues related to the meta-analysis preclude certainty when interpreting the results. Well-conducted multicentric trials from the U. S. or Europe representing relevant populations with adequate randomization procedures, blinded assessments, centralized oversight and publication in peer-reviewed journals are required. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have resectable HCC who receive TACE plus radiofrequency ablation (RFA), the evidence includes a single RCT. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. The RCT failed to show the superiority in survival benefit with combination TACE plus RFA treatment compared with surgery for HCC lesions 3 cm or smaller. Further, an ad hoc subgroup analysis showed a significant benefit for surgery in recurrence and OS in patients with lesions larger than 3 cm. It cannot be determined from this trial whether TACE plus RFA is as effective as a surgical resection for these small tumors. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have unresectable HCC who receive TACE plus RFA, the evidence includes multiple systematic reviews and RCTs. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. Multiple meta-analyses and RCTs have shown a consistent benefit in survival and recurrence-free survival favoring combination TACE plus RFA over RFA alone. However, results of these meta-analyses are difficult to interpret because the pooled data included heterogeneous patient populations and, in a few cases, data from a study retracted due to questions about data veracity. A larger well-conducted RCT has reported a relative reduction in the hazard of death by 44% and a 14% difference in 4-year survival favoring combination therapy. The major limitations of this trial were its lack of a TACE-alone arm and the generalizability of its findings to patient populations that have unmet needs such as those with multiple lesions larger than 3 cm and Child-Pugh class B or C. Further, this single-center trial was conducted in China, and until these results have been reproduced in patient populations representative of pathophysiology and clinical

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stage more commonly found in the U.S. or Europe, the results may not be generalizable. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Bridge to Liver Transplant**

For individuals who have a single HCC tumor less than 5 cm or no more than three tumors each less than 3 cm in size, absence of extrahepatic disease or vascular invasion, and Child-Pugh class A or B seeking to prevent further tumor growth and to maintain patient candidacy for liver transplant who receive pre-transplant TACE, the evidence includes multiple small prospective studies. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. There is a lack of comparative trials on various locoregional treatments as a bridge therapy for liver transplantation. Multiple small prospective studies have demonstrated that TACE can prevent dropouts from the transplant list. TACE has become an accepted method to prevent tumor growth and progression while patients are on the liver transplant waiting list. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Unresectable Cholangiocarcinoma**

For individuals who have unresectable cholangiocarcinoma who receive TACE, the evidence includes several retrospective observational studies and systematic reviews. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. RCT evaluating the benefit of adding TACE to the standard of care for patients with unresectable cholangiocarcinoma are lacking. Results of three retrospective studies have shown a survival benefit with TACE over the standard of care. These studies lacked matched patient controls. Although the observational data are consistent, the lack of randomization limits definitive conclusions. The evidence is insufficient to determine the effects of the technology on health outcomes.

**TACE for Symptomatic Unresectable Neuroendocrine Tumors**

For individuals who have symptomatic metastatic neuroendocrine tumors despite systemic therapy and are not candidates for surgical resection who receive TACE, the evidence includes retrospective single-cohort studies. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. There is a lack of evidence from RCTs supporting the use of TACE. Uncontrolled trials have suggested that TACE reduces symptoms and tumor burden and improves hormone profiles. Generally, the response rates are over 50% and include patients with massive hepatic tumor burden. While many studies have demonstrated symptom control, survival benefits are less clear. Despite the uncertain benefit on survival, the use of TACE to palliate the symptoms associated with hepatic neuroendocrine metastases can provide a clinically meaningful improvement in net health outcome. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Liver-Dominant Metastatic Uveal Melanoma**

For individuals who have liver-dominant metastatic uveal melanoma who receive TACE, the evidence includes observational studies and reviews. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. There is a lack of evidence from RCTs assessing the use of TACE. Non-comparative prospective and retrospective studies have reported improvements in tumor response and survival compared with historical controls. Given the very limited treatment response from systemic therapy and the rarity of this condition, the existing evidence may support conclusions that TACE meaningfully improves outcomes for patients with hepatic metastases from uveal melanoma. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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Other Unresectable Hepatic Metastases

For individuals who have unresectable hepatic metastases from any other types of primary tumors (eg, colorectal or breast cancer) who receive TACE, the evidence includes multiple RCTs, observational studies, and systematic reviews. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. Multiple RCTs and numerous nonrandomized studies have compared TACE with alternatives in patients who have colorectal cancer (CRC) and metastases to the liver. Nonrandomized studies have reported that TACE can stabilize disease in 40% to 60% of treated patients but whether this translates into a prolonged survival benefit relative to systemic chemotherapy alone is uncertain. Two small RCTs have reported that TACE with drug-eluting beads has resulted in statistically significant improvements in response rate and progression-free survival. Whether this translates into a prolonged survival benefit relative to systemic chemotherapy alone is uncertain. For cancers other than colorectal, the evidence is extremely limited and no conclusions can be made. Studies have assessed small numbers of patients and the results have varied due to differences in patient selection criteria and treatment regimens used. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network Guidelines

Hepatocellular Carcinoma

The NCCN (v.2.2019) guidelines on hepatocellular carcinoma list TACE as an option for patients, not candidates for surgically curative treatments or as a part of a strategy to bridge patients for other curative therapies (category 2A). The guidelines also recommend that patients with tumors size between 3 and 5 cm can be considered for combination therapy with ablation and arterial embolization and those with unresectable or inoperable tumors greater than 5 cm be treated using arterial embolic approaches or systemic therapies. Additionally, TACE in highly selected patients has been shown to be safe in the presence of limited tumor invasion of the portal vein.

Intrahepatic Cholangiocarcinoma

The NCCN (v.2.2019) guidelines on intrahepatic cholangiocarcinoma consider arterially directed therapies, including TACE, to be treatment options for unresectable and metastatic intrahepatic cholangiocarcinoma.

Neuroendocrine Tumors, Carcinoid, and Islet Cell Tumors

The NCCN (v.1.2019) guidelines on neuroendocrine tumors, carcinoid, and islet cell tumors consider chemoembolization as an effective approach for patients with hepatic-predominant metastatic disease (category 2A).

Uveal Cancer

No NCCN guidelines were identified for uveal malignancies as of May 2019.

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Colon Cancer

An update discussion is in process to establish the NCCN guidelines on the use of TACE for colorectal liver metastases (v.2.2019). As of this guideline version, the NCCN can recommend TACE only for clinical trials. 79.

Breast Cancer

The NCCN (v.1.2019) guidelines on breast cancer do not address TACE as a treatment option for breast cancer metastatic to the liver. 80.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES


2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transcatheter arterial chemoembolization of hepatic tumors. TEC Assessments. 2000;Volume 15;Tab 22.


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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tr>
<td>June 2012</td>
<td>New policy</td>
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<tr>
<td>March 2015</td>
<td>Replace policy</td>
<td>Policy updated with literature review. References 17 and 29 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>December 2016</td>
<td>Replace policy</td>
<td>Policy updated with literature review through June 14, 2016; references 6-7, 10, 16 and 47 added. Policy statements unchanged.</td>
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<tr>
<td>September 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through May 24, 2018; references 1, 5, 11, 12, 17, 29-42, 46, 55, 63 and 65 were added. A minor addition to policy was made to treat hepatocellular cancer that is unresectable but confined to the liver and not associated with portal vein thrombosis and liver function not characterized as Child-Pugh class C</td>
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<tr>
<td>September 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through May 6, 2019; references on NCCN updated. Policy statements unchanged.</td>
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