



FEP Medical Policy Manual

FEP 8.01.11 Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

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Related Policies:

7.01.75 - Cryosurgical Ablation of Primary or Metastatic Liver Tumors

7.01.91 - Radiofrequency Ablation of Primary or Metastatic Liver Tumors

8.01.43 - Radioembolization for Primary and Metastatic Tumors of the Liver

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 nonresectable tumors. Transcatheter arterial chemoembolization 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 2 independent blood supplies, and the ability of healthy hepatic tissue to grow and thus compensate for tissue mass lost during chemoembolization.

Transcatheter arterial chemoembolization (TACE) is a minimally invasive procedure performed by interventional radiologists who inject highly concentrated doses of chemotherapeutic agents into the tumor tissues and embolic agent(s) 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%).¹

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 posttreatment 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 1 lobe of the liver is treated during a single session, with subsequent embolization procedures scheduled 5 days to 6 weeks later. In addition, because the embolized vessel recanalizes, chemoembolization can be repeated as many times as necessary.

Adverse Events

Transcatheter arterial chemoembolization of the liver has been associated with potentially life-threatening toxicities and complications, including severe postembolization syndrome, hepatic insufficiency, abscess, or infarction. Transcatheter arterial chemoembolization 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, other locally ablative techniques (eg, radiofrequency ablation, cryoablation), and 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 individuals 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 individuals with hepatocellular cancer where the intent is to prevent further tumor growth and to maintain an individual's candidacy for liver transplant (see Policy Guidelines section);
- to treat liver metastasis in symptomatic individuals with metastatic neuroendocrine tumor whose symptoms persist despite systemic therapy and who are not candidates for surgical resection;
- to treat liver metastasis in individuals 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;
- as part of combination therapy (with radiofrequency ablation) for resectable or unresectable hepatocellular carcinoma;
- 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 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.

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 U.S. Food and Drug Administration approval.

RATIONALE

Summary of Evidence

Unresectable and Resectable Hepatocellular Carcinoma

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. Relevant outcomes are overall survival (OS), disease-specific survival, quality of life, and treatment-related mortality and morbidity. Evidence from 1 RCT has suggested that survival with TACE is at least as good as with systemic chemotherapy. One systematic review has highlighted possible biases associated with RCTs that compared TACE with no therapy. The evidence is sufficient to determine that the technology results in an 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. Relevant outcomes are OS, disease-specific survival, quality of life, 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-analyses 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-analyses 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 that the technology results in an improvement in the net health outcome.

For individuals who have resectable HCC who receive TACE plus radiofrequency ablation (RFA), the evidence includes a single RCT and a systematic review. Relevant outcomes are OS, disease-specific survival, quality of life, 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 systematic review, which included mostly retrospective observational studies, did not find a survival benefit with TACE plus RFA over surgery alone. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable HCC who receive TACE plus RFA, the evidence includes multiple systematic reviews and RCTs. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Multiple meta-analyses and RCTs have shown a consistent benefit in survival and recurrence-free survival (RFS) 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 stage more commonly found in the U.S. or Europe, the results may not be generalizable. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Bridge to Liver Transplant

For individuals who have a single hepatocellular 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 seeking to prevent further tumor growth and to maintain candidacy for liver transplant who receive pretransplant TACE, the evidence includes multiple small prospective studies. Relevant outcomes are OS, disease-specific survival, quality of life, 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. Transcatheter arterial chemoembolization 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 an 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. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Randomized controlled trials evaluating the benefit of adding TACE to the standard of care for patients with unresectable cholangiocarcinoma are lacking. Results of 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 that the technology results in an improvement in the net health outcome.

Transcatheter Arterial Chemoembolization 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. Relevant outcomes are OS, disease-specific survival, symptoms, quality of life, 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 an 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. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. There is a lack of evidence from RCTs assessing the use of TACE. Noncomparative 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 an improvement in the net health outcome.

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. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Multiple RCTs and numerous nonrandomized studies have compared TACE with alternatives in patients who have colorectal cancer 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 (PFS). 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 that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Hepatocellular Carcinoma

The National Comprehensive Cancer Network (NCCN) (v. v.1.2023) guidelines on hepatocellular carcinoma list TACE as an option for patients who are not candidates for surgically curative treatments or as a part of a strategy to bridge patients for other curative therapies.¹¹² Arterially directed therapies, including TACE, are appropriate for patients with unresectable or inoperable tumors that are not amenable to ablation therapy. Additionally, TACE in highly selected patients has been shown to be safe in the presence of limited tumor invasion of the portal vein. The American Association for the Study of Liver Diseases 2018 guidelines on hepatocellular carcinoma suggest using liver-directed therapies (which may include TACE) for bridging to liver transplant in patients with T2 lesions, in order to prevent disease progression and prevent dropouts from the waiting list.¹¹³ The guidelines recommend the use of locoregional therapies, including TACE, in patients with cirrhosis and T2 or T3 disease that is not amenable to resection or transplantation.

Intrahepatic Cholangiocarcinoma

The NCCN (v.2.2023) guidelines on biliary tract cancers including intrahepatic cholangiocarcinoma consider arterially directed therapies, including TACE, to be treatment options for unresectable and metastatic intrahepatic cholangiocarcinoma.¹¹²

Neuroendocrine and Adrenal Tumors

The NCCN (v.2.2022) guidelines on neuroendocrine and adrenal tumors recommend hepatic regional therapy, including arterial embolization, chemoembolization, or radioembolization, for unresectable liver metastases (category 2B).¹¹⁴

Uveal Melanoma Cancer

The NCCN (v.1.2023) guidelines on uveal melanoma state that in patients with disease that is confined to the liver, regional liver-directed therapies such as chemoembolization, radioembolization, or immunoembolization should be considered.¹¹⁵

Colon Cancer

The NCCN (v.2.2023) guidelines on colon cancer recommend TACE only for clinical trials.¹¹⁶ The American Society of Clinical Oncology (ASCO; 2020) resource-stratified guidelines on late-stage colorectal cancer state that patients with unresectable liver metastases may receive TACE (weak recommendation).¹¹⁷ However, this recommendation should only be implemented in centers with expertise in the technique, after multidisciplinary review, or in the context of a clinical trial. The 2022 guidelines for metastatic colorectal cancer from ASCO do not address TACE.¹¹⁸

Breast Cancer

The NCCN (v.4.2023) guidelines on breast cancer do not address TACE as a treatment option for breast cancer metastatic to the liver.¹¹⁹

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.

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

Date	Action	Description
June 2012	New policy	
March 2014	Replace policy	Policy updated with literature review. References added, updated. Policy statements unchanged.
March 2015	Replace policy	Policy updated with literature review. References 17 and 29 added. Policy statements unchanged
December 2016	Replace policy	Policy updated with literature review through June 14, 2016; references 6-7, 10, 16 and 47 added. Policy statements unchanged.
September 2018	Replace policy	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 statement 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
September 2019	Replace policy	Policy updated with literature review through May 6, 2019; references on NCCN updated. Policy statements unchanged.
September 2020	Replace policy	Policy updated with literature review through June 4, 2020; references added. The "as part of combination therapy (with radiofrequency ablation) for resectable or unresectable hepatocellular carcinoma" added to the investigational policy statement list in order to be consistent with the evidence appraisal; statements otherwise unchanged.
September 2021	Replace policy	Policy updated with literature review through June 3, 2021; references added. Policy statements unchanged.
September 2022	Replace policy	Policy updated with literature review through May 20, 2022; reference added and guidelines updated. Minor editorial refinements to policy statements; intent unchanged.
September 2023	Replace policy	Policy updated with literature review through May 23, 2023; reference added and guidelines updated. Policy statements unchanged.

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