

Protocol

Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

(80111)

Medical Benefit		Effective Date: 07/01/18	Next Review Date: 03/21
Preauthorization	No	Review Dates: 09/09, 09/10, 03/11, 03/12, 05/12, 03/13, 03/14, 03/15, 03/16, 03/17, 03/18, 03/19, 03/20	

Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With unresectable hepatocellular cancer confined to the liver and not associated with portal vein thrombosis	Interventions of interest are: • Transcatheter arterial chemoembolization	Comparators of interest are: • Other locally ablative techniques (e.g., radio-frequency ablation, cryoablation) • Systemic therapy • Supportive care	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With resectable hepatocellular cancer	Interventions of interest are: • Neoadjuvant or adjuvant transcatheter arterial chemoembolization	Comparators of interest are: • Other locally ablative techniques (e.g., radio-frequency ablation, cryoablation) • Systemic therapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With resectable hepatocellular cancer	Interventions of interest are: • Transcatheter arterial chemoembolization plus radiofrequency ablation	Comparators of interest are: • Surgery alone	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With unresectable hepatocellular cancer	Interventions of interest are: • Transcatheter arterial chemoembolization plus radiofrequency ablation	Comparators of interest are: • Radiofrequency ablation alone	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With one to three small hepatocellular tumors seeking to prevent tumor growth and maintain candidacy for liver transplant	Interventions of interest are: • Pretransplant transcatheter arterial chemoembolization	Comparators of interest are: • Other locally ablative techniques (e.g., radio-frequency ablation, cryoablation) • Systemic therapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With unresectable cholangiocarcinoma	Interventions of interest are: • Transcatheter arterial chemoembolization	Comparators of interest are: • Other locally ablative techniques (e.g., radio-frequency ablation, cryoablation) • Systemic therapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With symptomatic metastatic neuroendocrine tumor despite systemic therapy and are not candidates for surgical resection	Interventions of interest are: • Transcatheter arterial chemoembolization	Comparators of interest are: • Other locally ablative techniques (e.g., radio-frequency ablation, cryoablation) • Systemic therapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Symptoms • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With liver-dominant metastatic uveal melanoma	Interventions of interest are: • Transcatheter arterial chemoembolization	Comparators of interest are: • Other locally ablative techniques (e.g., radio-frequency ablation, cryoablation)	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With unresectable hepatic metastases from other types of primary tumors (e.g., colorectal, breast)	Interventions of interest are: • Transcatheter arterial chemoembolization	Comparators of interest are: • Other locally ablative techniques (e.g., radio-frequency ablation, cryoablation) • Systemic therapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related mortality • Treatment-related morbidity

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. 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.

SUMMARY OF EVIDENCE

UNRESECTABLE AND RESECTABLE HEPATOCELLULAR CARCINOMA

For individuals who have unresectable HCC confined to the liver and not associated with portal vein thrombosis who receive 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 (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. 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. 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. 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 four-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 the effects of the technology on health outcomes.

Bridge to Liver Transplant

For individuals who have a single hepatocellular 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 pretransplant TACE, the evidence includes multiple small prospective studies. 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. 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. 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. 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. 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 a meaningful improvement in the net health outcome.

Other Unresectable Hepatic Metastases

For individuals who have unresectable hepatic metastases from any other types of primary tumors (e.g., colorectal or breast cancer) who receive TACE, the evidence includes multiple RCTs, observational studies, and systematic reviews. 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 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.

POLICY

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).
- to treat liver metastasis in symptomatic patients with a 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 five cm or no more than three tumors each less than three cm in size, absence of extrahepatic disease or vascular invasion, and Child-Pugh class A or B.

BACKGROUND

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 to restrict tumor blood supply. The embolic agent(s) causes ischemia and necrosis of the tumor and slows anticancer drug washout. The most common anti-cancer 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 one lobe of the liver is treated during a single session, with subsequent embolization procedures scheduled five days to six weeks later. In addition, because the embolized vessel recanalizes, chemoembolization can be repeated as many times as necessary.

Adverse Events

TACE of the liver has been associated with potentially life-threatening toxicities and complications, including severe postembolization 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.

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.

RELATED PROTOCOLS

Cryosurgical Ablation of Primary or Metastatic Liver Tumors

Radioembolization for Primary and Metastatic Tumors of the Liver

Radiofrequency Ablation of Primary or Metastatic Liver Tumors

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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