Protocol

Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

(80111)

Medical Benefit		**Effective Date**: 07/01/18	**Next Review Date**: 03/19
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	

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	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)	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	Interventions of interest are: • Pretransplant 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

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)	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 who 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)	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

TACE for Unresectable Hepatocellular Carcinoma

For individuals who have unresectable hepatocellular carcinoma (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, disease-specific survival, quality of life, and treatment-related mortality and morbidity. There is evidence from a limited number of RCTs 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.

TACE for Resectable HCC as Neoadjuvant or Adjuvant Therapy

For individuals who have resectable HCC who receive neoadjuvant or adjuvant TACE, the evidence includes several RCTs and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Studies have shown little to no difference in overall survival 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 United States 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.

TACE Plus Radiofrequency Ablation for Resectable HCC

For individuals who have resectable hepatocellular cancer who receive TACE plus radiofrequency ablation (RFA), the evidence includes a single RCT. Relevant outcomes are overall survival, 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 to surgery for HCC lesions three cm or smaller. Further, an ad hoc subgroup analysis showed a significant benefit for surgery in recurrence and overall survival in patients with lesions larger than three cm. It cannot be determined from this trial whether TACE plus RFA is as effective as surgical resection for these small tumors. The evidence is insufficient to determine the effects of the technology on health outcomes.

TACE Plus RFA for Unresectable HCC

For individuals who have unresectable HCC who receive TACE plus RFA, the evidence includes multiple systematic reviews and RCTs. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Multiple meta-analyses and RCTs have shown a consistent benefit in survival or recurrence-free survival in favor of 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, included data from a study retracted due to questions about veracity of the data. A larger well-conducted RCT has reported relative reduction in the hazard of death by 44% and a 14% difference in four-year survival in favor of 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 need such as those with multiple lesions larger than three 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 United States or Europe, the results may not be generalizable. The evidence is insufficient to determine the effects of the technology on health outcomes.

TACE as a Bridge to Liver Transplant

For individuals who have a single hepatocellular 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 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 overall survival, 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 to 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.

TACE for Unresectable Cholangiocarcinoma

For individuals who have unresectable cholangiocarcinoma who receive TACE, the evidence includes several retrospective observational studies and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. RCTs evaluating the benefit of adding TACE to standard of care for patients with unresectable cholangiocarcinoma are lacking. Results of three retrospective studies have shown a survival benefit with TACE over 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 tumor despite systemic therapy who are not candidates for surgical resection who receive TACE, the evidence includes retrospective single-cohort studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. There is a lack of evidence from RCTs supporting use of TACE. Uncontrolled trials have reported that TACE reduces symptoms and tumor burden, and improves hormone profiles. Generally, the response rates are over 50% including 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 transcatheter arterial chemoembolization 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.

TACE for 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 overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. There is a lack of evidence from RCTs assessing use of TACE. Noncomparative prospective and retrospective studies have reported improvement 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.

TACE for Other Unresectable Hepatic Metastases

For individuals who have unresectable hepatic metastases from any other types of primary tumor (e.g., colorectal or breast cancer) who receive TACE, the evidence includes multiple RCTs, observational studies, and systematic reviews. Relevant outcomes are overall survival, 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 with metastases to the liver. Nonrandomized studies report that TACE can stabilize disease in 40% to 60% of treated patients but whether this translates into 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 conclu-

sions can be made. Studies have 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 metastatic neuroendocrine tumors 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 hepatic arterial chemoembolization 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 of either 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 anticancer drugs used in published TACE studies for HCC 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.

Hepatocellular Carcinoma

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 HCC, cholangiocarcinoma, liver metastases, and in the liver transplant setting. Treatment alternatives include resection when possible, chemotherapy administered systemically or by hepatic artery infusion (HAI). HAI involves continuous infusion of chemotherapy with an implanted pump, while TACE is administered episodically. HAI does not involve the use of embolic material.

Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy after HCC (10% vs. 90%, respectively). Surgical resection represents the only form of curative therapy, however, most ICC patients are not surgical candidates due to their advanced disease at diagnosis, which is caused by the lack of symptoms until late in the disease. The overall prognosis of ICC is far worse than for extrahepatic cholangiocarcinoma because of its late presentation. Most patients with ICC qualify for palliative therapy, including systemic chemotherapy and radiotherapy. However, such palliative options afford little to no survival improvement over supportive therapy alone, because ICC responds poorly to such existing therapies.[2] Survival prognosis for patients with unresectable ICC is five to eight months.

TACE has been explored in various settings as a technique to prevent tumor progression in patients on the liver transplant waiting list, to downstage tumors so a patient may be considered a better candidate for liver transplantation, and to decrease the incidence of posttransplant recurrence in patients with larger (T3) tumors. All uses are in part related to the United Network for Organ Sharing (UNOS) liver allocation policy, which prioritizes patients for receiving donor livers. The UNOS policy and the three treatment settings are discussed further in the following sections.

Neuroendocrine Tumors

Neuroendocrine tumors are a heterogeneous group of typically slow-growing tumors with an indolent course, with the capacity to synthesize and secrete hormones. Liver metastases may result in significant hormonal symptoms and are associated with a poor prognosis. Systemic chemotherapy for these tumors has shown modest response rates of limited duration, and, although somatostatin analogues are usually effective at controlling symptoms, the disease eventually becomes refractory. Therefore, liver-directed therapies aim to reduce tumor burden, to lower hormone levels, and to palliate symptoms in patients with unresectable neuroendocrine metastases.

Uveal Melanoma

Uveal melanoma (also called ocular melanoma) is the most common primary ocular malignancy in adults and shows a strong predilection for liver metastases. Even with successful treatment of the primary tumor, up to 50% of patients will subsequently develop systemic metastases, with liver involvement in up to 90% of these patients. Metastatic uveal melanoma is resistant to systemic chemotherapy, leading to the evaluation of locoregional treatment modalities to control tumor progression in the liver, including TACE.

UNOS Liver Allocation Policy

In 2002, UNOS introduced the Model for End-Stage Liver Disease (MELD) system for allocating new livers to adults awaiting transplant.[3] The MELD score is a continuous disease severity scale incorporating bilirubin, pro-

thrombin time (i.e., international normalized ratio), and creatinine into an equation, producing a number that ranges from six (less ill) to 40 (gravely ill). Aside from those in fulminant liver failure, donor livers are prioritized to those with the highest MELD score. This system accurately predicts the risk of dying from liver disease except for those with HCC, who often have low MELD scores, because bilirubin, international normalized ratio, and creatinine levels are near normal. Therefore, patients with HCC are assigned additional allocation points according to the size and number (T stage) of tumor nodules as follows:

T1: one nodule greater than one cm and 1.9 cm or smaller

T2: one nodule between two and five cm, or two or three nodules each one cm or greater and up to three cm

T3: one nodule larger than five cm, or two or three nodules with at least one larger than three cm.

Patients with T1 lesions are considered at low risk of death on the waiting list, while those with T3 lesions are at high risk of posttransplant recurrence and are generally not considered transplant candidates. Patients with T2 tumors have an increased risk of dying while on the waiting list compared to those with T1 lesions, and are an acceptable risk of posttransplant tumor recurrence. Therefore, UNOS criteria, which were updated in 2013, prioritize only T2 HCC patients who meet specified staging and imaging criteria by allocating additional points equivalent to a MELD score predicting a 15% probability of death within three months. This definition of T2 lesions is often referred to as the Milan criteria, in reference to a key 1996 study that examined the recurrence rate of HCC according to the size of the initial tumor.[4] Liver transplantation for those with T3 HCC is not prohibited, but these patients do not receive any priority on the waiting list. All patients with HCC awaiting transplantation are reassessed at three-month intervals. Those whose tumors have progressed and are no longer T2 tumors lose the additional allocation points.

Additionally, nodules identified through imaging of cirrhotic livers are given an Organ Procurement and Transplantation Network class 5 designation. Class 5B and 5T nodules are eligible for automatic priority. Class 5B criteria consist of a single nodule two cm or larger and up to five cm (T2 stage) that meets specified imaging criteria. Class 5T nodules have undergone subsequent locoregional treatment after being automatically approved on initial application or extension. A single class 5A nodule (> one cm and < two cm) corresponds to T1 HCC and does not qualify for automatic priority. However, combinations of class 5A nodules are eligible for automatic priority if they meet stage T2 criteria. Class 5X lesions are outside of stage T2 and are not eligible for automatic exception points. Nodules less than one cm are considered indeterminate and are not considered for additional priority.

The UNOS allocation system provides strong incentives to use locoregional therapies to downsize tumors to T2 status and to prevent progression while on the waiting list. A 2010 report of a national conference in the United States addressed the need to characterize better the long-term outcomes of liver transplantation for patients with HCC and to assess justification for continuing the policy of assigning increased priority for candidates with early-stage HCC on the U.S. transplant waiting list.[5] There was a general consensus for developing a calculated continuous HCC priority score for ranking HCC candidates on the list that would incorporate the calculated MELD score, α-fetoprotein, tumor size, and rate of tumor growth and that only candidates with at least stage T2 tumors would receive additional HCC priority points. The report addressed the role of locoregional therapy to downstage patients from T3 to T2 and stated that the results of downstaging before liver transplantation are heterogeneous, with no upper limits for tumor size and number before downstaging across studies, and the use of different end points for downstaging before transplantation.

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 (FDA). However, the embolizing agents and drugs are subject to FDA 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

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

References

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

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