MEDICAL POLICY – 8.01.505

Transcatheter Arterial Chemoembolization as a Treatment for Primary or Metastatic Liver Malignancies

BCBSA Ref. Policy: 8.01.11

Effective Date: Oct. 1, 2018
Last Revised: Oct. 10, 2018
Replaces: 8.01.11

RELATED MEDICAL POLICIES:
7.01.95 Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors
7.01.133 Microwave Tumor Ablation
8.01.521 Radioembolization for Primary and Metastatic Tumors of the Liver

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Embolization is procedure to block blood flow. When the material used to block the blood flow contains chemotherapy agents as well, it is a way to treat liver cancer in some situations. This treatment is usually known as TACE. In this procedure a catheter (a long, thin, hollow tube) is inserted in an artery near the groin. It’s threaded to the tumor’s blood supply. Chemotherapy and tiny particles are then sent directly into the tumor. The particles block off — embolize — the artery feeding the tumor, causing it to shrink. The chemotherapy works to kill the cancer cells. This treatment can be used in the liver because it has two sources of blood: the portal vein and the hepatic artery. The portal vein supplies most of the blood to the liver. The hepatic artery supplies a lesser amount, and tumors that grow in the liver usually get their blood supply from the hepatic artery. As a result, TACE can be used to starve the blood supply of the tumor usually without affecting the blood supply to the rest of the liver. This policy describes when TACE may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
# Policy Coverage Criteria

## Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcatheter hepatic arterial chemoembolization</td>
<td>Transcatheter hepatic arterial chemoembolization may be considered medically necessary for the following situations:</td>
</tr>
<tr>
<td></td>
<td>• Hepatocellular cancer that is unresectable but confined to the liver and not associated with portal vein thrombosis</td>
</tr>
<tr>
<td></td>
<td>• 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, and the following is true:</td>
</tr>
<tr>
<td></td>
<td>o A single tumor less than 5 cm or no more than 3 tumors each less than 3 cm in size</td>
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<td></td>
<td>o Absence of extrahepatic disease or vascular invasion</td>
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<tr>
<td></td>
<td>o Child-Pugh score of either A or B</td>
</tr>
<tr>
<td></td>
<td>• Treat liver metastasis in patients with metastatic neuroendocrine tumor with both of the following:</td>
</tr>
<tr>
<td></td>
<td>o Whose symptoms persist despite systemic therapy AND</td>
</tr>
<tr>
<td></td>
<td>o Who are not candidates for surgical resection</td>
</tr>
<tr>
<td></td>
<td>• To treat liver metastasis in patients with liver-dominant metastatic uveal melanoma</td>
</tr>
</tbody>
</table>

## Investigational

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcatheter hepatic arterial chemoembolization</td>
<td>Transcatheter hepatic arterial chemoembolization is considered investigational in all of the following situations:</td>
</tr>
<tr>
<td></td>
<td>• As neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable</td>
</tr>
<tr>
<td></td>
<td>• When used with radiofrequency ablation (RFA) to treat resectable or unresectable hepatocellular carcinoma</td>
</tr>
<tr>
<td></td>
<td>• To treat unresectable cholangiocarcinoma</td>
</tr>
<tr>
<td></td>
<td>• 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</td>
</tr>
</tbody>
</table>
### Treatment

<table>
<thead>
<tr>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>• To treat hepatocellular tumors prior to liver transplantation except as noted above</td>
</tr>
</tbody>
</table>

### Documentation Requirements

The patient’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the relevant history and physical of ANY these situations:
  - Patient has primary liver cancer that cannot be surgically removed, located only in the liver and does not involve clot or narrowing of the portal vein
  - As a short-term treatment for patient with primary liver cancer waiting for a liver transplant, and the following are true
    - 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
    - Child-Pugh score of either A or B
  - Patient has tumors from neuroendocrine cancer that have spread to the liver when the tumors can’t be removed surgically and have not responded to other therapy
  - Patient has tumors in the liver that have spread from liver-dominant metastatic uveal melanoma

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction</td>
</tr>
<tr>
<td>37243</td>
<td>Transcatheter therapy, embolization, any method, radiological supervision and interpretation</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

### Related Information
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 2 independent blood supplies, and the ability of healthy hepatic tissue to grow and thus compensate for tissue mass lost during chemoembolization.

**Background**

*Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma*

In 2015, an estimated 71,990 people in the United States live with hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma (ICC). Of the primary intrahepatic cancers, HCC and ICC account for 90% and 10% of cases, respectively. The number of new cases of HCC and ICC are estimated at 8.8 per 100,000 men and women per year. The number of deaths are estimated at 6.4 per 100000 men and women per year.¹

**Treatment**

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 disease progression. 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 benefit over supportive therapy alone, because ICC responds poorly to such existing therapies.\textsuperscript{2} Survival prognosis for patients with unresectable ICC is 5 to 8 months.

Transcatheter arterial chemoembolization (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 3 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.

**Treatment**

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.
Treatment

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.

Transcatheter Arterial 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 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 (HCC) 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 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

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 the continuous infusion of chemotherapy with an implanted pump, while TACE is administered episodically. HAI does not involve the use of embolic material.


**UNOS Liver Allocation Policy**

In 2002, UNOS introduced the Model for End-Stage Liver Disease (MELD) system for allocating new livers to adult patients awaiting transplant. The MELD score is a continuous disease severity scale incorporating bilirubin, prothrombin time (ie, international normalized ratio [INR]), and creatinine into an equation, producing a number that ranges from 6 (less ill) to 40 (gravely ill). Aside from those in fulminant liver failure, donor livers are prioritized to those with the highest MELD number. This system accurately predicts the risk of dying from liver disease except for those with HCC, who often have low MELD scores, because bilirubin, INR, 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**: 1 nodule greater than 1 cm and 1.9 cm or smaller
- **T2**: 1 nodule between 2.0 and 5.0 cm, or 2 or 3 nodules each 1 cm or greater and up to 3.0 cm
- **T3**: 1 nodule larger than 5.0 cm, or 2 or 3 nodules with at least 1 larger than 3.0 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 3 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. 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 3-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 OPTN (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 2 cm or larger and up to 5 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 (>1 cm and <2 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 1 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 better characterize 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. 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.

**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 RCTs, large observational studies, and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, 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 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 the 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.

For individuals who have resectable HCC who receive TACE plus 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 with surgery for HCC lesions 3.0 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 3 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.

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 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 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.

**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 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.

**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. RCT evaluating the benefit of adding TACE to standard of care for patients with unresectable cholangiocarcinoma are lacking. Results of 3 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 tumors 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 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 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.

Other Unresectable Hepatic Metastases

For individuals who have unresectable hepatic metastases from any other types of primary tumor (eg, 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 conclusions 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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.
Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01869088</td>
<td>Phase III Trial of Transcatheter Arterial Chemoembolization (TACE) Plus Recombinant Human Adenovirus Type 5 Injection for Unresectable Hepatocellular Carcinoma (HCC)</td>
<td>266</td>
<td>Jan 2018 (ongoing)</td>
</tr>
<tr>
<td>NCT01004978</td>
<td>A Phase III Randomized, Double-Blind Trial of Chemoembolization With or Without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients With and Without Vascular Invasion</td>
<td>400</td>
<td>Jul 2018</td>
</tr>
<tr>
<td>NCT02936388</td>
<td>Transarterial Radioembolisation in Comparison to Transarterial Chemoembolisation in Uveal Melanoma Liver Metastasis (SirTac)</td>
<td>108</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT01906216</td>
<td>Sorafenib With or Without Transarterial Chemoembolization (TACE) in Advanced Hepatocellular Carcinoma: A Multicenter, Randomized, Controlled Trial</td>
<td>246</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT01833286</td>
<td>Radiofrequency Ablation Combined With Transcatheter Arterial Chemoembolization Versus Re-resection for Recurrent Hepatocellular Carcinoma</td>
<td>200</td>
<td>Jul 2019</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
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<tr>
<td>NCT01676194</td>
<td>Efficacy of Transarterial Chemoembolization With DC-BeadsR Prior to Liver Transplantation for Hepatocellular Carcinoma on Patient Survival: A Prospective Multicentre and Randomized Study</td>
<td>140</td>
<td>Aug 2017 (unknown)</td>
</tr>
<tr>
<td>NCT01512407</td>
<td>Randomised Controlled Trial on Adjuvant Transarterial Chemoembolisation After Curative Hepatectomy for Hepatocellular Carcinoma</td>
<td>144</td>
<td>Jan 2018 (unknown)</td>
</tr>
<tr>
<td>NCT00908752a</td>
<td>A Randomized, Double-blind, Multicenter Phase III Study of Brivanib Versus Placebo as Adjuvant Therapy to Trans-Arterial Chemo-Embolization (TACE) in Patients With Unresectable Hepatocellular Carcinoma (The BRISK TA Study)</td>
<td>734</td>
<td>Jan 2018 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.
Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 1 specialty medical society (2 reviewers) and 3 academic medical centers while this policy was under review in 2012. There was general agreement among reviewers that use of TACE was medically necessary for indications in the policy; however, they were split for the use as a bridge to transplant. There was general support for the investigational policy statement for the use of TACE as neoadjuvant or adjuvant therapy in resectable HCC. Reviewers were split over the investigational policy statement to treat other liver metastases or for recurrent HCC. Four reviewers provided input on the use of TACE in unresectable cholangiocarcinoma; 2 consider it investigational and 2 consider it investigational but also medically necessary, the latter citing data showing a survival benefit of TACE compared with supportive therapy.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network Guidelines

Hepatocellular Carcinoma

National Comprehensive Cancer Network (NCCN) guidelines on hepatocellular carcinoma (v.2.2018) list transarterial chemoembolization as an option for patients not candidates for surgically curative treatments or as a part of 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**

NCCN guidelines on intrahepatic cholangiocarcinoma (v.2.2018) consider arterially directed therapies, including TACE, to be treatment options for unresectable and metastatic intrahepatic cholangiocarcinoma.\(^77\)

**Neuroendocrine Tumors, Carcinoid, and Islet Cell Tumors**

NCCN guidelines on neuroendocrine tumors, carcinoid, and islet cell tumors (v.2.2018) consider chemoembolization as an effective approach for patients with hepatic-predominant metastatic disease (category 2A).\(^78\)

**Uveal Cancer**

No NCCN guidelines were identified for uveal malignancies.

**Colon Cancer**

NCCN guidelines on colon cancer (v.2.2018) recommend that, for highly selected patients with chemotherapy-resistant and -refractory disease and with predominant hepatic metastases, arterially directed catheter therapy and, in particular, yttrium-90 microsphere selective internal radiation is an option.\(^79\)

**Breast Cancer**

NCCN guidelines on breast cancer (v.1.2018) do not address TACE as a treatment option for breast cancer metastatic to the liver.\(^80\)

**Medicare National Coverage**

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

References


43. Cheng BQ, Jia CQ, Liu CT, et al. Chemoembolization combined with radiofrequency ablation for patients with hepatocellular carcinoma larger than 3 cm: a randomized controlled trial. JAMA. Apr 09 2008;299(14):1669-1677. PMID 18398079


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/01/99</td>
<td>Add to Therapy Section - New Policy</td>
</tr>
<tr>
<td>12/10/02</td>
<td>Replace Policy - Policy reviewed; no criteria changes.</td>
</tr>
<tr>
<td>08/12/03</td>
<td>Replace Policy - Reviewed and recommended for adoption without any changes by Company Oncology Advisory Panel July 22, 2003</td>
</tr>
<tr>
<td>01/13/04</td>
<td>Replace Policy - Policy reviewed; no change to policy statement. References added.</td>
</tr>
<tr>
<td>09/01/04</td>
<td>Replace Policy - Policy renumbered from PR.8.01.105. No changes to dates.</td>
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<tr>
<td>12/14/04</td>
<td>Replace Policy - Scheduled review; policy statement unchanged. Reviewed and approved by OAP 10/29/04</td>
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<tr>
<td>11/11/05</td>
<td>Replace Policy - Scheduled review; policy statement unchanged. To OAP 1st quarter 2006.</td>
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<tr>
<td>06/02/06</td>
<td>Disclaimer and Scope update - No other changes.</td>
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<tr>
<td>11/14/06</td>
<td>Replace Policy - Policy updated with literature review; references added; no change in policy statement.</td>
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<tr>
<td>04/10/07</td>
<td>Cross Reference Update - No other changes.</td>
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<td>06/15/07</td>
<td>Cross Reference Update - No other changes.</td>
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<tr>
<td>11/13/07</td>
<td>Replace Policy - Policy updated with literature review; reference added; no change in policy statement.</td>
</tr>
<tr>
<td>06/10/08</td>
<td>Replace Policy - Policy updated with literature search. Policy statement updated to include “hepatocellular carcinoma or unresectable hepatocellular carcinoma (HCC) in patients who may be waiting for a liver transplant” as a medically necessary indication. References and cross reference added. Reviewed and recommended by the Oncology Advisory Panel on February 21, 2008.</td>
</tr>
<tr>
<td>10/14/08</td>
<td>Code Updates - S2095 removed from policy, no other changes.</td>
</tr>
<tr>
<td>11/11/08</td>
<td>Cross Reference Update - No other changes.</td>
</tr>
<tr>
<td>08/11/09</td>
<td>Replace Policy - Policy updated with literature review; reference added; no change in policy statement.</td>
</tr>
<tr>
<td>08/10/10</td>
<td>Replace Policy - Policy updated with added guidelines to limit treatment to patients with a single lesion of less than 5 cm or no more than 3 tumors each less than 3 cm in size per OAP recommendation following review in May 2010.</td>
</tr>
<tr>
<td>07/12/11</td>
<td>Replace Policy - Policy updated with literature search and NCCN Practice Guidelines update. No change to the policy statement.</td>
</tr>
<tr>
<td>02/27/12</td>
<td>Related policies updated; 7.01.133 added.</td>
</tr>
<tr>
<td>04/10/12</td>
<td>Replace policy. Policy updated with extensive reorganization to the Rationale and References sections; Description and Policy Guidelines also updated. Policy statements expanded to outline medical necessity coverage for treatment of hepatocellular cancer that is unresectable but confined to the liver and not associated with portal vein thrombosis; as a bridge to transplant for patients with hepatocellular cancer with the intention of preventing further tumor growth and maintaining patient’s candidacy for liver transplant; to treat liver metastasis in symptomatic patients with metastatic neuroendocrine tumor with persisting symptoms despite systemic therapy who are not candidates for surgical resection; and to treat liver metastasis in patients with liver-dominant metastatic uveal melanoma. Two new investigational policy statements have been added, one addressing treatment of liver metastases for any other tumors, the other addressing the treatment of unresectable cholangiocarcinoma. Reviewed by OAP</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>on February 16, 2012.</td>
<td></td>
</tr>
<tr>
<td>10/09/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
</tr>
<tr>
<td>05/28/13</td>
<td>Replace policy. Policy updated with literature search. References reordered and 3, 12, and 28 added. Policy statement was unchanged.</td>
</tr>
<tr>
<td>12/23/13</td>
<td>Coding Update. CPT code 37204 discontinued effective 12/31/13.</td>
</tr>
<tr>
<td>05/05/14</td>
<td>Annual Review. Policy updated with literature search. References 7,8,10,13,44,47 added, No change to policy statements. Coding update: deleted code 37204 replaced with 37243 (added to policy); HCPCS code Q0083 removed – not specific to policy. ICD-9 code 9925 removed, as it is not applicable; ICD-9 and ICD-10 diagnosis codes remove – these are not utilized in adjudication of policy.</td>
</tr>
<tr>
<td>09/11/14</td>
<td>Update Related Policies. Add 7.01.95.</td>
</tr>
<tr>
<td>10/13/15</td>
<td>Annual Review. Policy updated with literature review; no change in policy statements.</td>
</tr>
<tr>
<td>10/01/17</td>
<td>Annual Review, approved September 5, 2017. References updated through June 12, 2017; references 11, 12, 29–42, 46, 63, and 65 were added. No changes made to the intent of the policy statements, minor addition 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>
</tr>
<tr>
<td>10/01/18</td>
<td>Annual Review, approved September 11, 2018. Policy updated with literature review through May 2018; references 1, 5, 17, 35–37, and 55 added; references 77–80 updated. Policy statements unchanged.</td>
</tr>
<tr>
<td>10/10/18</td>
<td>Minor update, added Documentation Requirements section.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at:
https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at:

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):

Deutsche (German):

Hmoob (Hmong):
Tsaab ntawv tshaj xo no muaj cov ntsiab lus tsen ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntsiab lus tseem ceeb tao koj daitwv thov kve pab los yoy koj khev kve pab cuam los ntawv Premera Blue Cross. Tej zaum muaj cov hnbv tseem ceeb uss aau rau hauv daim daitwv no. Tej zaum koj kuj yaw uaa que eem saw peb kum koj us teb pib dhaa cov caj nyong uaa teev tsev rau hauv daim ntawv no mas koj tshaj yuuva baiv kve pab cuam kuh moob los yoy khev pab thaj tey nqi kho moob ntawv. Koj muaj cai kom laww mub cov ntsiab lus no uaa tae mbu aai saa koj hom lus pab daww rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Illoko (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyonno weny coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikulur a naituding nga aladw tapno mapagatlaidenyo a coverage ti salun-atayo weny tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagasasao nga awan ti bayadan. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Premera Blue Cross Agency, Inc. (TTY: 800-842-5357)

Este aviso continua información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

TAGALOG (Tagalog):

Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

RUS (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

ESPAÑOL (Spanish):
Este aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

한국어 (Korean):
본 통지서에는 중요한 정보들이 있습니다. 즉 이 통지서는 귀하는 Premera Blue Cross를 통해 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 귀하는 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하는 이러한 정보로 인한 귀하의 면책 또는 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357)로 문의하시오.

Română (Romanian):

日本語 (Japanese):
この通知には重要な情報が含まれています。この通知では、Premera Blue Crossの申請または補償範囲に関する重要な情報が含まれています。この通知には記載されている情報が重要な日を確認してください。健康保険や無料サポートを維持するには、特定の期間までに行動を取りなければなりません。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):
본 통지서에는 중요한 정보들이 있습니다. 즉 이 통지서는 귀하는 Premera Blue Cross를 통해 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 귀하는 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하는 이러한 정보로 인한 귀하의 면책 또는 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357)로 문의하시오.

Indonesia (Bahasa Indonesia):

Polski (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie przeszedłego poprzednio Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utraty polisy ubezpieczeniowej lub pomocy związanej z kobietą. Macie prawo do bezpłatnej informacji we własnym języku. Zadzwoń pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde e ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).