



MASSACHUSETTS

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## Medical Policy

# Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

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### Related Policies

- Cryosurgical Ablation of Primary or Metastatic Liver Tumors, [#633](#)
- Radiofrequency Ablation of Primary or Metastatic Liver Tumors, [#286](#)
- Radioembolization for Primary and Metastatic Tumors of the Liver, [#292](#)

### Policy

#### Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue<sup>SM</sup> and Medicare PPO Blue<sup>SM</sup> Members

Transcatheter hepatic arterial chemoembolization, including the use of drug-eluting beads<sup>1</sup>, may be **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.
- To treat liver metastasis in symptomatic patients with metastatic neuroendocrine tumor whose symptoms persist despite systemic therapy and who are not candidates for surgical resection, or
- To treat liver metastasis in patients with liver-dominant metastatic uveal melanoma.

Transcatheter hepatic arterial chemoembolization, including the use of drug-eluting beads<sup>1</sup>, is **INVESTIGATIONAL**:

- As neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable,
- To treat hepatocellular tumors prior to liver transplantation except as noted above,
- 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, or
- To treat unresectable cholangiocarcinoma.

## Prior Authorization Information

### Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

### Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is <b>required</b> .
Commercial PPO and Indemnity	Prior authorization is <b>required</b> .
Medicare HMO Blue <sup>SM</sup>	Prior authorization is <b>required</b> .
Medicare PPO Blue <sup>SM</sup>	Prior authorization is <b>required</b> .

## CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above **medical necessity criteria MUST** be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue, and Medicare PPO Blue:

### CPT Codes

CPT Codes	Code Description
37243	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
75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation

## Description

### 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 100,000 men and women per year.

### 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.<sup>2</sup> 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 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 adults awaiting transplant. The MELD score is a continuous disease severity scale incorporating bilirubin, prothrombin time (ie, international normalized ratio), 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 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: 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 with those who had T1 lesions and are an acceptable risk of posttransplant tumor recurrence. Therefore, UNOS criteria, which were updated in 2018, 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 study by Mazzaferro et al (1996) 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 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 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. In a report from a national conference in the United States, Pomfret et al (2010) addressed the need to characterize better the long-term outcomes of liver transplantation for patients with HCC and to assess the 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,  $\alpha$ -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

### 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 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 overall survival, disease-specific survival, quality of life, 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 3 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 overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. There is a lack of evidence from RCTs supporting the use of TACE. Uncontrolled trials have suggested that TACE reduces symptoms and tumor burden and improves hormone profiles. Generally, the response rates are over 50% and include patients with massive hepatic tumor burden. While many studies have demonstrated symptom control, survival benefits are less clear. Despite the uncertain benefit on survival, the use of TACE to palliate the symptoms associated with hepatic neuroendocrine metastases can provide a clinically meaningful improvement in net health outcome. The evidence is sufficient to determine that the technology results in 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 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 (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 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 History**

<b>Date</b>	<b>Action</b>
9/2018	BCBSA National medical policy review. No changes to policy statements. New references added. Background and summary clarified.
12/2017	BCBSA National medical policy review.

	Medically necessary criteria revised. Effective 12/1/2017.
10/2016	New references added from BCBSA National medical policy.
11/2015	New references added from BCBSA National medical policy.
12/2014	New references added from BCBSA National medical policy.
8/2014	Clarified coding information.
1/2014	New references added from BCBSA National medical policy.
1/2014	Updated to remove deleted code 37204.
2/2013	BCBSA National medical policy review. Changes to policy statement. Effective 2/4/2013.
11/2011- 4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
12/2011	BCBSA National medical policy review. No changes to policy statements.
10/2011	Reviewed - Medical Policy Group - Gastroenterology, Nutrition and Organ Transplantation. No changes to policy statements.
7/2011	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
11/2010	Reviewed - Medical Policy Group - Gastroenterology, Nutrition and Organ Transplantation. No changes to policy statements.
9/2010	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
6/2010	BCBSA National medical policy review. No changes to policy statements.
9/2009	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
9/2009	BCBSA National medical policy review. No changes to policy statements.
11/2008	Reviewed - Medical Policy Group - Gastroenterology, Nutrition and Organ Transplantation. No changes to policy statements.
10/2008	BCBSA National medical policy review. No changes to policy statements.
9/2008	BCBSA National medical policy review. Changes to policy statements.
1/2008	BCBSA National medical policy review. Changes to policy statements.
9/2007	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.

## Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

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## Endnotes

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<sup>1</sup> Based on local expert opinion