

Corporate Medical Policy

Chemoembolization of the Hepatic Artery, Transcatheter Approach

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Description of Procedure or Service

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

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 the time of 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. Survival prognosis for patients with unresectable ICC is approximately 5 to 8 months.

TACE of the liver is associated with its own potentially life-threatening toxicities and complications, including severe postembolization syndrome, hepatic insufficiency, abscess, or infarction. TACE has been investigated to treat resectable, unresectable, and recurrent hepatocellular carcinoma, cholangiocarcinoma, liver metastases, and in the liver transplant setting. Treatment alternatives include resection when possible, chemotherapy administered systemically or by hepatic artery infusion. Hepatic artery infusion involves continuous infusion of chemotherapy with an implanted pump while TACE is administered episodically. Also, hepatic artery infusion does not involve the use of embolic material.

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 such that the patient is considered a better candidate for liver transplantation, and to decrease the incidence of posttransplant recurrence in patients with larger (T3) tumors. All of these 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 previous 3 uses are discussed further in the following sections.

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 analogs are usually effective in controlling symptoms, the disease eventually becomes refractory. Therefore, liver-directed

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therapies aim to reduce tumor burden to lower hormone levels and to palliate symptoms in patients with unresectable neuroendocrine metastases.

The TACE procedure requires hospitalization for placement of the hepatic artery catheter and workup to establish eligibility for chemoembolization. Prior to the procedure, the patency of the portal vein must be demonstrated to ensure an adequate post-treatment 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 from 5 days to 6 weeks later. In addition, since the embolized vessel recanalizes, chemoembolization can be repeated as many times as necessary.

Uveal (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 a new liver allocation system model for end-stage liver disease (referred to as MELD) for adult patients awaiting liver 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 scale 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

In considering how to allocate the scarce donor organs, UNOS sought to balance risk of death on the waiting list against risk of recurrence after transplant. 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 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.³ 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 will 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

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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 on liver allocation in patients with HCC in the United States addressed the need to better characterize the long-term outcomes of liver transplantation for patients with HCC and to assess whether it is justified to continue the policy of assigning increased priority for candidates with early-stage HCC on the U.S. transplant waiting list. There was a general consensus at the meeting for the development of 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.

Related Policies:

Cryosurgical Ablation of Primary or Metastatic Liver Tumors
Radioembolization for Primary and Metastatic Tumors of the Liver

This policy does not pertain to Intrahepatic Arterial Chemotherapy or Selective Internal Radiation Therapy for Tumors of the Liver.

****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.*

Policy

BCBSNC may provide coverage for Chemoembolization of the Hepatic Artery, Transcatheter Approach when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Chemoembolization of the Hepatic Artery, Transcatheter Approach is covered

Transcatheter hepatic arterial chemoembolization may be **medically necessary** for the following:

1. Hepatocellular cancer (HCC) 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; **Or**
2. 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; **Or**
3. Liver metastasis in symptomatic patients with metastatic neuroendocrine tumors whose symptoms persist despite systemic treatment and who are not candidates for surgical resection; **Or**
4. Liver metastasis in patients with liver-dominant metastatic uveal melanoma.

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When Chemoembolization of the Hepatic Artery, Transcatheter Approach is not covered

1. For indications other than those listed above.
2. Transcatheter hepatic arterial chemoembolization is considered **investigational**:
 - a. To treat liver metastases from any other tumors or to treat hepatocellular cancer that does not meet criteria noted above, including recurrent hepatocellular carcinoma.
 - b. To treat hepatocellular tumors prior to liver transplantation except as noted above.
 - c. As neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable.
 - d. To treat unresectable cholangiocarcinoma.

Policy Guidelines

When using transcatheter hepatic arterial chemoembolization as a bridge to transplant to prevent further tumor growth, the following patient characteristics apply:

1. a single tumor less than 5 cm or no more than 3 tumors each less than 3 cm in size, and
2. absence of extrahepatic disease or vascular invasion, and
3. Child-Pugh score of either A or B.

TACE for Unresectable Hepatocellular Carcinoma

There is evidence from a limited number of RCTs that TACE offers a survival advantage compared to no therapy and survival with TACE is at least as good as with systemic chemotherapy. There are no high-quality RCTs that compare TACE to other locoregional therapies such as radiofrequency ablation (RFA). As a result, no conclusions can be made about the comparative efficacy of TACE and other locoregional therapies.

TACE for Resectable HCC as Neoadjuvant or Adjuvant Therapy

Randomized and nonrandomized trials have evaluated TACE as adjuvant therapy to hepatic resection in HCC, either preoperatively or postoperatively. Most trials, including the highest quality RCTs, did not report differences in the survival rates when TACE was added to hepatic resection. Meta-analyses of these studies also reported no differences in outcomes on pooled analyses.

TACE as a Bridge to Liver Transplant

There is a lack of comparative trials on TACE as a bridge to liver transplantation. However, a number of uncontrolled studies report that TACE is associated with low rates of dropout from the transplant list, and is likely to reduce dropouts from the list. As a result, TACE has become an accepted component of care for patients with HCC on the waiting list for liver transplant.

TACE for Unresectable Cholangiocarcinoma

There are no RCTs on TACE for unresectable cholangiocarcinoma, and only a small amount of nonrandomized evidence. The nonrandomized evidence does not report that TACE is superior to alternatives for this population. Although this evidence has limitations, it does not rule out a beneficial effect of TACE. Therefore, no conclusions can be made on the efficacy of TACE for this indication.

TACE for Symptomatic Unresectable Neuroendocrine Tumors

For patients with unresectable neuroendocrine tumors, there is a lack of RCT evidence for TACE. Uncontrolled trials have reported that TACE reduces symptoms and tumor burden, and improves hormone profile. In addition, for this relatively rare condition, there are limited alternative treatments for these tumors.

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TACE for Hepatic Metastases From Uveal (Ocular) Melanoma

There is a lack of comparative trials for patients with hepatic metastases from uveal melanoma. Case series of treated patients have reported that tumor response and survival are improved compared to historical controls. There are limited treatment options and this condition is rare, making the performance of high-quality RCTs difficult or impossible. As a result, it is possible to conclude that TACE improves outcomes for patients with hepatic metastases from uveal melanoma.

TACE for Other Hepatic Metastases

For other types of hepatic metastases, the largest amount of evidence is for colorectal cancer. There is a single RCT and numerous nonrandomized studies that have compared TACE to alternatives. There is no evidence that TACE is superior or inferior to other therapies, however, the evidence base is limited by low-quality studies and meaningful differences in outcomes cannot be ruled out. For cancers other than colorectal, the evidence is extremely limited and no conclusions can be made.

Recurrent Hepatic Cancer

The evidence on TACE for patients who have recurrent HCC includes few cases typically reported within observational series; no comparative evidence is available on the use of TACE to treat HCC recurrence. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Studies have small numbers of patients and the results have been variable across studies due to differences in patient selection criteria and regimens used between different studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbssc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 37243, 75894, 75898

Diagnoses that are subject to medical necessity review:

ICD-10 Diagnosis Codes: C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C22.0, C22.1, C22.2, C22.3, C22.4, C22.7, C22.8, C22.9, K76.89, K76.9, C78.7, N94.89

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

TEC - 1/96

BCBSA Medical Policy Reference Manual, 8.01.11, issued 7/31/96.

Consultant Review - 6/98.

Medical Policy Advisory Group 11/98

Medical Policy Advisory Group - 12/99

BCBSA Medical Policy Reference Manual, 8.01.11; 5/31/01

Specialty Matched Consultant Advisory Panel - 6/01

Specialty Matched Consultant Advisory Panel - 6/03

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Specialty Matched Consultant Advisory Panel - 4/05

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.11. 4/1/2005

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.11. 4/25/2006

Specialty Matched Consultant Advisory Panel - 4/07

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.11. 2/14/2008

Specialty Matched Consultant Advisory Panel - 4/2009

BCBSA-Medical Policy Reference Manual [Electronic Version]. 8.01.11. 7/2009

Specialty Matched Consultant Advisory Panel- 5/2010

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.11. 10/8/2010

Specialty Matched Consultant Advisory Panel 5/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.11, 3/8/2012

Medical Director review 5/2012

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.11, 10/11/12

Specialty Matched Consultant Advisory Panel 7/2013

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.11, 10/10/13

Specialty Matched Consultant Advisory Panel 7/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.11, 10/9/14

Specialty Matched Consultant Advisory Panel 6/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.11, 9/10/15

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary cancer. Version 2.2016.

http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf.

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.11, 8/11/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.11, 7/13/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.11, 7/12/2018

Policy Implementation/Update Information

3/96	Original local policy issued.
11/96	Reaffirm: National Issued policy. No changes.
6/98	Reaffirm: Consultant review continues to indicate investigational.
6/99	Reformatted, Description of Procedure or Service changed, Medical Term Definitions added.
12/99	Medical Policy Advisory Group
4/01	System changes.

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- 7/01 Policy name changed from Transcatheter Chemoembolization of the Hepatic Artery to Chemoembolization of the Hepatic Artery, Transcatheter Approach
- 8/01 Specialty Matched Consultant Advisory Panel, 6/2001. Revised the policy statement for investigational status and added statement to policy guidelines.
- 6/03 Specialty Matched Consultant Advisory Panel review. No criteria changes.
- 11/11/04 CPT codes 75896 and 75898 were removed as they do not apply to this policy. Policy remains unchanged. Chemoembolization of the hepatic artery, transcatheter approach is considered investigational. Listed codes will be reviewed. Updated format of Benefit Application and Billing/Coding sections for consistency. Notification given 11/11/2004. Effective date 1/20/2005.
- 05/05/05 Specialty Matched Consultant Advisory Panel review 4/14/05. No changes to criteria. Information added in the "Description of Procedure or Service" indicating "*****Please note that this policy does not pertain to Intrahepatic Arterial Chemotherapy or Selective Internal Radiation Therapy for Tumors of the Liver.****" Policy guidelines added. References added.
- 6/2/05 Updated References.
- 5/21/07 Specialty Matched Consultant Advisory Panel review 4/25/2007. Revised "Description" section. Changed "Policy" to state that "BCBSNC may provide coverage for Chemoembolization of the Hepatic Artery, Transcatheter Approach when it is determined to be medically necessary because the medical criteria and guidelines shown below are met." Added criteria to the "When covered" section to indicate: "Chemoembolization of the hepatic artery, transcatheter approach may be medically necessary for the following: 1. For unresectable primary hepatocellular cancers (HCC); or 2. Prior to liver transplantation for hepatocellular cancer (HCC); or 3. For palliative treatment of functional neuroendocrine cancers that are symptomatic and involve the liver, such as: 3a. carcinoid tumors that have failed systemic therapy to control the carcinoid syndrome. Symptoms of carcinoid syndrome are debilitating wheezing, diarrhea, and flushing. 3b. pancreatic endocrine tumors that involve the liver." Added the following to the "When not covered" section; "1. For indications other than those listed above. 2. Transcatheter hepatic arterial chemoembolization is considered investigational for palliative treatment of liver metastases from other non-endocrine primaries such as colon cancer, melanoma, and unknown primaries." Updated rationale in the "Policy Guidelines" section. References added.
- 7/28/08 Updated the "When Covered" section to allow additional indications; "1. Hepatocellular cancer (HCC) that is unresectable but confined to the liver and not associated with portal vein thrombosis; or 2. 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 transplantation; or 3. Liver metastasis in symptomatic patients with metastatic neuroendocrine tumors whose symptoms persist despite systemic treatment and who are not candidates for surgical resection; or 4. Liver metastasis in patients with liver-dominant metastatic uveal melanoma." Updated the "When Not Covered" section to remove new allowed indications. Updated the "Policy Guidelines" section to indicate; "When using transcatheter hepatic arterial chemoembolization as a bridge to transplant to prevent further tumor growth, the following patient characteristics apply: 1. A single tumor less than 5 cm or no more than 3 tumors each less than 3 cm in size, and 2. Absence of extrahepatic disease or vascular invasion, and 3. Child-Pugh score of either A or B." References added.
- 5/18/09 Revised Description section for clarity. Updated Policy Guidelines section. Specialty Matched Consultant Advisory Panel review 4/21/09. No change to policy statement. (btw)
- 6/22/10 Specialty Matched Consultant Advisory Panel review 5/24/10. No policy statement changes.(lr)
- 10/26/10 Added diagnoses codes to the "Billing/Coding" section. (lpr)

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- 6/7/11 Under “Not Covered” section: added policy statement “As neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable” is investigational. Specialty Matched Consultant Advisory panel review 5/25/2011. References added. (lpr)
- 11/22/11 Corrected coding format for diagnoses in the “Billing/Coding” section. (btw)
- 6/29/12 Description section revised. Added the following statement to the When Not Covered section to indicate; “Transcatheter hepatic arterial chemoembolization is considered investigational to treat unresectable cholangiocarcinoma.” No change to policy intent. Policy Guidelines updated. Reference added. Medical Director review 5/2012. (sk)
- 11/27/12 Reference added. No change to Policy statement. (sk)
- 1/1/13 CPT codes 75896 and 75898 added to Billing/Coding section. (sk)
- 7/1/13 ICD-10 diagnosis codes added to Billing/Coding section. (sk)
- 8/13/13 Specialty Matched Consultant Advisory Panel review 7/17/2013. No change to Policy statement. (sk)
- 12/31/13 Reference added. CPT code updated with new 2014 coding. CPT code 37204 deleted and CPT code 37243 added to Billing/Coding section. Policy statements unchanged. (sk)
- 10/28/14 Specialty Matched Consultant Advisory Panel review 7/29/2014. Removed effective date 10/1/2014 from ICD-10 list. No change to Policy statement. (sk)
- 7/28/15 Specialty Matched Consultant Advisory Panel review 6/24/2015. Reference added. No change to policy statement. (lpr)
- 10/30/15 Updated Description and Policy Guidelines sections. Reference added. No change to policy statement. (lpr)
- 7/26/2016 CPT 75896 deleted, no longer a valid code. Specialty Matched Consultant Advisory Panel review 6/29/2016. No change to policy statement. (an)
- 6/30/17 Policy Guidelines updated. References added. Specialty Matched Consultant Advisory Panel review 5/26/2017. No change to policy statement. (an)
- 6/29/18 References added. ICD-9 codes deleted from Billing/Coding section. Specialty Matched Consultant Advisory Panel review 5/23/2018. No change to policy statement. (an)
- 6/11/19 Revised Item 1 in the Covered Section to read: “Hepatocellular cancer (HCC) 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”. References added. Specialty Matched Consultant Advisory Panel review 5/15/2019. (an)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.