Subject: Transarterial Chemoembolization (TACE) & Transarterial Embolization (TAE) for Liver Tumors		Original Effective Date: 10/31/12
Policy Number: MCP-120	**Revision Date(s):** 7/16/15, 9/13/18	
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Contents

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.[1]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL [34 35 42 43]

TACE and TAE are catheter-based embolization procedures. TACE is combined with a prior injection of a chemotherapeutic agent into the hepatic artery, and TAE is not combined with a chemotherapeutic agent (bland embolization). Both embolization procedures lead to ischemia of the tumor by blockage of the nutrient supply. These procedures have been investigated to treat resectable, unresectable, and recurrent HCC, as a bridge to

liver transplantation, and to treat liver metastases, most commonly from colorectal cancer. These procedures are a two-step process that involves placing a catheter in the artery that is supplying blood to a tumor to precisely infuse first, a chemotherapeutic agent and then, an embolic agent. This process effectively delivers a drug and blocks blood flow to the tumor. TAE is proposed as a palliative treatment for primary hepatic or metastatic tumors including neuroendocrine tumors with hepatic metastases. TAE is conducted during selective hepatic arterial catheterization through the arteries supplying a tumor and involves the infusion of lipiodol (without a chemotherapeutic agent) followed by embolization using any of the embolic agents (ie, gelatin sponge cubes) as during TACE procedures. TACE and TAE require hospitalization and multiple treatments may be required to treat all lesions as well as recurrences, however, the benefit of repetition needs to be balanced against the progressive liver damage associated with the treatment. The most common adverse effect of TACE and TAE are post-embolization syndrome which consists of varying degrees of right upper quadrant pain, nausea, a moderate degree of ileus, fatigue, fever, and transient elevation of AST, ALT and bilirubin values. Symptoms are usually self-limited, lasting three to four days; full recovery is typical within 7 to 10 days.

Drug-eluting beads transarterial chemoembolization (DEB-TACE) is an adaptation of TACE and is a single-step process where beads of uniform size are loaded with a drug and delivered to the feeder artery in a single step. This procedure is easier to perform than two-step TACE. Since the drug is contained within the beads, its elution is more localized and longer lasting than in traditional TACE. Embolic beads, or microspheres, are either synthetic polymers such as ethylene vinyl acetate, or natural materials such as albumin, chitosan, gelatin, or alginate. Doxorubicin is the most commonly used chemotherapeutic agent for DEB-TACE, however mitomycin C, cisplatin, methotrexate, and paclitaxel are also used. DEB-TACE is prescribed by an oncologist and performed in an angiography suite by an interventional radiologist. The procedure takes approximately 2 hours and patients are hospitalized for 1 to 2 days. Bilateral disease is treated in separate procedures at an interval of approximately 2 weeks. Repeat DEB-TACE procedures may be conducted, up to 4 times over a 6-month period. [25] Embozene Microspheres are spherical, tightly calibrated, biocompatible, nonresorbable, hydrogel microspheres coated with an inorganic perfluorinated polymer (Polyzene-F) and are used during transarterial embolization (TAE) to decrease the blood supply of unresectable, intermediate- and advanced-stage hepatocellular carcinoma (HCC).

General Information

Hepatocellular carcinoma (HCC): a primary tumor of the liver that usually develops in the setting of chronic liver disease, particularly in patients with chronic hepatitis B and C. TACE is an appropriate option for patients with a large unresectable or multifocal HCC without main or lobar branch portal vein thrombus that is not amenable to local ablation. TACE is also commonly used as a bridging maneuver in patients awaiting liver transplantation. For most patients who are candidates for resection, preoperative TACE is not indicated.
Neuroendocrine tumors (NETs): a heterogeneous group of neoplasms that are thought to arise from neuroendocrine cells and their precursors located throughout the body. TACE is applied as a palliative technique in patients with a hepatic-predominant metastatic NET who are not candidates for surgical resection.
Uveal melanoma: a rare malignancy that arises from melanocytes within the uveal tract of the eye, which includes the iris, ciliary body, and choroid. Uveal melanoma comprises approximately 95 percent of melanomas arising from the eye, with the remainder arising from the conjunctiva. Among patients with hepatic metastases,

TACE directed specifically toward the liver metastases has been associated with responses that may have clinical utility.

Colorectal Cancer: the gold standard in management of colon cancer metastatic to the liver remains resection. However, most patients are not candidates for surgery due to either disease bulk or the presence of extrahepatic metastases. Arterial therapies such as TACE and SIRT, either as monotherapy or in combination with other therapeutic regimens, have shown survival benefit.

CLINICAL CRITERIA RECOMMENDATION [2-15 24-33 36-41 44 45]

Transarterial chemoembolization (TACE) or Transarterial embolization (TAE) is considered medically necessary for any of the following conditions:

- ❑ Treatment of primary hepatocellular liver carcinoma (HCC) or as a bridge to liver transplant when ALL of the following criteria are met:
  - Preserved liver function defined as Childs-Turcotte-Pugh Class A or B; and
  - Localized unresectable or multifocal tumor with all of the following: [ALL]
    - Three or fewer encapsulated nodules, and
    - each nodule is less than or equal to 5 centimeters in diameter; and
  - No evidence of extra-hepatic metastases; and
  - No evidence of severe renal function impairment; and
  - No evidence of portal vein occlusion.

- ❑ Treatment of primary HCC [36-41] in individuals who may become eligible for liver transplantation when the following criteria are met:
  - One lesion greater than 5 cm and less than or equal to 8 cm; or
  - Two or three lesions each greater than 3 cm and less than or equal to 5 cm; and
  - A total diameter of all lesions less than or equal to 8 cm; or
  - Four to five lesions each less than 3 cm, and a total diameter of all lesions less than or equal to 8 cm; or

- ❑ Treatment of liver metastasis in symptomatic patients with metastatic neuroendocrine tumors [36 44 45] whose symptoms persist despite systemic treatment and who are not candidates for surgical resection; or

- ❑ Treatment of liver metastasis in patients with liver-dominant metastatic uveal melanoma; or [36-41]

- ❑ Treatment of liver metastasis in select patients with colorectal cancer whose symptoms persist despite systemic treatment and who are not candidates for surgical resection [36 44]

***** The Child-Turcote-Pugh (CPT) score determines short-term prognosis among groups of patients awaiting liver transplantation and has been widely adopted for risk-stratifying patients before transplantation.

Child-Turcote-Pugh Score of Severity of Liver Disease [34]

Points	**1**	**2**	**3**
Encephalopathy	None	1 – 2	3 – 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	< 2	2 – 3	> 3
For PBC/PSC, Bilirubin	< 4	4 – 10	> 10

Albumin (g/dL)	> 3.5	2.8 – 3.5	< 2.8
INR*	< 1.7	1.7 – 2.3	> 2.3
PT (seconds prolonged)	< 4	4 - 6	> 6

The individual scores are summed and then grouped as a classification:

< 7 = A
7-9 = B
> 9 = C (forecasts a survival of less than 12 months)

*INR = International Normalized Ratio; PT = prothrombin time.

CONTINUATION OF THERAPY [42]

The TACE procedure may be repeated if there is clear evidence of progressive tumor growth in the treated areas.

Note:

- *Multiple courses of TACE, especially if spaced too closely together, can increase deaths from liver failure despite successful tumor shrinkage, and these excess deaths from deterioration of liver function may counterbalance any prolongation of survival that results from enhanced tumor control.*
- *TACE may cause hepatic artery damage, the likelihood of which is higher in patients with impaired liver function.*
- *Hepatic artery interruption by repeated TACE or arterial dissection also leads to the development of extrahepatic collateralization, which may create an alternative blood supply to the tumor, and contribute to treatment failure.*

LIMITATIONS [36 37 42]

- ❑ TACE utilizing chemotherapy-loaded microspheres (i.e. drug-loaded microspheres, drug-eluting beads, and doxorubicin drug-eluting bead transarterial chemoembolization [DEB-TACE] and Embozene Microspheres are considered experimental, investigational and unproven for all liver-related conditions.

- ❑ TACE is contraindicated for any of the following conditions:
  - Absent or severely reduced portal vein flow (eg, tumoral or nontumoral portal vein occlusion, or hepatofugal blood flow); and
  - Decompensated cirrhosis (Child-Turcotte-Pugh C, or Child-Turcotte-Pugh B score >8 including jaundice, clinical hepatic encephalopathy, refractory ascites, and/or hepatorenal syndrome)

- ❑ Relative contraindications include any of the following:
  - Serum bilirubin >2 mg/dL
  - Lactate dehydrogenase >425 units/L
  - Aspartate aminotransferase >100 units/L
  - Tumor burden involving >50 percent of the liver
  - Severe comorbidities
  - Untreated esophageal varices at high risk of bleeding
  - Prior transjugular intrahepatic portosystemic shunting (TIPS)

SUMMARY OF MEDICAL EVIDENCE

The available evidence on the efficacy and safety of DEB-TACE with doxorubicin for unresectable HCC is conflicting and consists of RCTs (n=30-201), that compared the efficacy and safety of treatment with DEB-TACE with conventional TACE or compared it with bland embolization with inert beads. Additional published evidence consists of controlled retrospective, uncontrolled, and prospective trials (n=62-71). The overall quality of the evidence is low because of study size, limitations of the uncontrolled studies, and the lack of RCTs. The available evidence suggests that DEB-TACE with doxorubicin is a safe and efficacious treatment for unresectable HCC, however there is insufficient evidence to draw conclusions regarding superiority of DEB-TACE over conventional TACE. Additional trials are necessary to compare the efficacy and safety of DEB-TACE with conventional TACE, assess quality of life and assess a consistent imaging method to monitor the tumor response to DEB-TACE. [16-23]

The available evidence on the efficacy and safety of TACE or TAE to treat unresectable HCC is from limited RCT's, (n=40-400) systematic reviews, retrospective reviews, and prospective studies (n=120-1293). Overall survival rates for chemoembolization as palliative treatment of unresectable disease ranged from 42% to 93% at 1 year, 22% to 87% at 2 years, and 3% to 43% at 3 years. Although the data is limited it does demonstrate that TACE provides a survival benefit for the treatment of unresectable primary hepatocellular carcinoma (HCC) when compared with supportive care only or when added as an additional therapy versus supportive care or systemic chemotherapy alone in the management of unresectable HCC. [2-15] Consensus opinion from professional organizations suggests that TACE may be a treatment option for unresectable HCC. [36-41]

The available evidence on the efficacy and safety of TACE or TAE as a bridge to liver transplant consists of a number of uncontrolled studies that 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. The available evidence on the efficacy and safety of TACE for patients with unresectable neuroendocrine tumors consists of uncontrolled trials and case studies that have reported that TACE reduces symptoms and tumor burden, improves hormone profile and a prolonged hepatic progression-free survival. Reports state that TACE generally achieves average symptomatic, biological and radiological responses of 75%, 56% and 50%, with progression-free survival of 12-18 months, with acceptable tolerance. In addition, for is relatively rare condition, there are limited alternative treatments for these tumors. The available evidence on the efficacy and safety of TACE for hepatic metastases from uveal (ocular) melanoma includes retrospective studies, case series of treated patients that have reported that tumor response and survival are improved compared to historical controls. The treatment with TACE conferred a survival advantage (median 16.5 vs. 12.2 months for other first line treatments). There are limited treatment options and this condition is rare, making the performance of high-quality RCTs difficult or impossible. These reports conclude that TACE improves outcomes for patients with hepatic metastases from uveal melanoma. [25-33]

PROFESSIONAL SOCIETY GUIDELINES [36-41]

Organ Procurement and Transplantation Network (OPTN): According to OPTN Policy, lesions eligible for down staging protocols to qualify for liver transplantation must meet one of the following criteria: One lesion greater than 5 cm and less than or equal to 8 cm or two or three lesions each greater than 3 cm and less than or

equal to 5 cm, and a total diameter of all lesions less than or equal to 8 cm or four to five lesions each less than 3 cm, and a total diameter of all lesions less than or equal to 8 cm.

American Association for the Study of Liver Disease (AASLD) Practice Guidelines: Treatment of Hepatocellular Carcinoma (2018) suggest that bridging to transplant with liver-directed therapy (LRT) in patients listed for liver transplantation within OPTN T2 (Milan) criteria to decrease progression of disease and subsequent dropout from the waiting list. The AASLD does not recommend one form of LRT over another for the purposes of bridging to liver transplantation for patients within OPTN T2 (Milan) criteria.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines (CPG) in Oncology. [40]

- The CPG for hepatobiliary cancer (V1.2018), principles of locoregional therapy report that lesions 3 cm to 5 cm may be treated to prolong survival using arterially directed therapies, or with combination of an arterially directed therapy and ablation as long as tumor location is accessible for ablation. Unresectable/inoperable lesions >5 cm should be considered for treatment using arterially directed or systemic therapy. For bridge therapy to transplant arterially directed therapy is used to decrease tumor progression and the dropout rate from the liver transplant list and may be considered for patients who meet the transplant criteria.
- The CPG for neuroendocrine tumors of the gastrointestinal tract and/or distant metastases (V3.2017) includes a recommendation to consider hepatic-directed therapy for hepatic-predominant disease including arterial embolization and TACE for individuals with locoregional unresectable disease and/or distant (liver) metastases (symptomatic, clinically significant tumor burden, or clinically significant progressive disease).
- The CPG for uveal melanoma (V1.2018) includes the following recommendation: In general, uveal melanomas may have lower response rates to drug-based therapies than cutaneous melanoma, but efficacy has in general been more limited; however, individual patients on occasion may derive substantial benefit. Regionally directed therapies such as hepatic chemoembolization or radioembolization should be considered.
- The CPG for colorectal cancer (V2.2018) states that the data is not strong enough to recommend TACE for the treatment of colorectal liver metastases except in the setting of a clinical trial. The panel believes that arterial directed catheter therapy (radioembolization) is an option in highly selected patients with chemotherapy resistant refractive disease with predominant hepatic metastases.

CODING INFORMATION THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	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

HCPCS	Description
	N/A

ICD-10	Description: [For dates of service on or after 10/01/2015]
C22.0	Carcinoma malignant, hepatocellular
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C7A.00-C7A.8	Malignant neuroendocrine tumors
C7B.02	Secondary carcinoid tumors of liver
C69.30-C69.32	Malignant neoplasm of choroid
C69.40-C69.42	Malignant neoplasm of ciliary body

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REVIEW/REVISION HISTORY

10/31/12: New Policy
07/16/15: The policy was reviewed and updated with revisions made to criteria to include that TACE utilizing chemotherapy-loaded microspheres (i.e. drug-loaded microspheres, drug-eluting beads, and doxorubicin drug-eluting bead transarterial chemoembolization [DEB-TACE] and Embozene Microspheres are considered experimental, investigational and unproven for all liver-related conditions.
12/14/16: Policy reviewed, no changes
6/22/17: Policy reviewed, no changes
7/10/18: Policy was reviewed and updated with revisions made to criteria to include medically necessary criteria for TACE and the addition of TAE for conditions including metastatic colorectal cancer,

neuroendocrine tumors, uveal melanoma, as a bridge to liver transplant and in individuals who may become eligible for liver transplantation. Contraindications to TACE were updated with additional recommendations and the following sections were updated: general information, summary of medical evidence, professional society guidelines, coding tables and references.
9/18/19, 4/23/20 & 4/5/21: Policy reviewed, no changes. Updated references.