DRAFT

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

Policy #: 737
Category: Surgical

Latest Review Date: August 2020
Policy Grade: B

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Effective for dates of service on or after August 17, 2020:
Blue Advantage will treat transcatheter arterial chemoembolization (TACE) as a **covered benefit** for patients with one of the following indications:

- hepatocellular carcinoma (HCC)
- metastatic liver carcinoma

Blue Advantage will treat transcatheter arterial chemoembolization of the liver as a **noncovered benefit** and **investigational**:

- as part of combination therapy (with radiofrequency ablation) for resectable or unresectable hepatocellular carcinoma

Effective for dates of service prior to August 17, 2020:
Blue Advantage will treat transcatheter arterial chemoembolization (TACE) as a **covered benefit** for patients with one of the following indications:

- hepatocellular carcinoma (HCC)
- metastatic liver carcinoma

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

Transcatheter Arterial Chemoembolization (TACE)
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.

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.

KEY POINTS:

The most recent literature update was performed through June 4, 2020.

Summary of Evidence

TACE

TACE for Unresectable HCC

For individuals who have unresectable hepatocellular carcinoma (HCC) confined to the liver and not associated with portal vein thrombosis who receive TACE, the evidence includes several randomized controlled trials (RCTs), large observational studies, and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Overall, studies have shown improved overall survival compared with only supportive care. There is evidence from a limited number of RCTs that TACE offers a survival advantage compared with no therapy and survival with TACE is at least as good as with systemic chemotherapy. One systematic review has highlighted possible biases associated with these studies. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

TACE for Resectable HCC as Neoadjuvant or Adjuvant Therapy

For individuals who have resectable HCC who receive neoadjuvant or adjuvant TACE, the evidence includes several RCTs and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Overall, studies have shown a slightly higher percentage in overall survival rates with neoadjuvant or adjuvant TACE compared with surgery alone. Both RCTs and the meta-analysis that evaluated TACE as adjuvant therapy to hepatic resection in HCC reported positive results. Results of the meta-analysis, which included RCTs and retrospective studies, showed that adjuvant TACE was associated with a 30% relative reduction in the hazard of death and a 31% relative reduction in the hazard of recurrence (HR=0.69; 95% CI, 0.63 to 0.76; $p<0.001$). The evidence does not rule out a beneficial effect of TACE.

TACE for Unresectable Cholangiocarcinoma
For individuals who have unresectable cholangiocarcinoma who receive TACE, the evidence includes several retrospective observational studies and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, QOL, and treatment-related mortality and morbidity. RCTs evaluating the benefit of adding TACE to the standard of care for patients with unresectable cholangiocarcinoma are lacking. Results of 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 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 transcatheter arterial chemoembolization to palliate the symptoms associated with hepatic neuroendocrine metastases can provide a clinically meaningful improvement in net health outcome. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

TACE for Liver Dominant Metastatic Uveal Melanoma
For individuals who have 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 qualitatively that the technology results in a meaningful improvement in net health outcome.

TACE for other Metastases
For individuals who have unresectable hepatic metastases from any other types of primary tumor (e.g., colorectal or breast cancer) who receive TACE, the evidence includes RCTs, numerous 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, and two small RCTs have reported that TACE with drug-eluting beads has resulted in statistically significant improvements in response

rate and progression-free survival. Although available studies have small numbers of patients, several studies have shown that TACE has a slightly higher overall survival rate compared with other treatments.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network (NCCN) Guidelines
Hepatocellular carcinoma (v.2.2019): Chemoembolization is listed 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.2.2019) consider arterially directed therapies, including TACE, to be treatment options for unresectable and metastatic intrahepatic cholangiocarcinoma.

Neuroendocrine tumors, carcinoid, and islet cell tumors: NCCN guidelines on neuroendocrine tumors, carcinoid, and islet cell tumors (v.1.2019) consider chemoembolization as an effective approach for patients with hepatic-predominant metastatic disease (category 2A).

Colon cancer (v. 2. 2018): 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.

In 2019, an update discussion is in process to establish the NCCN guidelines on the use of TACE for colorectal liver metastases (v.2.2019). As of this guideline version, the NCCN can recommend TACE only for clinical trials

Uveal Cancer: No NCCN guidelines were identified for uveal malignancies.

Breast cancer (v1. 2019): TACE is not addressed as a treatment option for breast cancer metastatic to the liver.

U.S. Preventive Services Task Force Recommendations
TACE is not a Preventive Service.

KEY WORDS:
Transcatheter Arterial Chemoembolization (TACE)

APPROVED BY GOVERNING BODIES:

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.

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT Codes:

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 (this code cannot be reported with code 37243 in the same surgical field)

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POLICY HISTORY:

Medical Policy Group, August 2020: New policy. Available for comment August 24, 2020, through October 8, 2020.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.

The plan does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. The plan administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

As a general rule, benefits are payable under health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*