MEDICAL POLICY

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POLICY TITLE	TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION (TACE) TO TREAT PRIMARY OR METASTATIC LIVER MALIGNANCIES
POLICY NUMBER	MP-4.006

Original Issue Date (Created):	**July 1, 2002**
Most Recent Review Date (Revised):	**September 24, 2013**
Effective Date:	**November 1, 2013**

I. POLICY

Hepatocellular carcinoma

Transcatheter hepatic arterial chemoembolization may be considered **medically necessary** to treat hepatocellular cancer that is unresectable but confined to the liver and not associated with portal vein thrombosis.

Transcatheter hepatic arterial chemoembolization is considered **investigational** as neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable, and recurrent hepatocellular carcinoma, as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Neuroendocrine Tumors

Transcatheter hepatic arterial chemoembolization may be considered **medically necessary** to treat liver metastasis in symptomatic patients with metastatic neuroendocrine tumors whose symptoms persist despite systemic therapy and who are not candidates for surgical resection.

Metastatic Uveal Melanoma

Transcatheter hepatic arterial chemoembolization may be considered **medically necessary** to treat liver metastasis in patients with liver-dominant metastatic uveal melanoma.

Bridge to Liver Transplant

Transcatheter hepatic arterial chemoembolization may be considered **medically necessary** 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 when the following patient characteristics apply:

- 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
- A Child-Pugh score of either A or B

Transcatheter hepatic arterial chemoembolization is considered **investigational** to treat hepatocellular tumors prior to liver transplantation except as noted in the policy criteria above. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Cholangiocarcinoma

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Transcatheter hepatic arterial chemoembolization is considered **investigational** to treat unresectable cholangiocarcinoma. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Other indications

Transcatheter hepatic arterial chemoembolization is considered **investigational** to treat liver metastases from any other tumors or to treat hepatocellular cancer that does not meet the policy criteria noted above. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids
[N] PPO
[N] HMO
[N] SeniorBlue HMO
[N] SeniorBlue PPO
[N] Indemnity
[N] SpecialCare
[N] POS
[Y] FEP PPO*

*Refer to FEP Medical Policy Manual MP-8.01.11 Transcatheter Arterial Chemoembolization (TACE) to Treat Primary or Metastatic Liver Malignancies. The FEP Medical Policy manual can be found at: http://bluewebportal.bcbs.com/landingpagelevel3/504100?docId=23980

III. DESCRIPTION/BACKGROUND

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

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

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.

IV. RATIONALE

This policy is regularly updated with searches of the MEDLINE database. The most recent literature was performed for the period of August 2011 through August 2012. The following is a summary of key findings to date.

This policy was originally based on a 2000 TEC Assessment (1) that offered the following observations and conclusions:

- Five randomized trials focused on the use of TACE [transcatheter arterial chemoembolization] to treat resectable hepatocellular carcinoma, either in the adjuvant or neoadjuvant setting. These trials reported inconsistent results in terms of survival rates. Treatment-related morbidity and mortality were not reported consistently across studies.
- No randomized study focused on TACE to treat postoperative recurrent hepatocellular carcinoma, and data were insufficient to permit scientific conclusions on its effectiveness in this setting.
- Three randomized trials focused on the use of TACE to treat unresectable hepatocellular carcinoma compared to supportive care. Survival did not differ significantly among groups in any of the trials.
- There were no controlled trials focusing on patients with unresectable hepatic metastases from colon cancer. The outcomes of TACE in the available uncontrolled series appeared similar to outcomes reported of hepatic artery infusion and systemic chemotherapy. The

available data also did not show superiority for either TACE or alternatives with respect to complication rates or treatment-related mortality.

- There were no controlled trials comparing TACE to alternatives in the treatment of hepatic metastases from carcinoid or islet cell tumors. While 3 case series reported that TACE reduced symptoms due to excess hormone production, there was no information regarding the efficacy of medical management to control symptoms. Data were also inadequate to permit conclusions regarding tumor response rates and survival.

The role of TACE in the management of patients with HCC who are awaiting liver transplantation is an indication that was not addressed in the 2000 TEC Assessment.

TACE for unresectable hepatocellular carcinoma (HCC)

Since the 2000 TEC Assessment, additional randomized, controlled trials have compared TACE to conservative (i.e., symptomatic) treatment in patients with unresectable HCC, as well as TACE versus systemic chemotherapy. Several case series and a cohort study are also outlined in the following sections.

A 2011 systematic review included 9 trials with 645 patients treated with TACE or transarterial embolization for unresectable HCC. (2) Six of these trials compared TACE versus control. The review concluded that all of the trials suffered from bias, larger trials should be conducted and that, despite the fact that TACE has been advocated as standard loco-regional treatment, there was no firm evidence to support or refute the use of TACE in patients with unresectable HCC. Also in 2011, Xie and colleagues reported on a meta-analysis of 13 studies on treatment for unresectable HCC using chemoembolization (1,233 patients) or microsphere embolization (597 patients, using a glass or resin hepatic artery infusion). (3) Microsphere embolization treatment was found to result in statistically significant longer overall survival (HR: 0.73; 95% CI: 0.60–0.88; p=0.0009) and time to progression (HR: 0.61; 95% CI: 0.41–0.89; p=0.01) than chemoembolization. However, this meta-analysis included uncontrolled observational studies, which limits interpretation.

Two randomized studies comparing TACE to conservative treatment enrolled consecutive patients who met study criteria for unresectable HCC from among larger series of patents seeking treatment at the respective institutions. (4, 5) Patients in the Lo et al. study (5) tended to have more advanced disease based on Okuda stage, *Eastern Cooperative Oncology Group* (*ECOG*) performance status, and presence of tumor-related symptoms. The studies used a similar embolization regimen (lipiodol and gelatin sponge) but different cytotoxic agents (doxorubicin or cisplatin). Both studies reported significantly increased response and overall survival rates following treatment with TACE. In the Lo study, the chemoembolization group received a total of 192 courses of chemoembolization with a median of 4.5 (range: 1-15) courses per patient. Chemoembolization resulted in a marked tumor response, and the actuarial survival was significantly better in the TACE group (1 year, 57%; 2 years, 31%; 3 years, 26%) than in the control group (1 year, 32%; 2 years, 11%; 3 years, 3%; p=0.002). After adjustments for baseline variables that were prognostic on univariate analysis made with

a multivariate Cox model, the survival benefit of chemoembolization remained significant (relative risk of death, 0.49; 95% confidence interval [CI]: 0.29-0.81; p=0.006). In the Llovet et al. study, (4) patients received arterial embolization with gelatin sponge, TACE, or conservative therapy. The trial was stopped when it was shown that chemoembolization had survival benefits compared with conservative treatment (hazard ratio [HR] of death: 0.47 [95% CI: 0.25–0.91], p=0.025). Survival probabilities at 1 year and 2 years were 75% and 50% for embolization; 82% and 63% for chemoembolization, and 63% and 27% for the control group (chemoembolization vs. control p=0.009), all respectively. Neither the Lo nor the Llovet study reported an increase in serious or life-threatening treatment-related adverse events after TACE.

A randomized controlled trial compared TACE versus systemic chemotherapy for patients with unresectable HCC. (6) Mabed and colleagues randomized 100 patients to be treated with either TACE or intravenous doxorubicin. Fifty patients were treated with TACE using lipiodol, doxorubicin, and cisplatin, and 50 patients were treated with systemic doxorubicin alone. A significantly higher response rate was seen in patients treated with TACE, with a partial response achieved in 32% versus 10% of patients in the chemotherapy arm (p=0.007). A significantly more favorable tumor response to TACE was observed in patients with a single lesion (p=0.02), Child class A (p=0.007), Okuda stage 1 (p=0.005) and alpha-fetoprotein less than 400 ng/mL (p<0.001). The probability of tumor progression was significantly lower with TACE, where the median progression-free survival was 32 weeks (range: 16–70 weeks) versus 26 weeks (range: 14–54 weeks) for patients treated with systemic chemotherapy (p=0.03). The median overall survival did not differ significantly in cases treated with TACE (38 weeks) versus those treated with chemotherapy (32 weeks) (p=0.08), except for patients with serum albumin greater than 3.3 g/dL (60 vs. 36 weeks; p=0.003). Mortality in the chemoembolization arm was due to tumor progression in 53% of patients, liver failure in 32%, and gastrointestinal tract bleeding in 15%. Mortality in the chemotherapy arm was due to tumor progression in 64% of patients, liver failure in 25%, and gastrointestinal bleeding in 11%. Treatment-related mortality was 4% in the TACE arm versus 0% in the chemotherapy arm. The authors concluded that the overall survival benefits of TACE and systemic doxorubicin were similar for patients with unresectable HCC amenable to either treatment and that it is necessary to optimize the risk/benefit ratio of TACE and select the proper patient population that may benefit from this procedure.

Takayasu and colleagues reported results from an 8-year prospective cohort study of TACE from Japan. (7) In this study, 8,510 patients with unresectable HCC underwent TACE using emulsion of lipiodol and anticancer agents followed by gelatin sponge particles as an initial treatment. Exclusion criteria were extrahepatic metastases and/or any previous treatment prior to the present TACE. The mean follow-up period was 1.77 years. For overall survival rates by TACE, median and 1-, 3-, and 5-year survivals were 34 months, 82%, 47%, and 26%, respectively. The multivariate analyses showed significant difference in degree of liver damage (p=0.0001), alpha-fetoprotein value (p=0.0001), maximum tumor size (p=0.0001),

number of lesions (p=0.0001), and portal vein invasion (p=0.0001). The TACE-related mortality rate after the initial therapy was 0.5%.

A large cohort study from Biselli and colleagues reported on 56 cirrhotic patients with unresectable HCC undergoing at least one course of TACE who were matched 1:1 for sex, age (in 5-year periods), parameters of Child-Pugh score, Okuda stage, and tumor type with a control group who had received only supportive care. (8) The two groups were comparable for cause of cirrhosis, alpha-fetoprotein serum levels, and "Cancer of the Liver Italian Program" (CLIP) score. The 56 patients in the TACE group received a total of 123 treatment courses. Survival rates at 12, 24, and 30 months in patients receiving TACE were 74.3%, 52.1%, and 38.8%, respectively, with a median survival time of 25 months, whereas in supportive-care patients, the rates were 39.4%, 25.4%, and 19%, respectively, with a median survival time of 7 months (p=0.0004). At univariate analysis, TACE, tumor type, presence of ascites, alpha-fetoprotein serum level, CLIP score, and Okuda stage were associated significantly with survival. Only TACE and CLIP score proved to be independent predictors of survival at multivariate analysis.

In a prospective study from a single center in Canada, Molinari and colleagues reported on the effectiveness of TACE for HCC in a North American population. (9) Child-Pugh A cirrhosis or better patients with unresectable HCC and without radiologic evidence of metastatic disease or segmental portal vein thrombosis were assessed between November 2001 and May 2004. Of 54 patients who satisfied the inclusion criteria, 47 underwent 80 TACE sessions. Chemoembolization was carried out using doxorubicin and lipiodol followed by an injection of embolic particles, when necessary. Repeat treatments were carried out at 2- to 3-month intervals for recurrent disease. The survival probabilities at 1, 2, and 3 years were 76.6%, 55.5%, and 50%, respectively. At 6 months after the first intervention, 31% of patients had a partial response and 60% had stable disease. Major adverse events occurred after 20% of sessions, including 2 treatment-related deaths (4% of patients). The authors concluded that these survival probabilities at 1 and 2 years after TACE were comparable with results in randomized studies from Europe and Asia.

TACE for resectable hepatocellular carcinoma (HCC) - (TACE as neoadjuvant or adjuvant therapy)

Preoperative TACE

In 2009, Chua and colleagues conducted a systematic review of neoadjuvant transarterial chemoembolization for resectable hepatocellular carcinoma. (10) They evaluated 18 studies, including 3 randomized trials and 15 observational studies, some of which are outlined in detail in the following section. The review comprised 3,927 patients, 1,293 of whom underwent neoadjuvant TACE. The conclusions were that TACE could be used safely and resulted in high rates of pathologic responses but did not appear to improve disease-free survival in the TACE group. No conclusions could be drawn with respect to overall survival

differences between the TACE and non-TACE groups due to the heterogeneity of the results across studies.

From July 2001 to December 2003, Zhou and colleagues randomized 108 patients with resectable HCC (≥5 cm suitable for a partial hepatectomy) to preoperative TACE treatment (n=52) or no preoperative treatment (control group) (n=56). (11) Five patients (9.6%) in the preoperative TACE group did not receive surgical therapy because of extrahepatic metastasis or liver failure. The preoperative TACE group had a lower resection rate (n=47, 90.4% vs. n=56, 100%; p=0.017), and longer operative time (mean: 176.5 minutes vs. 149.3 minutes; p=0.042). No significant difference was found between the 2 groups in mortality. At a median follow-up of 57 months, 41 (78.8%) of 52 patients in the preoperative TACE group and 51 (91.1%) of 56 patients in the control group had recurrent disease (p=0.087). The 1-, 3-, and 5-year disease-free survival rates were 48.9%, 25.5%, and 12.8%, respectively, for the preoperative TACE group and 39.2%, 21.4%, and 8.9%, respectively, for the control group (p=0.372). The 1-, 3-, and 5-year overall survival rates were 73.1%, 40.4%, and 30.7%, respectively, for the preoperative TACE group and 69.6%, 32.1%, and 21.1%, respectively, for the control group (p=0.679). Preoperative TACE did not improve surgical outcome, and it resulted in drop-out from definitive surgery because of progression of disease and liver failure.

Kaibori et al. reported on a trial of 124 patients randomized to receive preoperative tumor-targeted TACE (42 patients), whole liver TACE (39 patients), or no TACE (43 patients) prior to surgical resection for HCC. (12) No significant differences were found between the pooled preoperative TACE groups and the control group in disease-free survival (p=0.6603) or overall survival (p=0.4115). Nor were there significant differences between the 3 groups in disease-free survival (p=0.8303) or overall survival (p=0.7126). Disease-free survival at 1 and 3 years for the tumor-targeted TACE group was 67% and 29%, 63% and 27% for the whole liver TACE group and 53% and 32% for the control group. Overall survival at 1 and 3 years for the tumor-targeted TACE group was 91% and 80%, 84% and 70% for the whole liver TACE group and 83% and 60% in the control group.

Zhang et al. retrospectively analyzed the therapeutic results of 1,457 HCC patients treated with hepatectomy, 120 of whom had received TACE before surgical resection. (13) They showed that the 5-year disease-free survival rates of the patients who received more than 2 sessions of TACE, those who received one session of TACE, and no TACE patients were 51.0%, 35.5%, and 21.4%, respectively, and that the mean disease-free survival times of the 3 groups were 66.4, 22.5 and 12.5 months, respectively. They concluded that effective preoperative TACE may be one of the best methods that can be clinically performed at present for resectable HCC, including small HCC, for improving disease-free survival after hepatectomy. On the other hand, Choi et al. studied 273 patients who underwent curative resection for HCC; 120 of whom underwent preoperative TACE. The 1-, 3-, and 5-year disease-free survival rates were 76.0%, 57.7%, and 51.3%, respectively, in the TACE group

and 70.9%, 53.8%, and 46.8%, respectively, in the non-TACE group. Although a difference was noted between the TACE and non-TACE groups, it was not significant. (14)

Postoperative TACE

Li and colleagues described the results of their randomized study exploring the efficacy of postoperative TACE and portal vein chemotherapy (PVC) for patients with HCC complicated by portal vein tumor thrombosis (PVTT) and to evaluate prognostic factors. (15) The study cohort consisted of 112 patients with HCC and PVTT randomly divided into 3 groups: Group A (37 patients), surgery only; Group B (35 patients), operation plus TACE; Group C (40 patients), operation plus TACE and PVC. Portal vein thrombus extirpation was performed at the time of surgery. Adverse effects and complications were mostly related to the operation, catheters, and local chemotherapy and included liver decompensation (15.0%), catheter obstruction (11.6%), and nausea and loss of appetite (22.1%). The disease-free survival curve was significantly different among the 3 groups, as estimated by the Kaplan-Meier method (both $p<0.05$). Group C showed a higher disease-free survival rate than Group A ($p<0.05$), but no statistical differences were found between group A and group B, or group B and group C (both $p>0.05$). The 1–3, and 5-year disease-free survival rates in Group A (resection only, n=37) were 50.7, 17.8, and 0%, respectively; in Group B (resection + TACE, n=35), rates were 62.3, 23.7, and 4.0%, respectively, and in Group C (resection + TACE + PVC, n=40) increased to 74.4, 46.1, and 11.5%, respectively. Tumor size, tumor number, PVTT location, and treatment modalities were independent prognostic factors ($p<0.05$). The authors concluded that postoperative TACE combined with PVC may benefit the survival of patients with HCC complicated by PVTT in the short-term (less than 60 months), but long-term efficacy is not yet certain and needs to be confirmed by further studies.

TACE as a bridge to liver transplant

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 post-transplant recurrence in patients with larger (T3) tumors. All of these indications 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 above 3 indications are discussed further in the following sections.

UNOS Liver Allocation Policy

(available online at:
http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_8.pdf)

In 2002, UNOS introduced a new liver allocation system, model for endstage 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 (i.e., 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, since 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 1.9 cm or smaller

T2: 1 nodule between 2.0 and 5.0 cm, or 2 or 3 nodules each smaller than 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 post-transplant 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 an acceptable risk of post-transplant tumor recurrence. Therefore, UNOS criteria prioritize T2 HCC 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. (16) Note that 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.

Therefore, 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 hepatocellular carcinoma in the U.S. 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 transplant waiting list in the U.S. (17) At the completion of the meeting, there was a general consensus for the development of 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 endpoints for downstaging before transplantation.

TACE as a Technique to Prevent Tumor Progression While on the Waiting List

Several studies have reported dropout rates of wait-listed patients treated with locoregional therapy. However, lacking controlled data, it is difficult to assess contributions of locoregional therapy to time on the waiting list. In addition, in 2002, as discussed here, UNOS revised its liver allocation policy, such that wait times for patients with HCC meeting the "Milan criteria" have now declined.

Given these limitations, the following case series have been reported. Graziadei and colleagues reported on 48 patients with HCC awaiting transplantation; all underwent TACE every 6 to 8 weeks until a complete response or a donor organ became available. (18) None was removed from the list due to tumor progression, and mean waiting time was 178 (+/- 105) days. Maddala and colleagues studied the dropout rates of 54 patients receiving TACE while awaiting transplantation. (19) During a median waiting time of 211 days (range: 28–1,099 days), the dropout rate was 15%. More recently, Fisher and colleagues reported on 33 patients who received multimodality ablation therapy, consisting primarily of radiofrequency ablation or TACE. Five patients (12%) were removed from the waiting list after waits of 5 to 14 months. (20) In this protocol, patients with tumors larger than 5 cm were not considered transplant candidates until the tumor was completely ablated using TACE, radiofrequency ablation (RFA), or another technique. Yamashiki and colleagues reported on 288 patients given various ablative therapies; the dropout rate due to tumor progression at 1 and 3 years was 6.25 and 23%, respectively. Tumors larger than 3 cm affected the dropout rate due to tumor progression. (21)

Obed and colleagues reported on 20 patients with nonprogression of lesions after TACE who had liver transplantation; median survival in this group was 92.3 months. (22)

TACE to Downstage HCC Prior to Transplant/Reduce Recurrence Rates in Those with T3 Lesions

Published literature reflects an ongoing discussion as to whether the UNOS allocation criteria should expand to include patients with larger tumors. (17) Some patients with T3 lesions apparently are cured with liver transplant, although most experience recurrent tumor. For example, in the seminal 1996 study, (16) the 4-year recurrence-free survival was 92% in those who met the "Milan criteria" (T2 lesion) compared to 59% in those who did not; additional studies confirm this difference in recurrence-free survival rate. (23) However, other institutions have reported similar outcomes with expanded criteria. For example, Yao and colleagues at University of California at San Francisco (UCSF) reported similar recurrence-free survival after transplant in patients with T2 and a subset of those with T3 tumors. This T3 subset was defined as a single lesion 6.5 cm or smaller or no more than 3 lesions with none greater than 3 cm and with a sum of tumor diameters 8 cm or smaller. These expanded criteria are known as "the UCSF criteria." (24)

Lewandowski and colleagues compared radioembolization with chemoembolization in the efficacy of downstaging 86 patients with HCC from stage T3 to T2. (25) Patients were treated with either 90-yttrium microspheres (n=43) or TACE (n=43). Median tumor size was similar

between the 2 treatment groups (5.7 and 5.6 cm, for TACE vs. radioembolization, respectively.) Partial response rates were 61% versus 37% for radioembolization vs. TACE, respectively, with downstaging from T3 to T2 in 58% of patients treated with radioembolization versus 31% with TACE ($p<0.05$).

The results and efficacy of downstaging with TACE to achieve a reduction in tumor burden to a T2 lesion remain controversial. There are retrospective data showing the ability to downstage patients with TACE, however, there is no randomized evidence that tumor downstaging prior to liver transplant confers a survival advantage.

TACE for cholangiocarcinoma

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, the majority of 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 radiation therapy. However, such palliative options afford little to no survival improvement over supportive therapy alone, as ICC responds poorly to such existing therapies. (26) The prognosis for patients with unresectable ICC is approximately 5- to 8-month survival.

Park and colleagues conducted a retrospective review of the medical and imaging records of 155 patients with unresectable ICC who were treated between 1996 and 2009 with TACE. (26) Patients who had undergone previous local or systemic therapy were excluded. A total of 72 patients underwent TACE, and 83 received supportive care, based on physician and patient preference. Supportive care included pain and ascites control and biliary drainage. Survival was the primary endpoint. Baseline patient and tumor characteristics were well-balanced between the 2 groups. Most patients had stage 3 or 4 disease. Tumor multiplicity was single and multiple or diffuse in 43% and 57% of the TACE patients, respectively, and 53% and 47% in the supportive group, respectively. Maximum tumor size in the TACE group was 8.1 cm +/- 3.4 cm and 7.8 cm +/-3.1 cm in the supportive group. The median number of sessions per patient in the TACE group was 2.5 (range 1-17 sessions). After TACE, the incidence of significant (≥grade 3) hematologic and nonhematologic toxicities was 13% and 24%, respectively, and no patients died within 30 days following TACE. The Kaplan-Meier survival analysis showed a median survival in the TACE group of 12.2 months, versus a median of 3.3 months in the supportive therapy group ($p<0.0001$). Survival rates also differed significantly between the 2 groups according to the presence or absence of extrahepatic metastases. In patients with liver-only disease, the median survival period was 13.3 months (95% CI: 9.2-17.4 months) for the TACE group and 4 months (95% CI: 3-5 months; $p<0.001$) for the supportive treatment group. In patients with extrahepatic metastases, the median survival period was 11.3 months (95% CI: 8.9-13.7 months) for the TACE group and 3.2 months for the supportive treatment group (95% CI: 2.6-3.8 months; $p<0.001$).

Knüppel and colleagues reported a retrospective review of 195 patients with intrahepatic (57%) or extrahepatic (43%) cholangiocarcinoma. (27) Patients received either chemotherapy or a combination of photodynamic therapy or TACE with chemotherapy. Some of the patients underwent surgical resection. Patients who only received palliative care (no surgery) survived 9.8 months longer with combination chemotherapy and TACE (n=14) versus chemotherapy alone (n=81) (median survival for chemotherapy plus TACE 22.0 months versus for chemotherapy alone 12.2 months; p=0.039). Survival was not reported for extrahepatic versus intrahepatic cholangiocarcinoma.

Shen et al. retrospectively compared 53 patients who received TACE after surgical resection of intrahepatic cholangiocarcinoma to 73 patients who had surgical resection without TACE. (28) Disease-fee survival rates at 1-, 3-, and 5-years (24.5%, 17.0%, and 17.0%, respectively) in the patients receiving TACE were not significantly different from the group that did not receive post-surgical TACE [33.3%, 19.4%, and 15.3%, respectively (p=0.659)]. Overall survival rates were significantly better in the TACE group at 1-, 3-, and 5-years (69.8%, 37.7%, and 28.3%, respectively) than the non-TACE group [54.2%, 25.0%, and 20.8%, respectively (p=0.045)]. However, the retrospective nature of this study limits interpretation of its findings.

Herber and colleagues conducted a retrospective study in 15 patients with inoperable ICC treated with TACE between 2000 and 2006. (29) None of the patients had extrahepatic tumor spread. The decision for TACE was made by an interdisciplinary tumor board in each individual case. Fifty-eight TACE sessions were performed in the 15 patients (3.9 +/- 3.8; range 1-15). Eight patients had unifocal tumor and 7 had multifocal disease. The mean tumor size was 10.8 +/- 4.6 cm (range 2.0-18.0 cm). No deaths and no acute liver failure occurred under TACE therapy. Major complications were observed in 2 patients, having anaphylactic shock owing to contrast medium administration in one and gastric ulceration due to lipiodol displacement in the second patient. Mean survival was 21.1 months (95% CI: 9.4-32.5 months).

Burger and colleagues prospectively collected data on 17 patients with unresectable cholangiocarcinoma treated with TACE at their institution between 1995 and 2004. (30) Among the 17 patients, 11 presented without any previous treatment, whereas 6 had received previous therapy including chemotherapy with or without radiation with evidence of progression. Fifteen patients had intrahepatic tumors and 2 had perihilar tumors. The procedure was well-tolerated by 82% of the patients, who experienced mild or no side effects that resolved with conservative therapy alone. Two patients had minor complications (12%), which were managed successfully, and one had a major complication that resulted in a fatal outcome with a rapidly declining course from the time of diagnosis to death shortly after TACE. Median survival for the 17 patients was 23 months (95% CI: 15.4-30.6 months). Two patients with previously unresectable disease underwent successful resection after TACE.

TACE for hepatic metastases from neuroendocrine tumors

Neuroendocrine tumors are a heterogeneous group of tumors that are 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 therapies aim to reduce tumor burden to reduce hormone levels and palliate symptoms in patients with unresectable neuroendocrine metastases to the liver.

A 2010 review by Nazario and Gupta summarizes the experience to date with TACE (and transarterial embolization [TAE]), which is composed of many nonrandomized, retrospective reports that have demonstrated reduced tumor burden, reduced hormone levels, and palliation of symptoms with these interventions. (31) The article summarizes the experience with TACE and TAE and metastatic neuroendocrine tumors as showing radiologic response ranging from 25–95%, and symptomatic response in 53–100% of patients. Five-year overall survival rates have varied from 14–75%, likely a reflection of the heterogeneity of the patient populations and regimens of treatment used. Some of the studies in the review are detailed below.

Ruutiainen and colleagues reported on a study of 67 patients that compared bland embolization to TACE in neuroendocrine tumors metastatic to the liver. (32) In this study, 67 patients underwent 219 embolization procedures: 23 patients received primarily bland embolization with polyvinyl alcohol with or without iodized oil and 44 primarily received chemoembolization with cisplatin, doxorubicin, mitomycin-C, iodized oil, and polyvinyl alcohol. Patients with disease relapse were treated again when feasible. Ten of 67 patients (15%) were lost to follow-up. Toxicities of grade 3 or worse in severity occurred after 25% of chemoembolization procedures and 22% of bland embolization procedures. Rates of freedom from progression at 1, 2, and 3 years were 49%, 49%, and 35%, respectively, after chemoembolization and 0%, 0%, and 0%, respectively, after bland embolization, respectively (log-rank test, p=0.16). Patients treated with chemoembolization and bland embolization experienced symptomatic relief for means of 15 and 7.5 months, respectively (p=0.14). Survival rates at 1, 3, and 5 years after therapy were 86%, 67%, and 50%, respectively, after chemoembolization and 68%, 46%, and 33%, respectively, after bland embolization (p=0.18). The authors concluded that chemoembolization demonstrated trends toward improvement in TTP (time to progression), symptom control, and survival and indicated that a multicenter prospective randomized trial is warranted. These results are similar to those reported previously by Gupta et al., who noted that in a retrospective series of 81 patients, hepatic artery embolization or chemoembolization resulted in symptomatic and radiographic response in most patients with carcinoid metastases to the liver. (33)

Osborne and colleagues reported on a nonrandomized study of 59 patients with neuroendocrine tumors who received either cytoreduction or embolization for symptomatic hepatic metastases. (34) The duration of symptom relief (35 vs. 22 months) and survival (43 vs. 24 months) both favored the cytoreduction approach. The authors commented that

cytoreduction should be pursued when possible even if complete resection may not be achievable.

TACE for hepatic metastases from uveal (ocular) melanoma

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.

A 2010 review by Sato addresses the locoregional management of hepatic metastases from primary uveal melanoma and summarizes the published studies to date, many of which are detailed in the following section. (35)

Huppert et al. reported the results of a pilot trial of 14 patients with hepatic metastases from uveal melanoma who underwent TACE. (36) Patients received a mean of 2.4 treatments (34 total treatments among the 14 patients). Responses were partial for 8 patients (57%). Four patients (29%) had stable disease and 2 (14%) had tumor progression. Median time to progression was 8.5 months (range: 5–35 months), and median survival after the first TACE treatment was 14.5 months in responders and 10 months in nonresponders (p=NS). In this study, the survival rate was 86% at 6 months, 50% at 12 months, 28% at 18 months, and 14% at 24 months after the first TACE treatment. Survival advantage was most pronounced for patients with tumor occupying less than 25% of the liver volume (n=7) with a median of 17 months versus 11 months in the 7 patients with more than 25% involvement of the liver (p=0.02). The authors state that, for comparison, with no treatment, survival after detection of liver metastases is 2–7 months with a median 1-year survival rate less than 30%. Response rates for systemic chemotherapy are less than 10%, and 20–50% with immunochemotherapy, but with only a median survival of 5–9 months and serious toxicity.

Sharma and colleagues reported on the use of TACE in the treatment of melanoma metastatic to the liver reported in a series of 20 patients (17 with ocular melanoma) treated between 2004 and 2007. (37) The 20 patients underwent 46 TACE sessions (mean: 2.4 sessions; range: 1-5). The mean and median overall survival times were 334 and 271 days, respectively. There were no deaths within 30 days of treatment. The authors noted that this treatment resulted in longer survival than has been noted among historical controls. This work builds on results reported by Bedikien and colleagues in 1995 that showed that TACE had a 36% response rate (cisplatin chemoembolization) compared to a 1% response rate to systemic chemotherapy. (38)

Patel and colleagues reported on BCNU treatment for uveal melanoma and demonstrated that those who responded had improved survival. (39) In this study, 18 of the 24 patients experienced regression or stabilization of hepatic metastases for at least 6 weeks. The overall response rates (complete and partial responses) for the intention-to-treat population and for

patients who were evaluable for response were 16.7% and 20.4%, respectively. The median overall survival of the entire intention-to-treat group of patients was 5.2 months, for patients with complete or partial response in hepatic metastases it was 21.9 months, for patients with stable disease, 8.7 months, and for patients with progressive disease, 3.3 months. Thus, for patients with metastatic uveal melanoma who have disease confined to the liver, the metastatic liver disease may respond to TACE treatment and patients who respond to TACE have improved survival.

TACE for hepatic metastases from colorectal cancer

For patients with liver metastases from colorectal cancer who do not qualify for surgical resection, traditionally, systemic chemotherapy is first-line treatment. However, in more than 60% of cases, the treatment fails and disease progresses. For the large proportion of patients in whom second- and third-line medical treatment has failed, other palliative therapies to control disease progression and symptoms have been studied, including TACE. (40)

The literature has reported a median survival in patients with liver-dominant colorectal metastases treated with chemoembolization from 7–23 months. (41, 42) However, studies are difficult to compare, as some patients who were treated were still eligible for systemic chemotherapy, and survival was sometimes calculated and reported as a mean time from the date of diagnosis of liver metastases rather than from the first treatment with TACE.

Vogl and colleagues evaluated tumor control and survival in 463 patients with unresectable liver metastases of colorectal origin that did not respond to systemic chemotherapy and were treated with TACE. (43) Of the 463 patients, 67% had 5 or more metastases, 8% had 1 metastasis, 10% had 2, and 14% had 3 or 4. Patients were treated at 4-week intervals, with a total of 2,441 chemoembolization procedures performed (mean, 5.3 sessions per patient), using one of 3 local chemotherapy protocols. Local tumor control was partial response in 68 patients (14.7%), stable disease in 223 patients (48.2%), and progressive disease in 172 patients (37.1%). Median survival from the start of TACE treatments was 14 months (compared to the results from a previous study by the same author, in which untreated patients had a survival rate of 7–8 months). (44) One-year survival rate after TACE was 62% and 28%, respectively, at 2 years. No difference in survival was observed between the 3 different local chemotherapy protocols.

Hong and colleagues compared salvage therapy for liver-dominant colorectal metastatic adenocarcinoma using TACE or 90-yttrium radioembolization. (40) Mean dominant lesion sizes were 9.3 cm and 8.2 cm in the chemoembolization and radioembolization groups, respectively. Multilobar disease was present in 67% and 87% of the respective groups, and extrahepatic metastases were present in 43% and 33%, respectively. Of 36 patients, 21 underwent TACE, with a median survival of 7.7 months (survival measured from the date of the first TACE treatment to the date of death or to April 2007, if still living). Survival results were comparable to other studies addressing colorectal cancer and TACE, which ranged from 7–10 months. Median survival was 6.9 months for the radioembolization group (p=0.27). The

1-, 2-, and 5-year survival rates for the 2 groups were 43%, 10%, and 0%, respectively, for the chemoembolization group and 34%, 18%, and 0%, respectively, for the radioembolization group.

TACE for hepatic metastases from breast cancer

Vogl and colleagues reported the efficacy of repeated treatments with TACE in 208 patients with unresectable hepatic metastases from breast cancer. (45) A total of 1,068 chemoembolizations were performed (mean 5.1 sessions per patient, range: 3-25). Mean patient age was 56.4 years (range: 29-81). Patients received either one of 2 chemotherapeutic agents alone (mitomycin-C or gemcitabine) or in combination. Tumor response was evaluated by magnetic resonance imaging (MRI) according to RECIST criteria. For all chemotherapy protocols, local tumor control was partial response 13% (27/208), stable disease 50.5% (105/208), and progressive disease 36.5% (76/208). The 1-, 2-, and 3-year survival rates after TACE were 69, 40, and 33%. Median and mean survival times from the beginning of the TACE sessions were 18.5 and 30.7 months. Treatment with mitomycin-C only showed median and mean survival times of 13.3 and 24 months, and with gemcitabine only 11 and 22.3 months. With a combination of mitomycin-C and gemcitabine, median and mean survival were 24.8 and 35.5 months – all results are respectively.

Physician Specialty Society and Academic Medical Center Input

In January 2012, in response to requests, input was received related to the use of TACE to treat primary or metastatic liver malignancies from 3 academic medical centers and one specialty medical society (2 reviewers). 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. There was general agreement among the reviewers for the use of TACE for the medically necessary 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. Reviews were split for the investigational policy statement to treat other liver metastases or for recurrent HCC. Four reviewers provided input for the use of TACE in unresectable cholangiocarcinoma; 2 consider it investigational and 2 consider it investigational but also medically necessary, the latter citing data that have shown a survival benefit of TACE compared to supportive therapy.

2012 National Comprehensive Cancer Network (NCCN) Guidelines (46)

Hepatocellular carcinoma (v.2.2012): chemoembolization is listed as an option for patients with unresectable hepatocellular carcinoma with tumors not amenable to ablation therapy only and in the absence of large volume extrahepatic disease [category 2A] with the additional recommendation that tumor lesions larger than 5 cm should be treated using arterial embolic

approaches, whereas those tumors 3-5 cm can be considered for combination therapy with ablation and arterial embolization.

Intrahepatic cholangiocarcinoma (v.2.2012): does not address the use of TACE in intrahepatic cholangiocarcinoma.

Neuroendocrine tumors, carcinoid, and islet cell tumors (v.1.2012): chemoembolization is recommended for patients with unresectable liver metastases [category 2B].

Colon cancer (v.1.2013): the use of arterially-directed embolic therapy for metastatic colon cancer to the liver has a category 3 recommendation (based upon any level of evidence, there is major NCCN disagreement about whether the intervention is appropriate).

No NCCN guidelines were identified for ocular malignancies.

Breast cancer (v3.2012): TACE is not addressed as a treatment option for breast cancer metastatic to the liver.

National Cancer Institute Clinical Trials

A search of the online clinical trials database at ClinicalTrials.gov identified several studies on TACE.

A Phase III trial is recruiting patients with unresectable HCC to be randomized to TACE with versus without sorafenib. (NCT01004978) Primary outcome measure is progression-free survival, with secondary outcome measures including overall survival, anatomic patterns of failure, toxicity and tumor response. Estimated enrollment is 400, with estimated trial completion date September 2012.

A Phase III trial is recruiting patients with HCC with one lesion 5 cm or larger or multinodular disease with 4 or more lesions (at least one larger than 3 cm) to receive TACE with or without brivanib as adjuvant treatment. (NCT00908752) Estimated enrollment is 870 and estimated study completion date is March 2015.

A Phase III trial is recruiting patients to evaluate TACE prior to liver transplant for HCC (NCT01676194). Patients meeting UCSF criteria will be randomized to receive TACE every week until liver transplantation or complete response or no treatment until liver transplant. This trial is expected to enroll 140 patients with an estimated study completion date of August 2017.

Summary

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.

- Unresectable HCC: Studies (including randomized trials) of TACE for patients with unresectable HCC confined to the liver who meet specific selection criteria (i.e., good hepatic function/reserve and no portal vein thrombosis) have shown improved survival compared to only supportive care. A systematic review highlighted some of the possible biases associated with these studies.
- Resectable HCC: There are little data on the use of TACE in the neoadjuvant or adjuvant setting, and a significant long-term survival benefit has not been demonstrated.
- TACE in the liver transplant setting for HCC: TACE has become an accepted method to prevent tumor growth while patients are on the liver transplant wait list.
- Cholangiocarcinoma: Most of the data for the use of TACE to treat unresectable cholangiocarcinoma is for unresectable intrahepatic cholangiocarcinoma. Although the data suggest a survival advantage with TACE versus supportive care or systemic chemotherapy alone, the data consist mostly of retrospective reviews without matched patient controls, and clinical vetting did not uniformly support the use of TACE for this indication.
- Metastatic neuroendocrine tumors: Studies have included heterogeneous patient populations, and interpretation of survival data using TACE is difficult. Several studies have shown reduced tumor burden, reduced hormone levels, and palliation of symptoms with TACE.
- Metastatic uveal melanoma: Several studies have shown a survival advantage using locoregional treatment modalities, including TACE, in patients who have liver-dominant metastases from ocular melanoma.
- Metastatic colorectal cancer and other metastases: Studies have consisted of small numbers of patients, and the results have been variable across studies due to variation in patient selection criteria and regimens used between different studies. At this time, the data do not support the use of TACE in these settings

V. DEFINITIONS

CHEMOTHERAPY refers to the treatment of malignant and other diseases with chemical agents.

CHILD-PUGH SCORE refers to an assessment scale used to determine the severity of liver disease.

CHOLANGIOCARCINOMA is a malignant growth in one of the ducts that carries bile from the liver to the small intestine.

CYTOTOXIC DRUGS are drugs that destroy cells or prevent them from multiplying. They are used for the treatment of cancers and severe immunological disorders**.**

INFARCT is an area of tissue that undergoes death as a result of deprivation of its blood supply.

UVEAL pertains to the middle layer of the eye, or uvea.

POLICY TITLE	TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION (TACE) TO TREAT PRIMARY OR METASTATIC LIVER MALIGNANCIES
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VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

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IX. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

CPT Codes®

POLICY TITLE	TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION (TACE) TO TREAT PRIMARY OR METASTATIC LIVER MALIGNANCIES
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CPT Codes®								
36247	37204	75726	75774	75894	75898	96420		

HCPCS Code	Description
Q0083	CHEMOTHERAPY ADMINISTRATION BY OTHER THAN INFUSION TECHNIQUE ONLY (E.G., SUBCUTANEOUS, INTRAMUSCULAR, PUSH), PER VISIT

ICD-9-CM Diagnosis Code*	Description
155.0	MALIGNANT NEOPLASM OF LIVER, PRIMARY
155.2	MALIGNANT NEOPLASM OF LIVER, NOT SPECIFIED AS PRIMARY OR SECONDARY
157.4	MALIGNANT NEOPLASM OF ISLETS OF LANGERHANS
197.7	SECONDARY MALIGNANT NEOPLASM OF LIVER
V58.11-V58.12	ENCOUNTER FOR ANTINEOPLASTIC CHEMOTHERAPY AND IMMUNOTHERAPY

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

The following ICD-10 diagnosis codes will be effective October 1, 2014

ICD-10-CM Diagnosis Code*	Description
C22.0	Liver cell carcinoma
C22.1	Intrahepatic bile duct carcinoma
C22.2	Hepatoblastoma
C22.3	Angiosarcoma of liver
C22.4	Other sarcomas of liver
C22.7	Other specified carcinomas of liver
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C25.4	Malignant neoplasm of endocrine pancreas
Z51.11	Encounter for antineoplastic chemotherapy
Z51.12	Encounter for antineoplastic immunotherapy

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

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X. POLICY HISTORY

MP 4.006	**CAC 7/27/04**
	CAC 8/30/05
	CAC 3/28/06
	CAC 4/24/07
	CAC 7/29/08
	CAC 11/30/10 Adopted BCBSA policy, added investigational indication for TACE as neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable.
	CAC 11/22/11 Consensus
	CAC 6/26/12 Policy statement added that TACE for unresectable cholangiocarcinoma is considered investigational per BCBSA policy change. FEP variation added to reference the FEP Medical Policy Manual MP-8.01.11 Transcatheter Arterial Chemoembolization (TACE) to Treat Primary or Metastatic Liver Malignancies.
	7/26/13 Admin coding review complete--rsb
	CAC 9/24/13 Consensus. No change to policy statements. Added Rationale section. References updated.

[Note: Final page is signature page and is kept on file, but not issued with Policy.]