# Transcatheter Arterial Chemoembolization (TACE) to Treat Primary or Metastatic Liver Malignancies

**Policy #** 00227
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*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

*Note: Radioembolization for Primary and Metastatic Tumors of the Liver is addressed separately in medical policy 00110.*

*Note: Radiofrequency Ablation of Primary or Metastatic Liver Tumors is addressed separately in medical policy 00182.*

*Note: Cryosurgical Ablation of Primary or Metastatic Liver Tumors is addressed separately in medical policy 00220.*

**When Services Are Eligible for Coverage**
*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of transcatheter arterial chemoembolization (TACE) of the liver to treat patients with the following conditions to be **eligible for coverage:**

- Liver metastasis in symptomatic patients with metastatic neuroendocrine tumor whose symptoms persist despite systemic therapy and who are not candidates for surgical resection; and
- Liver-dominant metastatic uveal melanoma.

**When Services May Be Eligible for Coverage**
*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider TACE of the liver to treat hepatocellular cancer (HCC) to be **eligible for coverage.**

Patient Selection Criteria
Coverage eligibility for TACE of the liver to treat HCC will be considered when all of the following criteria are met:

- Tumor is unresectable; and
- Confined to the liver; and

- Not associated with portal vein thrombosis; and
- Child-Pugh class is either A or B.

Based on review of available data, the Company may consider the use of TACE of the liver as a bridge to transplant in patients with HCC where the intent is to prevent further tumor growth and to maintain a patient's candidacy for liver transplant to be **eligible for coverage.**

Patient Selection Criteria
Coverage eligibility when using TACE of the liver as a bridge to transplantation to prevent further tumor growth and to maintain a patient's candidacy for liver transplant will be considered when all of the following criteria are met:

- A single tumor < 5cm or no more than 3 tumors each < 3cm in size; and
- Absence of extrahepatic disease or vascular invasion; and
- Child-Pugh class of either A or B.

Child-Pugh Score Calculator:
https://www.mdcalc.com/child-pugh-score-cirrhosis-mortality

**When Services Are Considered Investigational**
*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers the use of TACE of the liver as neoadjuvant or adjuvant therapy in HCC that is considered resectable **to be investigational.***

Based on review of available data, the Company considers the use of TACE of the liver to treat hepatocellular tumors prior to liver transplantation, except as noted above, **to be investigational.***

Based on review of available data, the Company considers the use of TACE of the liver to treat liver metastases from any other tumors or to treat HCC for those conditions not listed as eligible for coverage, including recurrent HCC, **to be investigational.***

Based on review of available data, the Company considers the use of TACE of the liver to treat unresectable cholangiocarcinoma **to be investigational.***

The use of TACE of the liver when the patient selection criteria are not met is considered to be **investigational.***

## Background/Overview

### TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION

TACE is a minimally invasive procedure performed by interventional radiologists who inject highly concentrated doses of chemotherapeutic agents into the tumor tissues and to restrict tumor blood supply. The embolic agent(s) causes ischemia and necrosis of the tumor, and slows anticancer drug washout. The most common anticancer drugs used in published TACE studies for HCC include doxorubicin (36%), followed by cisplatin (31%), epirubicin (12%), mitoxantrone (8%), and mitomycin C (8%).

The TACE procedure requires hospitalization for placement of a hepatic artery catheter and workup to establish eligibility for chemoembolization. Before the procedure, the patency of the portal vein must be demonstrated to ensure an adequate posttreatment hepatic blood supply. With the patient under local anesthesia and mild sedation, a superselective catheter is inserted via the femoral artery and threaded into the hepatic artery. Angiography is then performed to delineate the hepatic vasculature, followed by injection of the embolic chemotherapy mixture. Embolic material varies but may include a viscous collagen agent, polyvinyl alcohol particles, or ethiodized oil. Typically, only 1 lobe of the liver is treated during a single session, with subsequent embolization procedures scheduled 5 days to 6 weeks later. In addition, because the embolized vessel recanalizes, chemoembolization can be repeated as many times as necessary.

### HEPATOCELLULAR CARCINOMA

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

### INTRAHEPATIC 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, most ICC patients are not surgical candidates due to their advanced disease at diagnosis, which is caused by the lack of symptoms until late in the disease. The overall prognosis of ICC is far worse than for extrahepatic cholangiocarcinoma because of its late presentation. Most patients with ICC qualify for palliative therapy, including systemic chemotherapy and radiotherapy. However, such palliative options afford little to no survival improvement over supportive therapy alone, because ICC responds poorly to such existing therapies. Survival prognosis for patients with unresectable ICC is 5 to 8 months.

TACE has been explored in various settings as a technique to prevent tumor progression in patients on the liver transplant waiting list, to downstage tumors so a patient may be considered a better candidate for liver transplantation, and to decrease the incidence of posttransplant recurrence in patients with larger (T3) tumors. All uses are in part related to the United Network for Organ Sharing (UNOS) liver allocation policy,

which prioritizes patients for receiving donor livers. The UNOS policy and the 3 treatment settings are discussed further in the following sections.

**NEUROENDOCRINE TUMORS**

Neuroendocrine tumors are a heterogeneous group of typically slow-growing tumors with an indolent course, with the capacity to synthesize and secrete hormones. Liver metastases may result in significant hormonal symptoms and are associated with a poor prognosis. Systemic chemotherapy for these tumors has shown modest response rates of limited duration, and, although somatostatin analogues are usually effective at controlling symptoms, the disease eventually becomes refractory. Therefore, liver-directed therapies aim to reduce tumor burden, to lower hormone levels, and to palliate symptoms in patients with unresectable neuroendocrine metastases.

**UVEAL MELANOMA**

Uveal melanoma (also called ocular melanoma) is the most common primary ocular malignancy in adults and shows a strong predilection for liver metastases. Even with successful treatment of the primary tumor, up to 50% of patients will subsequently develop systemic metastases, with liver involvement in up to 90% of these patients. Metastatic uveal melanoma is resistant to systemic chemotherapy, leading to the evaluation of locoregional treatment modalities to control tumor progression in the liver, including TACE.

**UNOS LIVER ALLOCATION POLICY**

In 2002, UNOS introduced the Model for End-Stage Liver Disease (MELD) system for allocating new livers to adults awaiting transplant. The MELD score is a continuous disease severity scale incorporating bilirubin, prothrombin time (i.e., international normalized ratio), and creatinine into an equation, producing a number that ranges from 6 (less ill) to 40 (gravely ill). Aside from those in fulminant liver failure, donor livers are prioritized to those with the highest MELD score. This system accurately predicts the risk of dying from liver disease except for those with HCC, who often have low MELD scores, because bilirubin, international normalized ratio, and creatinine levels are near normal. Therefore, patients with HCC are assigned additional allocation points according to the size and number (T stage) of tumor nodules as follows:

T1: 1 nodule greater than 1 cm and 1.9 cm or smaller
T2: 1 nodule between 2.0 and 5.0 cm, or 2 or 3 nodules each 1 cm or greater and up to 3.0 cm
T3: 1 nodule larger than 5.0 cm, or 2 or 3 nodules with at least 1 larger than 3.0 cm.

Patients with T1 lesions are considered at low risk of death on the waiting list, while those with T3 lesions are at high risk of posttransplant recurrence and are generally not considered transplant candidates. Patients with T2 tumors have an increased risk of dying while on the waiting list compared to those with T1 lesions, and are an acceptable risk of posttransplant tumor recurrence. Therefore, UNOS criteria, which were updated in 2013, prioritize only T2 HCC patients who meet specified staging and imaging criteria by allocating additional points equivalent to a MELD score predicting a 15% probability of death within 3 months. This definition of T2 lesions is often referred to as the Milan criteria, in reference to a key 1996 study that examined the recurrence rate of HCC according to the size of the initial tumor. 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 lose the additional allocation points.

Additionally, nodules identified through imaging of cirrhotic livers are given an Organ Procurement and Transplantation Network class 5 designation. Class 5B and 5T nodules are eligible for automatic priority. Class 5B criteria consist of a single nodule 2 cm or larger and up to 5 cm (T2 stage) that meets specified imaging criteria. Class 5T nodules have undergone subsequent locoregional treatment after being automatically approved on initial application or extension. A single class 5A nodule (>1 cm and <2 cm) corresponds to T1 HCC and does not qualify for automatic priority. However, combinations of class 5A nodules are eligible for automatic priority if they meet stage T2 criteria. Class 5X lesions are outside of stage T2 and are not eligible for automatic exception points. Nodules less than 1 cm are considered indeterminate and are not considered for additional priority.

The UNOS allocation system provides strong incentives to use locoregional therapies to downsize tumors to T2 status and to prevent progression while on the waiting list. A 2010 report of a national conference in the United States addressed the need to characterize better the long-term outcomes of liver transplantation for patients with HCC and to assess justification for continuing the policy of assigning increased priority for candidates with early-stage HCC on the U.S. transplant waiting list. There was a general consensus for developing a calculated continuous HCC priority score for ranking HCC candidates on the list that would incorporate the calculated MELD score, α-fetoprotein, tumor size, and rate of tumor growth and that only candidates with at least stage T2 tumors would receive additional HCC priority points. The report addressed the role of locoregional therapy to downstage patients from T3 to T2 and stated that the results of downstaging before liver transplantation are heterogeneous, with no upper limits for tumor size and number before downstaging across studies, and the use of different end points for downstaging before transplantation.

## FDA or Other Governmental Regulatory Approval

**U.S. Food and Drug Administration (FDA)**

Chemoembolization for hepatic tumors is a medical procedure and, as such, is not subject to regulation by the U.S. FDA. However, the embolizing agents and drugs are subject to FDA approval.

**Centers for Medicare and Medicaid Services (CMS)**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

## Rationale/Source

Assessment of efficacy for therapeutic intervention involves a determination of whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled

studies can sometimes provide useful information on health outcomes; however, they are also prone to biases, such as noncomparability of treatment groups, the placebo effect, and variable natural history of the condition.

**TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA**

**Systematic Reviews**

Numerous systematic reviews on TACE have evaluated the efficacy of TACE alone or its comparative efficacy with alternative treatments. Some have compared TACE with hepatic resection and concluded that hepatic resection is superior to TACE for eligible patients. For patients with unresectable HCC, the evidence is less, but does include some systematic reviews.

A 2011 Cochrane review included 9 trials involving 645 patients treated with TACE or transarterial embolization for unresectable HCC. Six of these trials compared TACE with control treatments. Reviewers concluded that all trials suffered from bias, larger trials should be conducted, and that, despite the fact that TACE has been advocated as standard locoregional treatment, there was no firm evidence to support or refute its use in patients with unresectable HCC.

Xie et al conducted a meta-analysis in 2012 of 13 studies on treatment for unresectable HCC using chemoembolization (1233 patients) or microsphere embolization (597 patients, using a glass or resin [HAI]). Microsphere embolization treatment resulted in statistically significant longer overall survival (OS; hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.60 to 0.88; p<0.001) and time to progression (HR=0.61; 95% CI, 0.41 to 0.89; p=0.01) than chemoembolization. However, this meta-analysis included uncontrolled observational studies, which limits interpretation.

**Randomized Controlled Trials**

Some examples of individual RCTs comparing TACE with alternative treatments are reviewed next. Bush et al (2016) published interim results of an RCT comparing TACE to proton beam radiotherapy for patients with unresectable HCC. This trial included 69 patients, with 36 randomized to TACE and 33 to proton beam. The primary outcome was progression-free survival (PFS) at 2 years and secondary outcomes were OS, local tumor control, and days of hospitalization following treatment. There was a trend toward worse PFS at 2 years in the TACE group (31%) compared with the proton beam group (48%; p=0.06). The total days of hospitalization in the 30 days posttreatment was significantly lower for the TACE group (24 days vs 166 days, p<0.01). For the outcome of local tumor control, there was a trend toward worse control in the TACE group (45% vs 88%, p=0.06), and there was no difference between groups in OS.

A 2009 RCT by Mabed et al compared TACE with systemic chemotherapy for patients who had unresectable HCC. One hundred patients were randomized to TACE or to 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% vs 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-Pugh class A (p=0.007), Okuda stage 1 (p=0.005), and α-fetoprotein level less than 400 ng/mL (p<0.001). The probability of tumor progression was significantly lower in patients treated with TACE, who had a median PFS of 32 weeks (range, 16-70 weeks) vs 26 weeks (range, 14-54 weeks) for patients treated with systemic chemotherapy (p=0.03). Median OS did not differ significantly between those treated with TACE (38 weeks) and those treated with chemotherapy (32 weeks; p=0.08), except for patients with a serum albumin greater than 3.3 g/dL (60 weeks 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%, liver failure in 25%, and gastrointestinal bleeding in 11%. Treatment-related mortality was 4% in the TACE arm and 0% in the chemotherapy arm.

A 2002 RCT by Lo et al enrolled patients with advanced disease based on Okuda stage, Eastern Cooperative Oncology Group Performance Status score, and presence of tumor-related symptoms. The trial used a similar embolization regimen (lipiodol and gelatin sponge) but different cytotoxic agents (doxorubicin or cisplatin). 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 adjusting for baseline variables that were prognostic on univariate analysis using a multivariate Cox model, the survival benefit of chemoembolization remained significant (relative risk [RR] of death, 0.49; 95% CI, 0.29 to 0.81; p=0.006).

Llovet et al (2002) reported on the results of a controlled trial that randomized 112 patients with unresectable HCC not suitable for curative treatment and Child-Pugh class A or B and Okuda stage I or II, to arterial embolization with gelatin sponge, to TACE, or to conservative therapy. The trial was stopped early when it was shown that chemoembolization had survival benefits compared with conservative treatment (HR of death, 0.47; 95% CI, 0.25 to 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. This trial did not report an increase in serious or life-threatening treatment-related adverse events after TACE.

**Nonrandomized Observational Studies**
Multiple noncomparative prospective single-center cohort studies, which included patients with unresectable HCC not suitable for curative treatment and Child-Pugh class A cirrhosis, have reported a favorable impact of TACE on objective response rate or 1-, 3-, and 5-year OS rates. The largest of these studies published from Japan reported results from an 8-year prospective cohort. In this study, 8510 patients with unresectable HCC underwent TACE using emulsion of lipiodol and anticancer agents followed by gelatin sponge particles as an initial treatment. The mean follow-up was 1.77 years. Median and 1-, 3-, and 5-year OS rates with TACE were 34 months, 82%, 47%, and 26%, respectively.

**Section Summary: Transcatheter Arterial Chemoembolization for Unresectable Hepatocellular Carcinoma**
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. There are no high-quality RCTs comparing TACE with other locoregional therapies such as radiofrequency ablation (RFA). As a result, no conclusions can be made about the comparative efficacy of TACE and other locoregional therapies.

**TACE FOR RESECTABLE HCC AS NEOADJUVANT OR ADJUVANT THERAPY**
Although hepatic resection is potentially curative, local recurrence rates after surgery are still high and those rates have led to use of neoadjuvant and adjuvant systemic therapy approaches to improve outcomes.

**Neoadjuvant Therapy**
***Systematic Reviews***
Si et al (2016) reported results of a meta-analysis of RCTs that compared the impact of neoadjuvant TACE with surgery alone. Individually, 2 of the 5 RCTs concluded no effect (no reduction in postoperative recurrence or effect on survival) while 3 suggested unfavorable effect (higher dropouts from definitive surgery, higher prevalence of intraoperative lesions, delayed definitive surgery). None of the studies was graded as low risk of bias in any of the 5 domains of the Cochrane risk of bias tool. Meta-analysis reported no difference between the 2 groups on OS (HR=1.25; 95% CI, 0.92 to 1.68), disease-free survival (DFS) rate (HR=0.95; 95% CI, 0.76 to 1.19), and perioperative mortality rate (odds ratio, 0.70; 95% CI, 0.22 to 2.30).

In 2013, Zhou et al conducted a meta-analysis of 21 studies evaluating preoperative TACE. Included were 4 were RCTs and 17 nonrandomized studies (total N=3210 patients). Preoperative TACE was given to 1431 patients, with the remaining 1779 serving as controls. In 18 studies, 5-year DFS for preoperative TACE ranged from 7.0% to 57% and from 8.0% to 48.8% in the controls. In 16 studies, 5-year OS rates for preoperative TACE ranged from 15.4% to 62.7% and from 19.0% to 62.5% in the controls. In pooled analyses, there were no significant improvements with preoperative TACE vs controls in 5-year DFS rates (32.1% vs 30.0%, p=0.17) or OS rates (40.2% vs 45.2%, p=0.37). Intra- and extrahepatic recurrence also did not differ significantly across pooled analyses (51.2% vs 53.6% and 12.9% vs 10.3%, p=0.19, respectively).

In 2010, Chua et al conducted a systematic review of neoadjuvant TACE for resectable HCC. They evaluated 18 studies, including 3 randomized trials and 15 observational studies, some of which are detailed in the following section. The review comprised 3927 patients, 1293 of whom underwent neoadjuvant TACE. Reviewers' conclusions were that TACE could be used safely and resulted in high rates of pathologic responses but did not appear to improve DFS in the TACE group. No conclusions could be drawn about OS differences between the TACE and non-TACE groups due to the heterogeneity of the results across studies.

***Randomized Controlled Trials***

In 2012, Kaibori et al reported on an RCT of 124 patients allocated to preoperative tumor-targeted TACE (42 patients), whole-liver TACE (39 patients), or no TACE (43 patients [controls]) before surgical resection for HCC. No statistically significant differences in DFS or OS were reported between the pooled preoperative TACE groups and the control group (p=0.660 and p=0.412, respectively) or between the 3 groups in DFS or OS (p=0.830 and p=0.713, respectively). DFS 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, respectively. OS 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, respectively.

In a 2009 RCT, Zhou et al randomized 108 patients with resectable HCC (≥5 cm suitable for a partial hepatectomy) to preoperative TACE treatment (n=52) or to no preoperative treatment (n=56 [control group]). Five (9.6%) patients 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) than the control group. 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 DFS rates were 48.9%, 25.5%, and 12.8% for the preoperative TACE group and 39.2%, 21.4%, and 8.9% for the control group (p=0.372), respectively. The 1-, 3-, and 5-year OS rates were 73.1%, 40.4%, and 30.7% for the preoperative TACE group and 69.6%, 32.1%, and 21.1% for the control group (p=0.679), respectively.

**Nonrandomized Observational Studies**

A 2015 retrospective cohort study by Yeh et al investigated whether TACE plus sequential curative therapy provides a survival benefit in patients with a single hepatocellular tumor compared with curative surgery, RFA, or percutaneous ethanol injection. A total of 470 patients with a diagnosis of a single hepatocellular tumor between 2005 and 2010 were included. The 1-, 3-, and 5-year OS rates of all patients were 93%, 73%, and 60%, respectively. Child-Pugh class A (HR=2.04; 95% CI, 1.28 to 3.25; p=0.003), very early stage classification on the Barcelona Clinic Liver Cancer staging system (HR=2.03; 95% CI, 1.02 to 4.03; p=0.043), tumor size less than 5 cm (HR=1.75; 95% CI, 1.12 to 2.75; p=0.015), α-fetoprotein level less than 200 ng/mL (HR=2.07; 95% CI, 1.35 to 3.18; p=0.001), and curative-based therapy (HR=2.16; 95% CI, 1.44 to 3.22; p<0.001) were factors associated with longer OS. The 1-, 3-, and 5-year DFS rates for all patients were 75%, 54%, and 36%, respectively. Only Child-Pugh class A (HR=1.57; 95% CI, 1.07 to 2.29; p=0.022) and curative-based therapy (HR=1.51; 95% CI, 1.13 to 2.03; p=0.006) were significantly associated with longer DFS. Neoadjuvant TACE did not provide benefit compared with curative therapy alone in subgroup analysis.

In 2007, Choi et al studied 273 patients who underwent curative resection for HCC, 120 of whom preoperative TACE. The 1-, 3-, and 5-year DFS rates were 76.0%, 57.7%, and 51.3% in the TACE group and 70.9%, 53.8%, and 46.8% in the non-TACE group, respectively. The differences between the TACE and non-TACE groups were not statistically significant.

In 2000, Zhang et al retrospectively analyzed the therapeutic results of 1457 HCC patients treated with hepatectomy, 120 of whom had received TACE before surgical resection. They showed that the 5-year DFS rates for patients who received more than 2 sessions of TACE, those who received 1 session of TACE, and those who did not receive TACE were 51.0%, 35.5%, and 21.4%, respectively, and that the mean DFS times for the 3 groups were 66.4, 22.5, and 12.5 months, respectively.

***Subsection Summary: TACE for Resectable HCC as Neoadjuvant Therapy***
Randomized and nonrandomized trials have evaluated TACE as neoadjuvant therapy to hepatic resection in HCC. Most trials, including the highest quality RCTs, did not report differences in the survival rates when TACE was added to hepatic resection. Meta-analyses of these studies also did not report differences in outcomes on pooled analyses.

**Adjuvant Therapy**
Liao et al (2017) reported results of a meta-analysis that included 8 RCTs and 12 retrospective studies with a total of 3191 patients (779 in RCT, 2412 in observational studies). Five of the 8 RCTs, reported OS and 7 reported recurrence-free survival (RFS). The larger and more contemporaneous trials are discussed next. Results showed that adjuvant TACE was associated with improved OS (HR=0.70; 95% CI, 0.63 to 0.78; p<0.001) and RFS (HR=0.69; 95% CI, 0.63 to 0.76; p<0.001). Results were also similar between the RCTs and retrospective studies for OS (HR=0.66 and 0.71, respectively) and RFS (HR=0.66 and 0.70, respectively). Meta-regression revealed that OS was similar among patients treated with various combinations of chemotherapeutic drugs. Most RCTs were rated as at moderate risk of bias due to lack of blinding and allocation concealment.

Li et al (2006) reported the results of an RCT in which 112 patients with HCC, portal vein tumor thrombosis (PVTT), and no extrahepatic metastasis were randomized to surgery (n=37), to surgery plus TACE (n=35), or to surgery plus TACE plus portal vein chemotherapy (n=40). Staging of HCC was not reported. Portal vein thrombus extirpation was performed at the time of surgery. Although the trial was randomized, no details for randomization including allocation concealment were provided for this single-center trial. Power calculations were also not reported. The DFS curve differed significantly across the 3 groups, as estimated using the Kaplan-Meier method (both p<0.05). OS was not reported. Patients who received surgery plus TACE plus portal vein chemotherapy showed a higher DFS rate than those who received surgery only (p<0.05). There was no statistical difference between patients who received surgery plus TACE and those who received surgery only or between those who received surgery plus TACE plus portal vein chemotherapy and those who received surgery plus TACE (both p>0.05). The 1-, 3-, and 5-year DFS rates for surgery only were 50.7%, 17.8%, and 0%, respectively; in surgery plus TACE, rates were 62.3%, 23.7%, and 4.0%, respectively; and in surgery plus TACE plus portal vein chemotherapy, rates were 74.4%, 46.1%, and 11.5%, respectively. Tumor size, tumor number, PVTT location, and treatment modalities were independent prognostic factors (p<0.05). Adverse events were mostly related to the surgery, catheters, and local chemotherapy, and included liver decompensation (15.0%), catheter obstruction (11.6%), and nausea and loss of appetite (22.1%). In the same year, a nearly identical RCT with a larger sample size (N=131) was published by the same group. Similarities between the 2 RCTs were same Chinese hospital, same enrollment time period (1998 to 2001), same trial arms (surgery alone, surgery plus TACE, or surgery plus

TACE plus portal vein chemotherapy), same outcomes (DFS), and same author group. Correspondence with the authors about study overlap did not yield a response.

Zhong et al (2009) reported on the results of an RCT in which 118 patients with stage IIIA HCC (multiple tumors >5 cm or tumor involving a major branch of the portal or hepatic vein) were randomized to hepatectomy followed by TACE (n=59) or to hepatectomy alone (n=59). Three patients were excluded from the final analysis (2 from adjuvant arm, 1 from hepatectomy arm). Although, the trial was randomized, no details on randomization including allocation concealment were provided in this single-center trial. With a sample size of 56 in each arm, the trial was adequately powered (80%) to detect a 20% difference in 5-year survival. The demographic data were well-matched between arms. The incremental median OS advantage for adjuvant TACE treatment was 9 months compared to surgery alone (23.0 months vs 14.0 months, respectively, p=0.048). CIs around median estimates and HR for death were not reported.

Peng et al (2009) reported on the results of an RCT assessing 126 patients with HCC and PVTT who were randomized to liver resection plus PVTT removal (n=63) or to liver resection plus adjuvant TACE (n=63). Staging of HCC was not reported. Twelve patients in the TACE group and 10 patients in the control group were lost during follow-up, and final analysis included 104 patients. Although the trial was randomized, no details for randomization including allocation concealment were provided in this single-center trial. Power calculations were also not reported. The median OS for the adjuvant TACE arm was 13 months (95% CI, 6.3 to 19.8 months) compared with 9 months (95% CI, 6.9 to 11.1 months) for the control arm (p<0.05). The HR for death was not reported. In addition, 80% of patients had liver tumor recurrence, with no significant differences between groups.

***Subsection Summary: TACE for Resectable HCC as Adjuvant Therapy***
Multiple RCTs and retrospective observational studies as well as 1 meta-analysis have evaluated TACE as adjuvant therapy to hepatic resection in HCC. 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). However, this meta-analysis counted the nearly identical RCTs published by Li et al in 2006 as separate RCTs. Absent any conclusive evidence that these 2 RCTs are distinct trials, the survival estimates of the meta-analysis likely overestimate due to double counting. Further, the entire body of RCTs is comprised of single-center trials from China published in open access journals with inadequate reporting of study procedures (e.g., randomization, allocation concealment), patient characteristics (stage of HCC), results (lack of HRs or CIs, inadequate description of the impact of interventions subsequent to recurrence on study end points). Well-conducted multicentric trials from the United States or Europe, with adequate randomization procedures, blinded assessments, centralized oversight, and publication in peer-reviewed journals, are required.

**COMBINATION TREATMENT OF LOCOREGIONAL RESECTABLE AND UNRESECTABLE HCC**
**TACE Plus RFA for Resectable HCC**
In 2016, Liu et al published a RCT in which 200 patients with a solitary HCC nodule of 5 cm or less or up to 3 nodules of 3 cm or less in size (Milan criteria) deemed treatable by partial hepatectomy or TACE plus

RFA and liver function characterized as Child-Pugh grade A or B were randomized to surgical resection or to TACE plus RFA. Tumor sizes ranged from 0.6 to 5.0 cm, with a median of 3.0 cm in the surgical resection group and 2.8 cm in the TACE plus RFA group. OS (p=0.007) and RFS (p=0.026) were significantly higher in the surgical resection group (see Table 1). Local tumor progression occurred in 1 patient in the surgical resection group and in 18 patients in the TACE plus RFA group (p<0.001). There was no significant difference in recurrence or OS between the 2 groups for HCC lesions 3.0 cm or smaller, but there was a significant benefit for surgery in recurrence (p=0.032) and OS (p=0.012) in patients with lesions larger than 3 cm. Tumor size was an independent prognostic factor for RFS ([HR], 1.76; p=0.006) along with hepatitis B deoxyribonucleic acid (HBV-DNA) and platelet count. HBV-DNA was a significant risk factor for length of OS. Complications were higher in the surgical resection group (23.0%) than in the TACE plus RFA group (11.0%; p=0.24). We could not determine from this trial whether TACE plus RFA is as effective as surgical resection for these small tumors.

**Table 1. Percent Survival Following Surgical Resection or TACE Plus RFA for Resectable HCC**

| Outcomes | 1 Year, % | 2 Years, % | 3 Years, % |
|---|---|---|---|
| Overall survival | | | |
| Surgical resection | 97.0 | 83.7 | 61.9 |
| TACE plus RFA | 96.0 | 67.2 | 45.7 |
| Recurrence-free survival | | | |
| Surgical resection | 94.0 | 68.2 | 48.4 |
| TACE plus RFA | 83.0 | 44.9 | 35.5 |

HCC: hepatocellular carcinoma; RFA: RFA; TACE: transcatheter arterial chemoembolization.

***Subsection Summary: TACE Plus RFA for Resectable HCC***

One RCT has evaluated the combination of TACE and RFA as primary treatment for resectable HCC. It failed to show superiority in survival benefit with combination treatment over surgery for HCC lesions 3.0 cm or smaller. Further, the ad hoc subgroup analysis showed a significant benefit for surgery in recurrence and OS in patients with lesions larger than 3 cm. It cannot be determined from this trial whether TACE plus RFA is as effective as surgical resection for these small tumors.

**TACE Plus RFA for Unresectable HCC**

Multiple meta-analyses have recently compared the impact of TACE plus RFA with either treatment alone on disease progression, RFS, and OS, with up to 5 years of follow-up. While many of these meta-analyses have used standard methodologies to pool estimates, including indirect network analysis as well as assessment of study quality, and publication bias, the fundamental flaws in the pooled RCTs render the results of meta-analysis uncertain. For example, Lan et al (2016) reported on a network meta-analysis of a combined treatment approach using RFA and TACE but pooled survival estimates from studies that, while individually homogeneous, were collectively heterogeneous in terms of patient populations. In addition, Peng et al (2012) reported the results of an RCT that enrolled patients with previously treated recurrent HCC tumors 5 cm or smaller while Morimoto et al (2010) enrolled treatment-naive patients with a solitary tumor measuring 3.1 to 5 cm and Shibata et al (2009) enrolled patients with tumors smaller than 3 cm without specifying whether they were treatment-naive or -experienced. Two of the 5 meta-analyses also

included results from the first RCT published in the Journal of the American Medical Association (*JAMA)* in 2008 that demonstrated combination treatment was better than RFA alone. However, that article was retracted in 2009 because of questions about data integrity and reporting. To assess the nature of the evidence that makes the case for combined used of TACE and RFA in HCC, we reviewed the contemporaneous RCTs published after 2009 (an arbitrary threshold). All trials were conducted in China and most were reported in open access journals, except one. In many of these trials where survival was assessed, the authors reported the results of log-rank testing only, which would indicate whether there were differences between the survival times of the 2 groups but would not allow other explanatory variables to be taken into account. No explanations were provided for not reporting results of a semiparametric (Cox) or parametric (exponential, Weibull) model testing for survival analysis.

***Locoregional Treatment-Naive Therapy for Tumors Less Than 7 cm***

Yi et al (2014) reported on the results of an RCT assessing 94 HCC patients with no previous treatment for HCC except liver resection and a solitary tumor measuring 7 cm or larger or multiple lesions each measuring less than 3 cm. Patients were randomized to sequential TACE plus RFA and microwave ablation (n=47) or RFA or to microwave ablation alone (n=47). The hazard of death was statistically significantly lower in the combined arm vs the RFA or microwave ablation alone arm (HR=0.53; 95% CI, 0.33 to 0.82; p=0.002). The 5-year OS was 62% in the combined arm and 45% in the RFA or microwave ablation alone arm. No subgroup analysis stratified by lesion size was reported.

Peng et al (2013) reported on the results of an adequately powered trial evaluating 189 HCC patients with no previous treatment and a solitary tumor measuring 7 cm or less or fewer than 3 lesions each measuring less than 3 cm. Patients were randomized to sequential TACE plus RFA (n=94) or to RFA alone (n=95). OS and RFS were longer in the TACE plus RFA group (HR=0.56; 95% CI, 0.34 to 0.82; p=0.002) than in the RFA group alone (HR=0.58; 95% CI, 0.37 to 0.90; p=0.009). Corresponding OS rates in the 2 groups were 92.6% and 85.3% at 1 year, 66.6% and 61.8% at 2 years, and 59% and 45.0% at 4 years, respectively. The major limitation of this well-conducted trial is the generalizability of findings. Over 50% of patients enrolled in the trial had a single lesion with tumor size less than 3 cm (median size, 3.43 cm) even though patients with multiple lesions and tumor measuring up to 7 cm were allowed to enroll. Further, this single-center trial was conducted in China and therefore results might not generalize to patients in Western countries.

Morimoto et al (2010) reported on the results of a smaller RCT in which 37 HCC treatment-naive patients with a solitary tumor measuring 3.1 to 5 cm were randomized to sequential TACE plus RFA (n=19) or to RFA alone (n=18). While the rates of local tumor progression at end of the third year were significantly lower in the combined arm (6%) than in the RFA-alone arm (39%; p=0.012), there was no difference in the 3-year survival rates (93% vs 80%, respectively, p=0.369). In addition to having the same statistical limitations as Peng et al (2012), the Morimoto trial had a small sample size with inadequate power to detect difference in survival.

***Locoregional Treatment-Experienced Therapy for Tumors Less Than 5 cm***

Peng et al (2012) also reported on the results of an RCT in which 139 patients with recurrent HCC (after curative treatment with RFA or hepatectomy but not liver transplantation) and tumors measuring up to 5 cm

in diameter were randomized to sequential TACE plus RFA (n=69) or to RFA alone (n=70). A p value less than 0.008 was considered statistically significant due to multiple comparisons. There were no statistically significant differences in the OS rates in the combined arm (94%, 69%, and 46%) vs RFA-alone arm (82%, 47%, and 36%; p=0.037) at 1, 2, and 5 years, respectively. RFS was statistically significant greater in the combined arm compared to RFA alone arm (80%, 45%, and 40% vs 64%, 18%, and 18% respectively; p=0.005). HR and CIs were not reported. Further, subgroup analyses showed that OS was longer for the combined arm vs the RFA-alone arm among patients with tumors measuring 3.1 to 5.0 cm (p=0.002) but not for tumors 3.0 cm or smaller (p=0.478).

***Subsection Summary: TACE Plus RFA for Unresectable HCC***
Multiple meta-analyses and RCTs have shown a consistent benefit in survival or RFS in favor of combination treatment with TACE plus RFA vs RFA alone. Results of these meta-analyses are difficult to interpret because the pooled data included heterogeneous patient populations and, in few cases, included data from a study that was retracted due to reporting veracity. Since 2009, several smaller studies, the majority of which are from China, have been published; they have favored the combination treatment of TACE and RFA. However, these studies have methodologic limitations. In 2013, a larger well-conducted RCT showed the relative reduction in the hazard of death by 44% and a 14% difference in favor of combination therapy in a proportion of patients surviving at 4 years. The major limitations of this trial were its lack of TACE-alone arm and the generalizability of its findings to patient population that have unmet needs such as those with multiple lesions larger than 3 cm and Child-Pugh class B or C. Further, this single-center trial was conducted in China and, therefore, the results might not be generalizable to patients in Western countries.

**TACE AS A BRIDGE TO LIVER TRANSPLANT**
HCC patients awaiting a liver transplant for more than 6 months are typically given locoregional treatment to reduce the risk of tumor progression to maintain their eligibility on the waiting list for transplant. However, the role of locoregional therapy for patients whose disease meets Milan criteria and who are expected to have a short stay on the wait list is uncertain. Multiple options for locoregional treatment such as RFA, TACE, stereotactic body radiotherapy, and radioembolization are used with TACE being the most common. While prospective cohort studies have demonstrated that TACE can reduce dropout rates from the waiting list, the evidence for use of TACE on perioperative mortality, vascular complications, and long-term survival is conflicting and limited to retrospective case-control and cohort studies. Further, we lack RCTs comparing various locoregional strategies for bridging to transplantation.

Graziadei et al (2003) 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. None was removed from the list due to tumor progression after a mean waiting time of 178 days. Of the 48 patients, 41 underwent liver transplant. The 1-, 2-, and 5-year intention-to-treat survival rates were 98%, 98%, and 94%, respectively. Tumor recurrence was only reported in 1 (2.4%) patient. Maddala et al (2004) reported on dropout rates for 54 patients who received TACE while awaiting transplantation. During a median waiting time of 211 days (range, 28-1099 days), the dropout rate was 15%. Obed et al (2007) reported on 20 patients with

nonprogressing lesions after TACE who had liver transplantation; median survival in this group was 92.3 months.

Si et al (2017) reported on the results of a meta-analysis evaluating the influence of preoperative TACE on liver transplant. This meta-analysis included 2902 patients (721 had TACE plus liver transplant, 2181 had liver transplant alone) from 7 retrospective cohort studies and 5 case-control studies. It is unclear as to how patients were selected in the control arm (i.e., those who did not receive TACE) in the individual studies. Further, it is not clear whether reviewers extracted unadjusted or adjusted estimates from individual studies. Because all studies were observational, it is important to know how the TACE groups differed at baseline from the control groups, particularly with respect to prognostic factors, and whether statistical controls were used (if any beyond case-control matching) to adjust the hazard estimates in the primary studies. Results of the meta-analysis showed no difference in OS (HR=1.05; 95% CI, 0.65 to 1.72; p=0.83), but a higher rate of vascular complications (RR=2.01; 95% CI, 1.23 to 3.27; p=0.005) and a reduction in DFS (HR=1.66; 95% CI, 1.02 to 2.70; p=0.04) with those receiving TACE compared with those who did not. Reviewers hypothesized that vascular complications resulting from repeated intubations and toxic damage of chemotherapeutic drugs could seriously affect the function of transplanted liver and that early hepatic artery thrombosis after liver transplant might result in graft loss. The meta-analysis also reported regional differences in TACE outcomes between Asia and Western countries potentially related to differences in mechanisms of hepatocarcinogenesis (alcoholic liver cirrhosis in the Western countries vs hepatitis B in the Asian subcontinent). Subgroup analysis of OS showed that the hazard of death was higher in 2 Asian studies (HR=2.65; 95% CI, 1.49 to 4.71) than in 4 European studies (HR=1.01; 95% CI, 0.74 to 1.37). Similarly, the hazard of death varied by whether the studies were retrospective cohort (HR=1.66) or case-control studies (HR=0.84) studies and whether they were higher (HR=1.46) or lower quality (HR=0.70) studies. Given that all studies pooled were nonrandomized with considerable heterogeneity and directional differences in the outcomes based on geography and study designs, interpretation of results is uncertain.

**TACE to Downstage HCC Prior to Transplant or to Reduce Recurrence in Those With T3 Lesions**
Published literature reflects an ongoing discussion whether the UNOS allocation criteria (see Background/Overview) should be expanded to include patients with larger tumors. Some patients with T3 lesions are cured with liver transplant, although most experience tumor recurrence. For example, in the seminal 1996 study, the 4-year RFS was 92% in those who met the Milan criteria (T2 lesion) compared with 59% in those who did not; additional studies confirm this difference in RFS rate.

However, other institutions have reported similar outcomes with expanded criteria. Yao at University of California at San Francisco (UCSF) reported similar RFS rates after transplant in patients with T2 tumors 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, with a sum of tumor diameters 8 cm or smaller. These expanded criteria are known as “the UCSF criteria.”

Lewandowski et al (2009) compared the efficacy of radioembolization with chemoembolization in downstaging 86 patients with HCC from stage T3 to T2. Patients were treated with yttrium-90 microspheres (n=43) or TACE (n=43). Median tumor size was similar between treatment groups (5.7 cm for TACE vs 5.6

cm for radioembolization). Partial response rates were 61% and 37% for radioembolization and TACE, respectively, with downstaging from T3 to T2 in 58% of patients treated with radioembolization and 31% with TACE ($p<0.05$).

**Section Summary: TACE as a Bridge to Liver Transplant**
There is a lack of comparative trials assessing TACE as a bridge to liver transplantation. Multiple small prospective studies have demonstrated that TACE can prevent dropouts from the transplant list. The evidence on vascular complications and long-term survival is conflicting and limited to retrospective case-control and cohort studies. A meta-analysis of these studies has shown no difference in OS among patients who received TACE as a bridging therapy and those who did not prior to transplant, but the meta-analysis did show a higher rate of vascular complications and a reduction in DFS with TACE. The significant limitations of the meta-analysis, including lack of clarity on use of unadjusted or adjusted estimates from individual studies, lack of randomized data, considerable heterogeneity and directional differences based on geography and study designs, limit the interpretation of its results. The consequences of dropping from a transplant lists is likely death and, therefore, any strategy that delays progression with an acceptable safety profile is a benefit and available data has demonstrated that for TACE. However, the relative efficacy and safety of various locoregional treatments as a bridge therapy or to downstage HCC have not been evaluated in an RCT setting.

**TACE FOR UNRESECTABLE CHOLANGIOCARCINOMA**
**Systematic Reviews**
In 2015 Boehm et al conducted a meta-analysis of 20 studies (total N=657 patients) on the hepatic artery therapies of TACE, HAI, and yttrium 90 for ICC. Median OS was lowest for TACE (12.4 months) and drug-eluting bead TACE (12.3 months) compared with HAI (22.8 months) and yttrium 90 (13.9 months). Complete and partial responses to therapy were also lowest with TACE (17.3%) compared with yttrium 90 (27.4%) and HAI (56.9%). TACE had lower grade 3 and 4 toxicity (0.26 events per patient) than HAI (0.35 events per patient).

**Nonrandomized Observational Studies**
In 2012, Knüppel et al reviewed 195 patients with intrahepatic (57%) or extrahepatic (43%) cholangiocarcinoma. Patients received chemotherapy or a combination of photodynamic therapy or TACE with chemotherapy. Some patients underwent surgical resection. Patients who only received palliative care (no surgery) survived 9.8 months longer with combination chemotherapy and TACE (n=14) than with chemotherapy alone (n=81) (median survival for chemotherapy plus TACE, 22.0 months vs chemotherapy alone, 12.2 months; p=0.039). Survival was not reported for extrahepatic vs ICC.

In 2011, Park et al reviewed the medical and imaging records of 155 patients with unresectable ICC who were treated with TACE between 1996 and 2009. Patients who had undergone 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 end point. Baseline patient and tumor characteristics were well-balanced between 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 in 53% and 47% of the supportive group, respectively. Maximum tumor size in the TACE group was 8.1 cm and 7.8 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 incidences of significant (≥ grade 3) hematologic and nonhematologic toxicities were 13% and 24%, respectively, and no patients died within 30 days of TACE. Across a range of outcomes, TACE outperformed supportive care. For example, Kaplan-Meier survival analysis showed a median survival in the TACE group of 12.2 months vs 3.3 months in the supportive therapy group ($p<0.001$). Survival rates differed significantly between groups according to the presence or absence of extrahepatic metastases. In patients with liver-only disease, median survival was 13.3 months (95% CI, 9.2 to 17.4 months) for the TACE group and 4 months (95% CI, 3 to 5 months; $p<0.001$) for the supportive treatment group. In patients with extrahepatic metastases, median survival was 11.3 months (95% CI, 8.9 to 13.7 months) for the TACE group and 3.2 months for the supportive treatment group (95% CI, 2.6 to 3.8 months; $p<0.001$).

In 2011 Shen et al retrospectively analyzed 53 patients who received TACE after surgical resection of ICC and 73 patients who had surgical resection without TACE. DFS rates at 1, 3, and 5 years (24.5%, 17.0%, and 17.0%, respectively) in the patients receiving TACE did not differ significantly from the group not receiving postsurgical TACE (33.3%, 19.4%, and 15.3%, respectively; $p=0.659$). OS rates were significantly better in the TACE group at 1, 3, and 5 years (69.8%, 37.7%, and 28.3%, respectively) than in the non-TACE group (54.2%, 25.0%, and 20.8%, respectively; $p=0.045$).

**Section Summary: TACE for Unresectable Cholangiocarcinoma**
RCTs evaluating the benefit of adding TACE to standard of care for patients with unresectable cholangiocarcinoma are lacking. Results from 3 retrospective studies have reported a survival benefit with TACE over standard of care. Although the observational data are consistent, the lack of randomization limits definitive conclusions.

**TACE FOR SYMPTOMATIC UNRESECTABLE NEUROENDOCRINE TUMORS**
A 2010 literature review by Nazario and Gupta summarized the experience with TACE (and transarterial embolization). They evaluated multiple nonrandomized, retrospective reports that demonstrated reduced tumor burden, lower hormone levels, and palliation of symptoms with these interventions. Radiologic responses ranging from 25% to 95% and symptomatic responses ranging from 53% to 100% were reported. Five-year OS rates varied from 14% to 75%, likely a reflection of the heterogeneity of the patient populations and treatment regimens used. Several studies are reviewed next.

**Nonrandomized Observational Studies**
In 2007, Ruutiainen et al reported on a retrospective study of 67 patients who 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 retreated when feasible. Ten (15%) of 67 patients were lost to follow-up. Toxicities of grade 3 or 4 occurred after 25% of chemoembolization procedures and 22% of bland embolization procedures. Rates of freedom from disease progression at 1, 2, and 3 years were numerically but not statistically superior for TACE (49%, 49%, and 35%) compared with bland

embolization (0%, 0%, and 0%; p=0.16). Patients treated with chemoembolization also experienced longer symptomatic relief (15 months) than those who received bland embolization (7.5 months; p=0.14). Posttherapy survival rates at 1, 3, and 5 years were 86%, 67%, and 50% and 68%, 46%, and 33%, respectively (p=0.18). These results are consistent with those reported by Gupta et al (2003) on a retrospective series of 81 patients given hepatic artery embolization or chemoembolization, which resulted in symptomatic and radiographic responses in most patients with carcinoid metastases to the liver. Osborne et al (2006) reported on a nonrandomized study of 59 patients with neuroendocrine tumors who received cytoreduction or embolization for symptomatic hepatic metastases. Both duration of symptom relief (35 months vs 22 months) and survival (43 months vs 24 months) favored the cytoreduction approach.

**Section Summary: TACE for Symptomatic Unresectable Neuroendocrine Tumors**
For patients with unresectable neuroendocrine tumors, there is a lack of RCT evidence assessing TACE. Uncontrolled trials have reported that TACE reduces symptoms and tumor burden, and improves hormone profile. Generally, the response rates are over 50% and includes patients with massive hepatic tumor burden. Despite the uncertain benefit on survival, the use of TACE to palliate the symptoms associated with hepatic neuroendocrine metastases can provide a clinically meaningful improvement in net health outcome.

**TACE FOR LIVER-DOMINANT METASTATIC UVEAL MELANOMA**
A 2010 literature review by Sato addressed the locoregional management of hepatic metastases from primary uveal melanoma and summarized the published studies available at that time, many of which are detailed below.

**Nonrandomized Observational Studies**
In 2010, Huppert et al reported on a single-arm prospective study of 14 patients with hepatic metastases from uveal melanoma who underwent TACE. Patients received a mean of 2.4 treatments (34 total treatments across 14 patients). Responses were partial for 8 (57%) patients, stable for 4 (29%) patients, and tumor progression for 2 (14%) patients. 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=0.18). Survival rates were 86% at 6 months, 50% at 12 months, 28% at 18 months, and 14% at 24 months after the first TACE treatment. A survival advantage was most pronounced for patients with tumors occupying less than 25% of the liver volume (n=7); that subgroup had a median survival of 17 months vs 11 months in the 7 patients with more than 25% involvement of the liver (p=0.02). The authors stated that, compared with no treatment, survival after detection of liver metastases was 2 to 7 months, with a median 1-year survival rate less than 30%. Response rates for systemic chemotherapy were less than 10%, and 20% to 50% with immunochemotherapy, but with only a median survival of 5 to 9 months and serious toxicity.

Sharma et al (2008) reported on the results of a retrospective single cohort study that assessed the use of TACE for melanoma metastatic to the liver in a series of 20 patients (17 with ocular melanoma) treated between 2004 and 2007. The 20 patients underwent 46 TACE sessions (mean, 2.4 sessions; range, 1-5 sessions). Mean and median OS times were 334 days and 271 days, respectively. There were no deaths within 30 days of treatment. The authors noted that TACE resulted in longer survival than had been noted

among historical controls. This work built on results reported by Bedikian et al (1995), which showed that TACE had a 36% response rate (cisplatin chemoembolization) compared with a 1% response rate to systemic chemotherapy.

Patel et al (2005) reported the results of a prospective single cohort study of chemoembolization using bis-chloroethylnitrosourea for treatment of hepatic metastasis from uveal melanoma. In this study, 18 of the 24 patients experienced regression or stabilization of hepatic metastases for at least 6 weeks. Overall response rates (complete responses and partial responses) for the intention-to-treat population and for patients evaluable for response were 16.7% and 20.4%, respectively. The median OS of the entire intention-to-treat group of patients was 5.2 months; for patients with complete responses or partial response in hepatic metastases, it was 21.9 months; for patients with stable disease, 8.7 months; and for patients with disease progression, 3.3 months.

**Section Summary: TACE for Liver-Dominant Metastatic Uveal Melanoma**
For patients with liver-dominant metastatic uveal melanoma, there is a lack of RCT evidence evaluating TACE likely due to rarity of this condition. Noncomparative prospective and retrospective case series have reported improvements in tumor response and survival compared to historical controls treated with systemic therapy. 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.

**TACE FOR OTHER UNRESECTABLE HEPATIC METASTASES**
**Colorectal Cancer**
***Systematic Reviews***
Zacharias et al (2015) published a meta-analysis on hepatic artery–based therapies for colorectal metastases. Techniques included TACE, HAI chemotherapy, and radioembolization. Ninety studies reported on outcomes of HAI-based therapy. Eight studies were RCTs, including 1 RCT of TACE. In combined analysis, OS for patients treated with TACE was 15.2 months, compared with 21.4 months with HAI and 29.4 months with radioembolization. Differences between groups were not statistically significant. Grade 3 or 4 toxicity was 40% in the HAI group, 19% in the radioembolization group, and 18% in the TACE group.

Richardson et al (2013) reported on a systematic review (1 RCT, 5 observational studies) of TACE with irinotecan-eluting beads for unresectable colorectal liver metastasis. Median survival times ranged from 15.2 to 25 months. The most common adverse events were postembolization syndrome (abdominal pain, nausea, vomiting) followed by hypertension.

In 2013, Riemsma et al reported the results of a Cochrane review that assessed the benefits and harms of TACE compared with no intervention or placebo in patients with liver metastases irrespective of the location of primary tumor. Only 1 RCT published in 1990 fulfilled their inclusion criteria. It randomized 61 patients with colorectal liver metastases to hepatic artery embolization, HAI chemotherapy, and to no active therapeutic intervention. Reviewers judged this trial to have a high risk of bias on the basis of lack of

sequence generation and lack of allocation concealment or blinding. Based on the results of this trial, reviewers concluded that, in patients with liver metastases, no significant survival benefit or benefit on extrahepatic recurrence was found in the embolization group compared with the palliation group.

***Randomized Controlled Trials***

In the RCT included in the Richardson systematic review, Fiorentini et al (2012) reported on 74 patients randomized to TACE with irinotecan-eluting beads (n=36) or to systemic irinotecan, fluorouracil, and leucovorin (FOLFIRI) (n=38). With irinotecan-eluting beads, OS was significantly longer with a median OS of 22 months (95% CI, 21 to 23 months) vs 15 months (95% CI, 12 to 18 months) for the systemic chemotherapy group (p=0.031). PFS was significantly longer, at 7 months (95% CI, 3 to 11 months) in the irinotecan-eluting beads group and 4 months (95% CI, 3 to 5 months) in the systemic chemotherapy group (p=0.006). However, the current standard for systemic chemotherapy is no longer FOLFIRI. Subsequent RCTs have shown that the addition of oxaliplatin, bevacizumab, cetuximab, and panitumumab to FOLFIRI and, more recently, the addition of check point inhibitors have increased survival compared with FOLFIRI alone. Martin et al (2015) reported on the results of an RCT in which 30 patients with colorectal cancer with metastasis to liver were randomized to the leucovorin, fluorouracil, and oxaliplatin (FOLFOX) plus irinotecan drug-eluting beads or FOLFOX plus bevacizumab arm. The overall response rate was significantly longer in the FOLFOX plus irinotecan drug-eluting beads arm than in the FOLFOX plus bevacizumab arm at 2 (78% vs 54%, p=0.02), 4 (95% vs 70%, p=0.03), and 6 months (76% vs 60%, p=0.05). There was also significantly more downsizing to resection in the FOLFOX plus irinotecan drug-eluting beads arm than the FOLFOX plus bevacizumab arm (35% vs 16%, p=0.05), as well as improved median PFS (15.3 months vs 7.6 months).

***Nonrandomized Trials***

In 2009, Vogl et al reported on tumor control and survival in 463 patients with unresectable liver metastases of colorectal origin that had not responded to systemic chemotherapy and were now treated with TACE. Of the 463 patients, 67% had 5 or more metastases, 14% had 3 or 4, 10% had 2, and 8% had 1 metastasis. Patients were treated at 4-week intervals, with a total of 2441 chemoembolization procedures performed (mean, 5.3 sessions per patient), using one of 3 local chemotherapy protocols. Local tumor control was partial response in 68 (14.7%) patients, stable disease in 223 (48.2%) patients, and progressive disease in 172 (37.1%) patients. Median survival from the start of TACE treatments was 14 months (vs 7-8 months from a 2003 study by the same authors). One-year survival rate after TACE was 62% and 28% at 2 years. No differences in survival were observed between the 3 chemotherapy protocols.

In a 2009 report, Hong et al compared salvage therapy for liver-dominant colorectal metastatic adenocarcinoma using TACE or yttrium-90 radioembolization. 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 patients from 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 (measured from the first TACE treatment). Median survival was 6.9 months in the radioembolization group (p=0.27). Survival results were comparable with other studies addressing colorectal cancer and TACE

(range, 7-10 months). The 1-, 2-, and 5-year survival rates were 43%, 10%, and 0%, respectively, for the chemoembolization group and 34%, 18%, and 0%, respectively, for the radioembolization group.

**Breast Cancer**
Vogl et al (2010) reported on the efficacy of repeated treatments with TACE in 208 patients with unresectable hepatic metastases from breast cancer. A total of 1068 chemoembolizations were performed (mean, 5.1 sessions per patient; range, 3-25). Patients received one of the chemotherapeutic agents alone (mitomycin-C or gemcitabine) or in combination. Tumor response was evaluated by magnetic resonance imaging using RECIST criteria. For all chemotherapy protocols, local tumor control was 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%, respectively. Median and mean survival times from the beginning of the TACE sessions were 18.5 months and 30.7 months, respectively. Treatment with mitomycin-C only showed median and mean survival times of 13.3 months and 24 months; and with gemcitabine, 11 months and 22.3 months, respectively. With combination mitomycin-C and gemcitabine, median and mean survival times were 24.8 months and 35.5 months, respectively.

**Section Summary: TACE for Other Unresectable Hepatic Metastases**
For other types of hepatic metastases, the largest amount of evidence assessing colorectal cancer. There are multiple RCTs and numerous nonrandomized studies that have compared TACE with alternatives. The nonrandomized studies have reported that TACE can stabilize 40% to 60% of treated patients but whether this translates into a prolonged survival benefit relative to systemic chemotherapy alone is uncertain. Two small RCTs have reported that TACE with drug-eluting beads results in statistically significant improvements in response rates and PFS. Whether this translates into a prolongation of survival relative to systemic chemotherapy alone is uncertain. For cancers other than colorectal, the evidence is extremely limited and no conclusions can be made.

**SUMMARY OF EVIDENCE**
**TACE for Unresectable Hepatocellular Carcinoma**
For individuals who have unresectable HCC confined to the liver and not associated with portal vein thrombosis who receive TACE, the evidence includes several RCTs, large observational studies, and systematic reviews. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. 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 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 OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Studies have shown little to no difference in OS rates with neoadjuvant TACE compared with surgery alone. A meta-analysis found no significant

improvements in survival or recurrence with preoperative TACE for resectable HCC. While both RCTs and the meta-analysis that evaluated TACE as adjuvant therapy to hepatic resection in HCC reported positive results, the quality of individual studies and the methodologic issues related to the meta-analysis preclude certainty when interpreting the results. Well-conducted multicentric trials from United States or Europe representing relevant populations with adequate randomization procedures, blinded assessments, centralized oversight and publication in peer-reviewed journals are required. The evidence is insufficient to determine the effects of the technology on health outcomes.

**TACE Plus Radiofrequency Ablation for Resectable HCC**
For individuals who have resectable HCC who receive TACE plus RFA, the evidence includes a single RCT. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The RCT failed to show the superiority in survival benefit with combination TACE plus RFA treatment compared to surgery for HCC lesions 3.0 cm or smaller. Further, an ad hoc subgroup analysis showed a significant benefit for surgery in recurrence and OS in patients with lesions larger than 3 cm. It cannot be determined from this trial whether TACE plus RFA is as effective as surgical resection for these small tumors. The evidence is insufficient to determine the effects of the technology on health outcomes.

**TACE Plus RFA for Unresectable HCC**
For individuals who have unresectable HCC who receive TACE plus RFA, the evidence includes multiple systematic reviews and RCTs. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Multiple meta-analyses and RCTs have shown a consistent benefit in survival or RFS in favor of combination TACE plus RFA over RFA alone. However, results of these meta-analyses are difficult to interpret because the pooled data included heterogeneous patient populations and, in a few cases, included data from a study retracted due to questions about data veracity of. A larger well-conducted RCT has reported relative reduction in the hazard of death by 44% and a 14% difference in 4-year survival in favor of combination therapy. The major limitations of this trial were its lack of a TACE-alone arm and the generalizability of its findings to patient populations that have unmet need such as those with multiple lesions larger than 3 cm and Child-Pugh class B or C. Further, this single-center trial was conducted in China, and until these results have been reproduced in patient populations representative of pathophysiology and clinical stage more commonly found in the United States or Europe, the results may not be generalizable. The evidence is insufficient to determine the effects of the technology on health outcomes.

**TACE as a Bridge to Liver Transplant**
For individuals who have a single hepatocellular tumor less than 5 cm or no more than 3 tumors each less than 3 cm in size, absence of extrahepatic disease or vascular invasion, and Child-Pugh class A or B seeking to prevent further tumor growth and to maintain patient candidacy for liver transplant who receive pretransplant TACE, the evidence includes multiple small prospective studies. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. There is a lack of comparative trials on various locoregional treatments as a bridge therapy to liver transplantation. Multiple small prospective studies have demonstrated that TACE can prevent dropouts from the transplant list. TACE has become an accepted method to prevent tumor growth and progression while patients are on the

liver transplant waiting list. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**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 OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. RCT evaluating the benefit of adding TACE to standard of care for patients with unresectable cholangiocarcinoma are lacking. Results of 3 retrospective studies have shown a survival benefit with TACE over standard of care. These studies lacked matched patient controls. Although the observational data are consistent, the lack of randomization limits definitive conclusions. The evidence is insufficient to determine the effects of the technology on health outcomes.

**TACE for Symptomatic Unresectable Neuroendocrine Tumors**
For individuals who have symptomatic metastatic neuroendocrine tumor despite systemic therapy who are not candidates for surgical resection who receive TACE, the evidence includes retrospective single- cohort studies. Relevant outcomes are OS, 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 TACE to palliate the symptoms associated with hepatic neuroendocrine metastases can provide a clinically meaningful improvement in net health outcome. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**TACE for Liver-Dominant Metastatic Uveal Melanoma**
For individuals who have liver-dominant metastatic uveal melanoma who receive TACE, the evidence includes observational studies and reviews. Relevant outcomes are OS, 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 that the technology results in a meaningful improvement in the net health outcome.

**TACE for Other Unresectable Hepatic 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 multiple RCTs, observational studies, and systematic reviews. Relevant outcomes are OS, 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 but whether this translates

into prolonged survival benefit relative to systemic chemotherapy alone is uncertain. Two small RCTs have reported that TACE with drug-eluting beads has resulted in statistically significant improvements in response rate and PFS. Whether this translates into a prolonged survival benefit relative to systemic chemotherapy alone is uncertain. For cancers other than colorectal, the evidence is extremely limited and no conclusions can be made. Studies have small numbers of patients and the results have varied due to differences in patient selection criteria and treatment regimens used. The evidence is insufficient to determine the effects of the technology on health outcomes.

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## Policy History

Original Effective Date: 03/19/2008
Current Effective Date: 05/16/2018

| | |
|---|---|
| 03/12/2008 | Medical Director review |
| 03/19/2008 | Medical Policy Committee approval. |
| 03/04/2009 | Medical Director review |
| 03/18/2009 | Medical Policy Committee approval. No change to coverage. |
| 06/03/2010 | Medical Policy Committee approval |
| 06/16/2010 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 05/05/2011 | Medical Policy Committee review |
| 05/18/2011 | Medical Policy Implementation Committee approval. Added that the use of transcatheter hepatic arterial chemoembolization as neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable is considered to be investigational. |
| 05/03/2012 | Medical Policy Committee review |
| 05/16/2012 | Medical Policy Implementation Committee approval. Added that TACE for unresectable cholangio-carcinoma is considered investigational. Revised the format of the remaining investigational statements while preserving their intent. |
| 05/02/2013 | Medical Policy Committee review |
| 05/22/2013 | Medical Policy Implementation Committee approval. Format Coverage eligibility unchanged. |
| 05/01/2014 | Medical Policy Committee review |
| 05/21/2014 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 05/07/2015 | Medical Policy Committee review |
| 05/20/2015 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged |
| 08/03/2015 | Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed. |
| 05/05/2016 | Medical Policy Committee review |

Policy # 00227
Original Effective Date: 03/19/2008
Current Effective Date: 05/16/2018

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|---|---|
| 05/18/2016 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes |
| 05/04/2017 | Medical Policy Committee review |
| 05/17/2017 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged |
| 05/03/2018 | Medical Policy Committee review |
| 05/16/2018 | Medical Policy Implementation Committee approval. Changed formatting from one statement to bulleted conditions in the "When Services Are Eligible for Coverage" section. Changed formatting by grouping individual coverage statements into 2 separate coverage statements for TACE with criteria by adding a "When Services May Be Eligible for Coverage" section. Added "Child-Pugh class is either A or B" as criteria for TACE to treat HCC. Replaced "hepatic" with "of the liver" in all statements in the coverage section. Added a link for the Child-Pugh Score calculator in the coverage section. |

Next Scheduled Review Date: 05/2019

## Coding

*The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician*.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

| Code Type | Code |
|---|---|
| CPT | 37243, 75894 |
| HCPCS | Q0083 |
| ICD-10 Diagnosis | C22.0-C22.9, C78.7 |

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means

of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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