Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

Policy Number: 8.01.11  Last Review: 6/2017

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for transcatheter arterial chemoembolization to treat liver malignancies when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
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 (TACE) 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. (See Considerations section)

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.

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

When Policy Topic is not covered
Transcatheter hepatic arterial chemoembolization is considered investigational as neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable.

Transcatheter hepatic arterial chemoembolization is considered investigational to treat hepatocellular tumors prior to liver transplantation except as noted above.
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 criteria noted above, including recurrent hepatocellular carcinoma.

Transcatheter hepatic arterial chemoembolization is considered *investigational* to treat unresectable cholangiocarcinoma.

**Considerations**
When using transcatheter hepatic arterial chemoembolization as a bridge to transplantation to prevent further tumor growth, 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, and Child-Pugh score of either A or B.

**Description of Procedure or Service**

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| **Individuals:**
  - With unresectable hepatocellular cancer confined to the liver and not associated with portal vein thrombosis | Interventions of interest are:
  - Transcatheter arterial chemoembolization | Comparators of interest are:
  - Other locally ablative techniques (eg, radiofrequency ablation, cryoablation)
  - Systemic therapy
  - Supportive care | Relevant outcomes include:
  - Overall survival
  - Disease-specific survival
  - Quality of life
  - Treatment-related mortality
  - Treatment-related morbidity |
| **Individuals:**
  - With resectable hepatocellular cancer | Interventions of interest are:
  - Neoadjuvant or adjuvant transcatheter arterial chemoembolization | Comparators of interest are:
  - Other locally ablative techniques (eg, radiofrequency ablation, cryoablation)
  - Systemic therapy | Relevant outcomes include:
  - Overall survival
  - Disease-specific survival
  - Quality of life
  - Treatment-related mortality
  - Treatment-related morbidity |
| **Individuals:**
  - With 1-3 small hepatocellular tumors seeking to prevent tumor growth and maintain candidacy for liver transplant | Interventions of interest are:
  - Pretransplant transcatheter arterial chemoembolization | Comparators of interest are:
  - Other locally ablative techniques (eg, radiofrequency ablation, cryoablation)
  - Systemic therapy | Relevant outcomes include:
  - Overall survival
  - Disease-specific survival
  - Quality of life
  - Treatment-related mortality
  - Treatment-related morbidity |
| **Individuals:**
  - With unresectable cholangiocarcinoma | Interventions of interest are:
  - Transcatheter arterial chemoembolization | Comparators of interest are:
  - Other locally ablative techniques (eg, radiofrequency ablation, cryoablation)
  - Systemic therapy | Relevant outcomes include:
  - Overall survival
  - Disease-specific survival |
<table>
<thead>
<tr>
<th>Individuals:</th>
<th>Interventions of interest are:</th>
<th>Comparators of interest are:</th>
<th>Relevant outcomes include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>With symptomatic metastatic neuroendocrine tumor despite systemic therapy who are not candidates for surgical resection</td>
<td>Transcatheter arterial chemoembolization</td>
<td>Other locally ablative techniques (eg, radiofrequency ablation, cryoablation)</td>
<td>Overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Disease-specific survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of life</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment-related mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment-related morbidity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals:</th>
<th>Interventions of interest are:</th>
<th>Comparators of interest are:</th>
<th>Relevant outcomes include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>With liver-dominant metastatic uveal melanoma</td>
<td>Transcatheter arterial chemoembolization</td>
<td>Other locally ablative techniques (eg, radiofrequency ablation, cryoablation)</td>
<td>Overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Disease-specific survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of life</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment-related mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment-related morbidity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals:</th>
<th>Interventions of interest are:</th>
<th>Comparators of interest are:</th>
<th>Relevant outcomes include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>With unresectable hepatic metastases from other types of primary tumors (eg, colorectal, breast)</td>
<td>Transcatheter arterial chemoembolization</td>
<td>Other locally ablative techniques (eg, radiofrequency ablation, cryoablation)</td>
<td>Overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Disease-specific survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of life</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment-related mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment-related morbidity</td>
</tr>
</tbody>
</table>

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 for Unresectable Hepatocellular Carcinoma**
The evidence on TACE for individuals who have unresectable hepatocellular carcinoma (HCC) confined to the liver and who meet specific selection criteria (ie, good hepatic function/reserve and no portal vein thrombosis) includes several randomized controlled trials (RCTs), large observational studies, and systematic
reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Overall, studies have shown improved overall survival compared with only supportive care. One systematic review highlighted some of the possible biases associated with these studies. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

**TACE for Resectable HCC as Neoadjuvant or Adjuvant Therapy**
The evidence on TACE in the neoadjuvant or adjuvant setting in patients who have resectable HCC includes several RCTs and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Overall, studies have shown little to no difference in overall survival rates with neoadjuvant or adjuvant TACE compared with surgery alone. A meta-analysis found no significant improvements in survival or recurrence with the use of preoperative TACE for resectable HCC. The evidence is insufficient to determine the effects of the technology on health outcomes.

**TACE as a Bridge to Liver Transplant**
The evidence on TACE for individuals who have unresectable HCC confined to the liver and who meet specific selection criteria for liver transplantation includes many observational studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. TACE has become an accepted method to prevent tumor growth and progression while patients are on the liver transplant wait list. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

**TACE for Unresectable Cholangiocarcinoma**
The evidence on TACE for patients who have unresectable cholangiocarcinoma includes several retrospective observational studies and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Most data on TACE are for unresectable intrahepatic cholangiocarcinoma. Although the data suggest an overall survival advantage with TACE versus supportive care or systemic chemotherapy alone, the data consist mostly of retrospective reviews without matched patient controls. The evidence is insufficient to determine the effects of the technology on health outcomes.

**TACE for Symptomatic Unresectable Neuroendocrine Tumors**
The evidence on TACE for patients who have unresectable metastatic neuroendocrine tumors includes observational studies and reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Several studies have shown reduced tumor burden, reduced hormone levels, and palliation of symptoms with TACE. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.
TACE for Hepatic Metastases From Uveal (Ocular) Melanoma
The evidence on TACE for patients who have unresectable metastatic uveal melanomas includes observational studies and reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Several studies have shown a survival advantage using locoregional treatment modalities, including TACE, in patients who have liver-dominant metastases from ocular melanoma. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

TACE for Other Hepatic Metastases
The evidence on TACE for patients who have unresectable, intrahepatic metastatic tumors (eg, colorectal or breast cancer) includes RCTs, numerous observational studies, and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Studies have small numbers of patients and the results have been variable across studies due to differences in patient selection criteria and regimens used. The evidence is insufficient to determine the effects of the technology on health outcomes.

Background

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 hepatocellular carcinoma, cholangiocarcinoma, liver metastases, and in the liver transplant setting. Treatment alternatives include resection when possible, chemotherapy administered systemically or by hepatic artery infusion (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.

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 the time of diagnosis, which is caused by the lack of symptoms until late in the disease. The overall prognosis of ICC is far worse than for extrahepatic cholangiocarcinoma because of its late presentation. Most patients with ICC qualify for palliative therapy, including systemic chemotherapy and radiotherapy. However, such palliative options afford little to no survival improvement over supportive therapy alone, because ICC responds poorly to such existing therapies.(1) Survival prognosis for patients with unresectable ICC is approximately 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
such that the patient is considered a better candidate for liver transplantation, and to decrease the incidence of posttransplant recurrence in patients with larger (T3) tumors. All of these uses are in part related to the United Network for Organ Sharing (UNOS) liver allocation policy, which prioritizes patients for receiving donor livers. The UNOS policy and the previous 3 uses are discussed further in the following sections.

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

Uveal 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.

Transcatheter Arterial Chemoembolization
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.

UNOS Liver Allocation Policy
In 2002, UNOS introduced a new liver allocation system—model for end-stage liver disease (referred to as MELD) for adult patients awaiting liver transplant.(2) The MELD score is a continuous disease severity scale incorporating bilirubin, prothrombin time (ie, international normalized ratio [INR]), and creatinine into an equation, producing a number that ranges from 6 (less ill) to 40 (gravely ill). Aside from those in fulminant liver failure, donor livers are prioritized to those with the
highest MELD number. This scale accurately predicts the risk of dying from liver
disease except for those with HCC, who often have low MELD scores, because
bilirubin, INR, and creatinine levels are near normal. Therefore, patients with HCC
are assigned additional allocation points according to the size and number (T
stage) of tumor nodules as follows:

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

In considering how to allocate the scarce donor organs, UNOS sought to balance
risk of death on the waiting list against risk of recurrence after transplant. Patients
with T1 lesions are considered at low risk of death on the waiting list, while those
with T3 lesions are at high risk of posttransplant recurrence and are generally not
considered transplant candidates. Patients with T2 tumors have an increased risk
of dying while on the waiting list compared with those with T1 lesions, and are an
acceptable risk of posttransplant tumor recurrence. Therefore, UNOS criteria,
which were updated in 2013, prioritize only T2 HCC patients who meet specified
staging and imaging criteria by allocating additional points equivalent to a MELD
score predicting a 15% probability of death within 3 months. This definition of T2
lesions is often referred to as the Milan criteria, in reference to a key 1996 study
that examined the recurrence rate of HCC according to the size of the initial
tumor.(3) Liver transplantation for those with T3 HCC is not prohibited, but these
patients do not receive any priority on the waiting list. All patients with HCC
awaiting transplantation are reassessed at 3-month intervals. Those whose tumors
have progressed and are no longer T2 tumors will lose the additional allocation
points.

Additionally, nodules identified through imaging of cirrhotic livers are given an
OPTN (Organ Procurement and Transplantation Network) class 5 designation.
Class 5B and 5T nodules are eligible for automatic priority. Class 5B criteria consist
of a single nodule 2 cm or larger and up to 5 cm (T2 stage) that meets specified
imaging criteria. Class 5T nodules have undergone subsequent locoregional
treatment after being automatically approved on initial application or extension. A
single class 5A nodule (>1 cm and <2 cm) corresponds to T1 HCC and does not
qualify for automatic priority. However, combinations of class 5A nodules are
eligible for automatic priority if they meet stage T2 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 better characterize the long-term outcomes of liver transplantation for
patients with HCC and to assess whether it is justified to continue the policy of

assigning increased priority for candidates with early-stage HCC on the U.S. transplant waiting list. There was a general consensus at the meeting for the development of a calculated continuous HCC priority score for ranking HCC candidates on the list that would incorporate the calculated MELD score, α-fetoprotein, tumor size, and rate of tumor growth and that only candidates with at least stage T2 tumors would receive additional HCC priority points. The report addressed the role of locoregional therapy to downstage patients from T3 to T2 and stated that the results of downstaging before liver transplantation are heterogeneous, with no upper limits for tumor size and number before downstaging across studies, and the use of different end points for downstaging before transplantation.

**Rationale**

This evidence review was originally created in July 1996 and has been regularly updated with literature reviews of the MEDLINE database. The most recent literature review was performed for the period through June 14, 2016. The following is a summary of key evidence to date.

This evidence review was originally based on a 2000 TEC Assessment that offered the following observations and conclusions:

- Five randomized trials focused on the use of transcatheter arterial chemoembolization (TACE) to treat resectable hepatocellular carcinoma (HCC), either in the adjuvant or neoadjuvant setting. These trials reported inconsistent results in terms of survival rates. Treatment-related morbidity (TRM) and mortality were not reported consistently across studies.
- No randomized study focused on TACE to treat postoperative recurrent HCC, 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 HCC compared with supportive care. Survival did not differ significantly across 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 (HAI) and systemic chemotherapy. The available data also did not show superiority for either TACE or alternatives with respect to complication rates or TRM.
- There were no controlled trials comparing TACE with 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 on the efficacy of medical management to control symptoms. Data were also inadequate to permit conclusions about tumor response rates and survival.

The role of TACE in the management of patients with HCC who are awaiting liver transplantation was not addressed in the 2000 TEC Assessment.
**TACE for Unresectable HCC**

**Systematic Reviews**
Numerous systematic reviews on TACE have evaluated the efficacy of TACE alone or the comparative efficacy of TACE with alternative treatments. Some have focused on comparing 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 to control. The 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 randomized controlled trials (RCTs) comparing TACE to alternative treatments are reviewed here. Bush et al 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 to 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 to systemic chemotherapy for patients with unresectable HCC. One hundred patients were randomly allocated to 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-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) versus 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%. TRM 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 studies used a similar embolization regimen (lipiodol and gelatin sponge) but different cytotoxic agents (doxorubicin or cisplatin). 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 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).

Nonrandomized Observational Trials
In the 2002 Llovet et al RCT, patients received arterial embolization with gelatin sponge, TACE, or 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 (AEs) after TACE.

In a 2006 prospective study, Molinari et al reported on the effectiveness of TACE for HCC at a single center in Canada. Patients with Child-Pugh class A cirrhosis or better and unresectable HCC without radiologic evidence of metastatic disease or segmental portal vein thrombosis were assessed between November 2001 and May 2004. Of 54 patients who met 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 AEs occurred after 20% of sessions, including 2 (4%) treatment-related deaths.

In 2006, Takayasu et al reported results from an 8-year prospective cohort study of TACE from Japan.(15) 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. Exclusion criteria were extrahepatic metastases and/or any previous treatment before the present TACE. The mean follow-up period was 1.77 years. Median and 1-, 3-, and 5-year OS rates with TACE were 34 months, 82%, 47%, and 26%, respectively. Multivariate analyses showed significant differences in degree of liver damage (p<0.001), α-fetoprotein values (p<0.001), maximum tumor size (p<0.001), number of lesions (p<0.001), and portal vein invasion (p<0.001). The TACE-related mortality rate after the initial therapy was 0.5%.

A 2005, large cohort study from Biselli et al reported on 56 cirrhotic patients with unresectable HCC undergoing at least 1 course of TACE who were matched 1:1 for sex, age (in 5-year periods), Child-Pugh class, Okuda stage, and tumor type with a control group that received only supportive care.(16) The 2 groups were comparable for cause of cirrhosis, α-fetoprotein serum levels, and Cancer of the Liver Italian Program score. The 56 patients in the TACE group received 123 treatment courses. Survival rates at 12, 24, and 30 months in patients receiving TACE were 74.3%, 52.1%, and 38.8%, respectively (median survival, 25 months), whereas in supportive care patients, the rates were 39.4%, 25.4%, and 19%, respectively (median survival, 7 months; p<0.001). At univariate analysis, TACE, tumor type, presence of ascites, α-fetoprotein serum level, CLIP score, and Okuda stage were significantly associated with survival. Only TACE and CLIP score proved to be independent predictors of survival at multivariate analysis.

**Section Summary: TACE for Unresectable HCC**

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

**TACE for Resectable HCC as Neoadjuvant or Adjuvant Therapy**

**Neoadjuvant TACE**

**Systematic Reviews**

In 2013, Zhou et al conducted a meta-analysis of 21 studies evaluating preoperative TACE.(17) 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 disease-free survival (DFS) for preoperative TACE ranged from 7.0% to 57% and from 8.0% to 48.8%
in the controls. In 16 studies, the 5-year OS 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 versus controls in 5-year DFS (32.1% vs 30.0%, p=0.17) or OS (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.(18) 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.

Clinical Trials
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, radiofrequency ablation, or percutaneous ethanol injection.(19) 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 better 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 better DFS. Neoadjuvant TACE did not provide benefit compared with curative therapy alone in subgroup analysis.

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.(20) No significant differences were found between the pooled preoperative TACE groups and the control group in DFS (p=0.660) or OS (p=0.412). Significant differences were not reported between the 3 groups in DFS (p=0.830) or OS (p=0.713). 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. 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.

In a 2009 RCT, Zhou et al randomly allocated 108 patients with resectable HCC (≥5 cm suitable for a partial heptatectomy) to preoperative TACE treatment (n=52)
or no preoperative treatment (n=56 [control group]). (21) 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%, 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 OS 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).

In 2007, Choi et al studied 273 patients who underwent curative resection for HCC, 120 of whom underwent preoperative TACE. (22) The 1-, 3-, and 5-year DFS 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. The differences between the TACE and non-TACE groups were not 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. (23) 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.

**Adjuvant TACE**

In 2006, Li et al described the results of an RCT that investigated the efficacy of postoperative TACE and portal vein chemotherapy (PVC) for patients with HCC complicated by portal vein tumor thrombosis (PVTT) and evaluated prognostic factors. (24) The trial cohort consisted of 112 patients with HCC and PVTT allocated to 3 groups: group A (37 patients), surgery only; group B (35 patients), surgery plus TACE; and group C (40 patients), surgery plus TACE and PVC. Portal vein thrombus extirpation was performed at the time of surgery. AEs 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%). The DFS curve differed significantly across the 3 groups, as estimated by the Kaplan-Meier method (both p<0.05). Group C showed a higher DFS rate than group A (p<0.05), but differences between group A and group B or between group B and group C (both p>0.05) were not statistically significant. The 1-, 3-, and 5-year DFS rates in group A were 50.7%, 17.8%, and 0%, respectively; in group B, rates were 62.3%, 23.7%, and 4.0%, respectively, and in group C rates 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).
Section Summary: TACE for Resectable HCC as Neoadjuvant or Adjuvant Therapy

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

TACE as a Bridge to Liver Transplant

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

Graziadei et al 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.(25) None was removed from the list due to tumor progression, and mean waiting time was 178 days.

Maddala et al studied dropout rates for 54 patients receiving TACE while awaiting transplantation.(26) During a median waiting time of 211 days (range, 28-1099 days), the rate was 15%.

Fisher et al assessed 33 patients who received multimodality ablation therapy, consisting primarily of RFA or TACE.(27) Five (12%) patients were removed from the waiting list after 5 to 14 months. In this protocol, patients with tumors larger than 5 cm were not considered transplant candidates until the tumor was completely ablated using TACE, RFA, or another technique.

Yamashiki et al evaluated 288 patients given various ablative therapies; the dropout rates due to tumor progression at 1 and 3 years were 6.25% and 23%, respectively.(28) Tumors larger than 3 cm affected the dropout rate due to tumor progression.

Obed et al reported on 20 patients with nonprogression of lesions after TACE who had liver transplantation; median survival in this group was 92.3 months.(29)

TACE to Downstage HCC Prior to Transplant or to Reduce Recurrence in Those With T3 Lesions

Published literature reflects an ongoing discussion as to whether the United Network for Organ Sharing allocation criteria (see Background) should be expanded to include patients with larger tumors.(4) Some patients with T3 lesions apparently are cured with liver transplant, although most experience recurrent tumor. For example, in the seminal 1996 study,(3) the 4-year recurrence-free survival (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.(30)

However, other institutions have reported similar outcomes with expanded criteria. Yao at University of California at San Francisco (UCSF) reported similar RFS 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.”(31)

Lewandowski et al compared the efficacy of radioembolization with chemoembolization in downstaging 86 patients with HCC from stage T3 to T2.(32) Patients were treated with either yttrium-90 microspheres (n=43) or TACE (n=43). Median tumor size was similar between the 2 treatment groups (5.7 cm for TACE vs 5.6 cm for radioembolization). Partial response rates were 61% versus 37% for radioembolization versus TACE, respectively, with downstaging from T3 to T2 in 58% of patients treated with radioembolization versus 31% with TACE (p<0.05).

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

TACE for Unresectable Cholangiocarcinoma

Systematic Reviews
In 2014 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 intrahepatic cholangiocarcinoma (ICC).(33) 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).

Clinical Trials
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.(34) 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 versus intrahepatic cholangiocarcinoma.

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.(1) 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 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. 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 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 versus 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.(35) 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 that did not receive 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).

In 2007, Herber et al retrospectively analyzed 15 patients with inoperable ICC treated with TACE between 2000 and 2006.(36) No patient had extrahepatic tumor spread. The decision for TACE was made by an interdisciplinary tumor board in each case. Fifty-eight TACE sessions were performed in the 15 patients (3.9; range, 1-15). Eight patients had unifocal tumor and 7 had multifocal disease. Mean tumor size was 10.8 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 (anaphylactic shock owing to contrast medium administration, gastric ulceration due to lipiodol displacement). Mean survival was 21.1 months (95% CI, 9.4 to 32.5 months).

In 2005, Burger et al reported on prospectively collected data from 17 patients with unresectable cholangiocarcinoma treated with TACE at their institution between 1995 and 2004.(37) Among the 17 patients, 11 presented without any previous treatment and 6 had had 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 patients, who experienced mild or no adverse effects, which resolved with conservative therapy.
alone. Two (12%) patients had minor complications, which were managed successfully, and 1 had a major complication that was fatal shortly after TACE. Median survival for the 17 patients was 23 months (95% CI, 15.4 to 30.6 months). Two patients with previously unresectable disease underwent successful resection after TACE.

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

TACE for Symptomatic Unresectable Neuroendocrine Tumors

Systematic Reviews
A 2010 review by Nazario and Gupta summarized the experience to date with TACE (and transarterial embolization [TAE]), which is composed of many nonrandomized, retrospective reports that have demonstrated reduced tumor burden, lower hormone levels, and palliation of symptoms with these interventions.(38) The review summarized the experience with TACE and TAE and metastatic neuroendocrine tumors as showing radiologic responses ranging from 25% to 95%, and symptomatic responses in 53% to 100% of patients. Five-year OS rates varied from 14% to 75%, likely a reflection of the heterogeneity of the patient populations and treatment regimens used. Some studies in the review are detailed next.

Clinical Trials
In 2007, Ruutiainen et al reported on a study of 67 patients that compared bland embolization with TACE in neuroendocrine tumors metastatic to the liver.(39) The 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 retreated when feasible. Ten (15%) of 67 patients 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 disease progression at 1, 2, and 3 years were 49%, 49%, and 35%, respectively, after chemoembolization and 0%, 0%, and 0%, respectively, after bland embolization (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). Posttherapy survival rates at 1, 3, and 5 years 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 time to progression, symptom control, and survival, and suggested that a multicenter prospective randomized trial was warranted. These results are similar to those reported by Gupta et al in 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.(40)

Osborne et al reported on a nonrandomized study of 59 patients with neuroendocrine tumors who received cytoreduction or embolization for symptomatic hepatic metastases.(41) 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 for TACE. Uncontrolled trials have reported that TACE reduces symptoms and tumor burden, and improves hormone profile. In addition, for is relatively rare condition, there are limited alternative treatments for these tumors.

**TACE for Liver-Dominant Metastatic Uveal Melanoma**

A 2010 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.(42)

In 2010, Huppert et al reported on a pilot trial of 14 patients with hepatic metastases from uveal melanoma who underwent TACE.(43) Patients received a mean of 2.4 treatments (34 total treatments among 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=NS). 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. 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 versus 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) compared use of TACE for melanoma metastatic to the liver in a series of 20 patients (17 with ocular melanoma) treated between 2004 and 2007.(44) 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 this treatment resulted in longer survival than had been noted among historical controls. This work built on results reported by Bedikian et al in 1995, which showed that TACE had a 36% response rate (cisplatin chemoembolization) compared with a 1% response rate to systemic chemotherapy.(45)
In a 2005 report, Patel et al described results of BCNU treatment for uveal melanoma and demonstrated that those who responded had improved survival.(46) 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

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

TACE for Other Unresectable Hepatic Metastases

Colorectal Cancer

Systematic Reviews

Zacharias et al published a meta-analysis on hepatic artery based therapies for colorectal metastases.(47) 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. On combined analysis, OS for patients treated with TACE was 15.2 months, compared to 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 reported on a systematic review (1 RCT, 5 observational studies) of TACE with irinotecan-eluting beads for unresectable colorectal liver metastasis.(48) Survival times ranged from a median of 15.2 to 25 months. The most common AEs were postembolization syndrome (abdominal pain, nausea, vomiting) followed by hypertension.

Randomized Controlled Trials

In the RCT included in the Richardson systematic review, Fiorentini et al (2012) reported on 74 patients randomly allocated to TACE with irinotecan-eluting beads (n=36) or systemic irinotecan, fluorouracil, and leucovorin (n=38).(49) With irinotecan-eluting beads, OS was significantly longer with a median OS of 22 months (95% CI, 21 to 23 months) versus 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 compared with 4 months (95% CI, 3 to 5 months) in the systemic chemotherapy group (p=0.006).

**Nonrandomized Trials**

In 2009, Vogl et al reported 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.50 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 1 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 the results from a 2003 study by the same authors, in which untreated patients had a survival rate of 7 to 8 months(51)). 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.(52) 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 (measured from the first TACE treatment). Survival results were comparable with other studies addressing colorectal cancer and TACE (range, 7-10 months). Median survival was 6.9 months for the radioembolization group (p=0.27). 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 reported the efficacy of repeated treatments with TACE in 208 patients with unresectable hepatic metastases from breast cancer.(53) A total of 1068 chemoembolizations were performed (mean, 5.1 sessions per patient; range, 3-25). Patients received either 1 of 2 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%. 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, only 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 is for colorectal cancer. There is a single RCT and numerous nonrandomized studies that have compared TACE to alternatives. There is no evidence that TACE is superior or inferior to other therapies, however, the evidence base is limited by low-quality studies and meaningful differences in outcomes cannot be ruled out. For cancers other than colorectal, the evidence is extremely limited and no conclusions can be made.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01906216</td>
<td>Sorafenib With or Without Transarterial Chemoembolization (TACE) in Advanced Hepatocellular Carcinoma: A Multicenter, Randomized, Controlled Trial</td>
<td>246</td>
<td>June 2016 (ongoing)</td>
</tr>
<tr>
<td>NCT00908752a</td>
<td>A Randomized, Double-blind, Multicenter Phase III Study of Brivanib Versus Placebo as Adjuvant Therapy to Trans-Arterial Chemo-Embolization (TACE) in Patients With Unresectable Hepatocellular Carcinoma (The BRISK TA Study)</td>
<td>870</td>
<td>Dec 2016</td>
</tr>
<tr>
<td>NCT01676194</td>
<td>Efficacy of Transarterial Chemoembolization With DC-BeadsR Prior to Liver Transplantation for Hepatocellular Carcinoma on Patient Survival: A Prospective Multicentre and Randomized Study</td>
<td>140</td>
<td>Aug 2017</td>
</tr>
<tr>
<td>NCT01512407</td>
<td>Randomised Controlled Trial on Adjuvant Transarterial Chemoembolisation After Curative Hepatectomy for Hepatocellular Carcinoma</td>
<td>144</td>
<td>Jan 2018</td>
</tr>
<tr>
<td>NCT01004978</td>
<td>A Phase III Randomized, Double-Blind Trial of Chemoembolization With or Without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients With and Without Vascular Invasion</td>
<td>400</td>
<td>Feb 2018</td>
</tr>
<tr>
<td>NCT01833286</td>
<td>Radiofrequency Ablation Combined With Transcatheter Arterial Chemoembolization Versus Re-resection for Recurrent Hepatocellular Carcinoma</td>
<td>200</td>
<td>Jul 2019</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01324076</td>
<td>TACE-2: A Randomized Placebo-Controlled, Double Blinded, Phase III Trial of Sorafenib in Combination With Transarterial Chemoembolization in Hepatocellular Cancer</td>
<td>412</td>
<td>Nov 2014 (unknown)</td>
</tr>
<tr>
<td>NCT01869088</td>
<td>Phase III Trial of Transcatheter Arterial Chemoembolization(TACE) Plus</td>
<td>120</td>
<td>Dec 2015 (unknown)</td>
</tr>
</tbody>
</table>
Recombinant Human Adenovirus Type 5 Injection for Unresectable Hepatocellular Carcinoma (HCC)

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

Summary of Evidence

**TACE for Unresectable Hepatocellular Carcinoma**
For individuals who have unresectable hepatocellular carcinoma (HCC) confined to the liver and not associated with portal vein thrombosis who receive transcatheter arterial chemoembolization (TACE), the evidence includes several randomized controlled trials (RCTs), large observational studies, and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Studies of TACE have shown improved overall survival compared with only supportive care. One systematic review highlighted some of the possible biases associated with these studies. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

**TACE for Resectable HCC as Neoadjuvant or Adjuvant Therapy**
For individuals who have resectable HCC who receive neoadjuvant or adjuvant TACE, the evidence includes several RCTs and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Studies have shown little to no difference in overall survival rates with neoadjuvant or adjuvant TACE compared with surgery alone. A meta-analysis found no significant improvements in survival or recurrence with preoperative TACE for resectable HCC. 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 TACE, the evidence includes many observational studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. 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 qualitatively 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 overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Most data on TACE are for unresectable intrahepatic cholangiocarcinoma. Although the data have suggested
an overall survival advantage with TACE versus supportive care or systemic chemotherapy alone, the data consist mostly of retrospective reviews without matched patient controls. 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 observational studies and reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Several studies have shown reduced tumor burden, reduced hormone levels, and palliation of symptoms with TACE. The evidence is sufficient to determine qualitatively 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 overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Several studies have shown a survival advantage using locoregional treatment modalities, including TACE, in patients who have liver-dominant metastases from uveal melanoma. The evidence is sufficient to determine qualitatively 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 type of primary tumor (eg, colorectal or breast cancer) who receive TACE, the evidence includes RCTs, numerous observational studies, and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Studies have small numbers of patients and the results have varied across studies 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.

**SUPPLEMENTAL INFORMATION**

**Clinical Input Received From Physician Specialty Societies and Academic Medical Centers**
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.

In response to requests, input was received from 1 specialty medical society (2 reviewers) and 3 academic medical centers while this policy was under review in 2012. There was general agreement among reviewers that use of TACE was
medically necessary for 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. Reviewers were split over the investigational policy statement to treat other liver metastases or for recurrent HCC. Four reviewers provided input on the use of TACE in unresectable cholangiocarcinoma; 2 consider it investigational and 2 consider it investigational but also medically necessary, the latter citing data showing a survival benefit of TACE compared with supportive therapy.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network Guidelines

**Hepatocellular Carcinoma**

The National Comprehensive Cancer Network (NCCN) guidelines on hepatocellular carcinoma (v.2.2016) list chemoembolization as an option for patients with hepatocellular tumors not amenable to ablation therapy only and, in absent large-volume extrahepatic disease (category 2A), with the additional recommendation that tumor lesions larger than 5 cm be treated using arterial embolic approaches, whereas tumors 3 to 5 cm can be considered for combination therapy with ablation and arterial embolization.(54) Additionally, TACE is relatively contraindicated in patients with portal vein thrombosis and bilirubin levels greater than 3 mg/dL, and is absolutely contraindicated with Child-Pugh class C liver function.

**Intrahepatic Cholangiocarcinoma**

NCCN guidelines on intrahepatic cholangiocarcinoma (v.2.2016) do not address the use of TACE in intrahepatic cholangiocarcinoma.(54)

**Neuroendocrine Tumors, Carcinoid, and Islet Cell Tumors**

NCCN guidelines on neuroendocrine tumors, carcinoid, and islet cell tumors (v.2.2016) recommend chemoembolization for patients with unresectable liver metastases (category 2B).(55)

**Uveal Cancer**

No NCCN guidelines were identified for uveal malignancies.

**Colon Cancer**

NCCN guidelines on colon cancer (v.2.2016) recommend the use of arterially directed embolic therapy for metastatic colon cancer to the liver (category 3 recommendation; based on any level of evidence. There is major NCCN disagreement about whether the intervention is appropriate.(56)

**Breast Cancer**

NCCN guidelines on breast cancer (v.2.2016) do not address TACE as a treatment option for breast cancer metastatic to the liver.(57)

**U.S. Preventive Services Task Force Recommendations**

Not applicable.
Medicare National Coverage

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

References:


42. Sato T. Locoregional management of hepatic metastasis from primary uveal melanoma. Semin Oncol. Apr 2010;37(2):127-138. PMID 20494705
Billing Coding/Physician Documentation Information

37243  Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction

75894  Transcatheter therapy, embolization, any method, radiological supervision and interpretation (this code cannot be reported with code 37243)

Q0083  Chemotherapy administration by other than infusion technique only (e.g., subcutaneous, intramuscular, push), per visit

ICD-10 Codes

C22.0- C22.9  Malignant neoplasm of liver and intrahepatic bile ducts code range

C78.7  Secondary malignant neoplasm of liver and intrahepatic bile duct

Additional Policy Key Words

N/A

Policy Implementation/Update Information

8/1/05  New policy, considered investigational.
8/1/06  No policy statement changes.
8/1/07  No policy statement changes.
6/1/08  Policy statements revised to indicate that when specific criteria are met, TACE may be considered medically necessary in cases of unresectable hepatocellular cancer, symptomatic metastatic neuroendocrine tumors, metastatic uveal melanomas, and for selected patients with HCC awaiting liver transplant.
6/1/09  No policy statement changes.
6/1/10  No policy statement changes.
6/1/11  Policy statement added that transcatheter hepatic arterial chemoembolization is considered investigational as neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable.
6/1/12  Policy statement added that TACE for unresectable cholangiocarcinoma is considered investigational.
6/1/13  No policy statement changes.
4/1/14  Removed deleted cpt code 37204.
6/1/14  No policy statement changes.
6/1/15  No policy statement changes.
6/1/16  No policy statement changes.
6/1/17  No policy statement changes.
State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.