Policy Statement

Transcatheter arterial chemoembolization (TACE) of the liver may be considered medically necessary for any of the following:

- To treat hepatocellular cancer that is unresectable but confined to the liver and not associated with portal vein thrombosis and liver function not characterized as Child-Pugh class C
- As a bridge to transplant in patients with hepatocellular cancer where all of the following are met:
  - Presence of hepatic tumor(s) meeting one of the following:
    - Single tumor less than or equal to 5 cm
    - Presence of no more than 3 tumors each less than 3 cm in size
  - Absence of extrahepatic disease or vascular invasion
  - Child-Pugh score of either A or B
- To treat liver metastasis in symptomatic patients (e.g., wheezing, flushing of the skin, abdominal cramps, diarrhea, heart disease) with metastatic neuroendocrine tumor whose symptoms persist despite systemic therapy (e.g., Octreotide therapy) and who are not candidates for surgical resection
- To treat liver metastasis in patients with liver-dominant metastatic uveal melanoma

Transcatheter arterial chemoembolization of the liver is considered investigational for any of the following:

- As neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable
- To treat unresectable cholangiocarcinoma
- 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
- To treat hepatocellular tumors prior to liver transplantation except as noted above

Policy Guidelines

Downstaging (downsizing) therapy is used to reduce the tumor burden in selected patients with more advanced hepatocellular carcinoma (HCC) (without distant metastasis) that are beyond the accepted transplant criteria.

Child-Pugh Score - Objective classification of operative risk in the setting of HCC based upon chemical and biochemical parameters.
- Class A: Good operative risk
- Class B: Moderate operative risk
- Class C: Poor operative risk

Neuroendocrine Tumors

Neuroendocrine tumors (NETs) may be referred to by their anatomical location (e.g., pulmonary neuroendocrine tumor, gastroenteropancreatic neuroendocrine tumor). Neuroendocrine tumors include the following:

- Carcinoid tumors
- Islet cell tumors (or pancreatic endocrine tumors)
- Neuroendocrine unknown primary
- Adrenal gland tumors
- Pheochromocytoma/paraganglioma
- Poorly differentiated (high grade or anaplastic)/small cell
- Multiple endocrine neoplasia, Type 1 (also known as MEN-1 syndrome or Wermer's syndrome)
- Multiple endocrine neoplasia, Type 2 a or b (also known as pheochromocytoma and amyloid producing medullary thyroid carcinoma, PTC syndrome, or Sipple syndrome)

Symptomatic disease from neuroendocrine tumors may include hot, red flushing of the face, severe and debilitating diarrhea, asthma attacks, palpitations, low blood pressure, fatigue, dizziness, and weakness. Extreme symptoms may include heart disease, bronchial constriction, and bowel obstruction.

Systemic therapies for neuroendocrine tumors vary depending on the location and characteristics. Therapies may include, but are not limited to: octreotide, interferon, cytotoxic chemotherapy, angiogenesis inhibitors, and epidermal growth factor inhibitors.

**Coding**

One of the following CPT codes may be used to describe the transcatheter hepatic arterial chemoembolization (TACE) procedure:

- **37243**: Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intra procedural 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

Note: CPT code 75894 cannot be reported with CPT code 37243

The following HCPCS code may be used to describe chemotherapy administration/chemoembolization:

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

**Description**

Transcatheter arterial chemoembolization (TACE) of the liver is a proposed alternative to conventional systemic or intra-arterial chemotherapy and to various nonsurgical ablative techniques, to treat resectable and nonresectable tumors. TACE combines the infusion of chemotherapeutic drugs with particle embolization. Tumor ischemia secondary to the embolization raises the drug concentration compared with infusion alone, extending the retention of the chemotherapeutic agent and decreasing systemic toxicity. The liver is especially amenable to such an approach, given its distinct lobular anatomy, the existence of two independent blood supplies, and the ability of healthy hepatic tissue to grow and thus compensate for tissue mass lost during chemoembolization.

**Related Policies**

- Cochlear Implant
- Cryosurgical Ablation of Primary or Metastatic Liver Tumors
- Radioembolization for Primary and Metastatic Tumors of the Liver

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the
contract language will control. Please refer to the member's contract benefits in effect at the
time of service to determine coverage or non-coverage of these services as it applies to an
individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from
denying Food and Drug Administration (FDA)-approved technologies as investigational. In these
instances, plans may have to consider the coverage eligibility of FDA-approved technologies on
the basis of medical necessity alone.

**Regulatory Status**

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

**Rationale**

**Background**

**Transcatheter Arterial Chemoembolization**

TACE is a minimally invasive procedure performed by interventional radiologists who inject highly
concentrated doses of chemotherapeutic agents into the tumor tissues and to restrict tumor
blood supply. The embolic agent(s) causes ischemia and necrosis of the tumor and slows
anticancer drug washout. The most common anticancer drugs used in published TACE studies
for hepatocellular carcinoma 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 super selective 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 one lobe of the liver is treated during a single session, with
subsequent embolization procedures scheduled five days to six weeks later. In addition,
because the embolized vessel recanalizes, chemoembolization can be repeated as many times
as necessary.

**Adverse Events**

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. Hepatic artery infusion involves the continuous infusion
of chemotherapy with an implanted pump, while TACE is administered episodically. Hepatic
artery infusion does not involve the use of embolic material.

**Literature Review**

This evidence review was informed by a Blue Cross Blue Shield Association Technology
Evaluation Center (TEC) Assessment (2000) that assessed the use of transcatheter arterial
chemoembolization (TACE) for hepatic tumors.

Evidence reviews assess the clinical evidence to determine whether the use of technology
improves the net health outcome. Broadly defined, health outcomes are the length of life,
quality of life (QOL), and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens, and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

**TACE for Unresectable and Resectable Hepatocellular Carcinoma**

In 2015, an estimated 71990 people in the U.S. lived with HCC or intrahepatic cholangiocarcinoma (ICC). Of the primary intrahepatic cancers, HCC and ICC account for 90% and 10% of cases, respectively. The number of new cases of HCC and ICC are estimated at 8.8 per 100000 men and women per year. The number of deaths are estimated at 6.4 per 100000 men and women per year.¹

**TACE for Unresectable HCC Not Confined to the Liver and Not Associated with Portal Vein Thrombosis**

The purpose of TACE is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as other locally ablative techniques (e.g., radiofrequency ablation [RFA], cryoablation), systemic therapy, and supportive care, in patients with unresectable HCC confined to the liver and not associated with portal vein thrombosis.

The question addressed in this evidence review: Does the use of TACE improves the net health outcome in patients with various resectable and unresectable malignancies confined to or deriving from the liver?

The following PICOs were used to select literature to inform this review.

The relevant population of interest are individuals with unresectable HCC confined to the liver and not associated with portal vein thrombosis.

The therapy being considered is TACE.

TACE of the liver is a proposed alternative to conventional systemic or intra-arterial chemotherapy and to various nonsurgical ablative techniques, to treat resectable and nonresectable tumors. TACE combines the infusion of chemotherapeutic drugs with particle embolization. Tumor ischemia secondary to the embolization raises the drug concentration compared with infusion alone, extending the retention of the chemotherapeutic agent and decreasing systemic toxicity.

TACE is performed by oncologists, radiologists and primary care providers in an outpatient clinical setting.

Comparators of interest include other locally ablative techniques (e.g., RFA, cryoablation), systemic therapy, and supportive care.
Other locally ablative techniques (e.g., RFA, cryoablation), systemic therapy, and supportive care are performed by oncologists, radiologists, and primary care providers in an outpatient clinical setting.

The general outcomes of interest are overall survival (OS), disease-specific survival, QOL, treatment-related mortality, and treatment-related morbidity.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
<th>Timing</th>
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<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td>≥ 5 years</td>
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<tr>
<td>Disease-specific survival</td>
<td>Progression-free survival/complete response</td>
<td>14 weeks to 2 years</td>
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<td>Local tumor control</td>
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<td>Time to secondary therapy</td>
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HCC: hepatocellular carcinoma.

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
d. Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Numerous systematic reviews on TACE have evaluated the efficacy of TACE alone or its comparative efficacy with alternative treatments. Table 1 provides a comparative breakdown of studies included in select systematic reviews. 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 Cochrane review by Oliveri et al (2011) 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 were biased, 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 (2012) conducted a meta-analysis of 13 studies on treatment for unresectable HCC using chemoembolization (1233 patients) or microsphere embolization (597 patients, using a glass or resin hepatic artery infusion [HAI]). Microsphere embolization treatment resulted in statistically significant longer 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.

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<tbody>
<tr>
<td>Akamatsu et al (2004)</td>
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<td>Bruix et al (1998)</td>
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<td>Cheng et al (2004)</td>
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<td>Cheng et al (2006)</td>
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<td>Choi et al (2013)</td>
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<tr>
<td>Ciria et al (2014)</td>
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<tr>
<td>Colella et al (1998)</td>
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<td>Doffoel et al (2008)</td>
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Some examples of individual RCTs comparing TACE with alternative treatments are reviewed next. See Tables 3 and 4 for select trial characteristics and results. Bush et al (2016) published interim results of an RCT comparing TACE with proton beam radiotherapy for patients who had unresectable HCC. This trial included 69 patients, with 36 randomized to TACE and 33 to the proton beam. There was a trend toward worse progression-free survival (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.

An RCT by Mabed et al (2009) compared TACE with systemic chemotherapy for patients who had unresectable HCC.9 One hundred patients were randomized to TACE ($n=50$) or intravenous doxorubicin ($n=50$). 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 ($p=0.007$). 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 TACE (38 weeks) and chemotherapy (32 weeks; $p=0.08$), except for patients with a serum albumin greater than 3.3 g/dL (60 weeks vs 36 weeks; $p=0.003$). Treatment-related mortality was 4% in the TACE arm and 0% in the chemotherapy arm.

An RCT by Lo et al (2002) enrolled patients with the advanced disease based on Okuda stage, Eastern Cooperative Oncology Group Performance Status score, and presence of tumor-related symptoms.10 The trial used a similar embolization regimen but different cytotoxic agents. 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 actutimes survival rates were 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, 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, to TACE, or to conservative therapy.11 The trial was stopped early when it was shown that chemoembolization had survival benefits compared with conservative treatment (HR, 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.

### Table 3. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bush et al (2016)</td>
<td>U.S.</td>
<td>1</td>
<td></td>
<td>69 patients with clinical or pathologic diagnosis of HCC using either Milan or San Francisco transplant criteria</td>
<td>TACE Proton beam radiotherapy</td>
</tr>
</tbody>
</table>

HCC: hepatocellular carcinoma; RCT: randomized controlled trial; TACE: transcatheter arterial chemoembolization.

### Table 4. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Median PFS, %</th>
<th>Overall Survival, %</th>
<th>Response Rate, %</th>
<th>TRM Adverse Events, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bush et al (2016)</td>
<td>48</td>
<td>30 (59)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Proton beam therapy</td>
<td>31</td>
<td>30 (59) mo</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>20.7 to 39.3 mo</td>
<td></td>
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<tr>
<td>$p$</td>
<td>0.006</td>
<td>0.38</td>
<td>$&lt;0.001$</td>
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Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

<table>
<thead>
<tr>
<th>Study</th>
<th>Median PFS, wk</th>
<th>Overall Survival, %</th>
<th>Response Rate, %</th>
<th>TRM Adverse Events, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACE</td>
<td>32 wks</td>
<td>38</td>
<td>16 (32)</td>
<td>4</td>
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<tr>
<td>Range</td>
<td>16-70 wks</td>
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<tr>
<td>Systemic chemotherapy</td>
<td>26</td>
<td>32</td>
<td>5 (10)</td>
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<tr>
<td>Range</td>
<td>14-52 wks</td>
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</table>

CI: confidence interval; PFS: progression-free survival; RCT: randomized controlled trial; TACE: transcatheter arterial chemoembolization; TRM: treatment-related mortality.

Nonrandomized Observational Studies
Biederman et al (2018) published a retrospective, single-center study comparing radiation segmentectomy and TACE as treatments for unresectable, solitary HCC of 3 cm or less.12 One hundred twelve patients, of whom 57 received TACE, were treated between 2012 and 2016. Results were reported both before and after conducting propensity score matching using the nearest neighbor algorithm (1:1). Before propensity score matching, the complete response rate was 49.1% for TACE and 81.2% for radiation segmentectomy (OR=2.2; 95% CI, 1.4 to 3.3; p<0.001). Median time to secondary therapy was 246 days for TACE and 700 days for radiation segmentectomy (HR=0.71; 95% CI, 0.55 to 0.92; p=0.009); there was no significant difference in OS (p=0.29). After matching, radiation segmentectomy still had significantly better results for complete response (p=0.005) and time to secondary therapy (p=0.001), and there was again no significant difference in OS (p=0.71). The study was limited by its retrospective nature and the possibility of treatment selection bias.

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.13,14,15 The largest of these studies published in Japan reported results from an eight year prospective cohort.14 In this study, 8510 patients with unresectable HCC underwent TACE using an 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: TACE for Unresectable HCC Not Confined to the Liver and Not Associated with Portal Vein Thrombosis
There is evidence from a limited number of RCTs that TACE offers a survival benefit 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 RFA.

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 the use of neoadjuvant and adjuvant systemic therapy approaches to improve outcomes.

The purpose of neoadjuvant or adjuvant TACE is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as other locally ablative techniques (e.g., RFA, cryoablation) and systemic therapy, in patients with resectable HCC.

The question addressed in this evidence review: Does the use of TACE as neoadjuvant or adjuvant therapy improve the net health outcome in patients with various resectable and unresectable malignancies confined to or deriving from the liver?

The following PICOs were used to select literature to inform this review.

The relevant population of interest are individuals with resectable HCC.

The therapy being considered is neoadjuvant or adjuvant TACE.
Comparators of interest include other locally ablative techniques (e.g., RFA, cryoablation) and systemic therapy.

The general outcomes of interest are OS, disease-specific survival, QOL, treatment-related mortality, and treatment-related morbidity.

Table 5. Outcomes of Interest for Individuals With Resectable HCC Treated with Neoadjuvant or Adjuvant TACE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
<th>Timing</th>
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<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td>Up to 5 years</td>
</tr>
<tr>
<td>Disease-specific survival</td>
<td>Intra- and extrahepatic recurrence</td>
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<td></td>
<td>Recurrence-free survival</td>
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HCC: hepatocellular carcinoma; TACE: transcatheter arterial chemoembolization.

**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, two of the five RCTs concluded no effect (no reduction in postoperative recurrence or effect on survival) while three suggested an 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 five 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).

Zhou et al (2013) 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 rates also did not differ significantly across pooled analyses for TACE vs controls (51.2% vs 53.6% and 12.9% vs 10.3%, p=0.19, respectively).

Chua et al (2010) 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.

Table 6 provides a comparative breakdown of studies included in select systematic reviews.

Table 6. Comparison of Trials and Studies Included in Systematic Reviews

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<thead>
<tr>
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<tr>
<td>Kaibori et al (2012)19</td>
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<tr>
<td>Zhou et al (2009)20</td>
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<td>Cui et al (2003)</td>
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<td>Yamasaki et al (1996)</td>
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<td>Wu et al (1995)</td>
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Randomized Controlled Trials

Kaibori et al (2012) 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 (p=0.660) and the control group (p=0.412) or between the 3 groups in DFS (p=0.830) or OS (p=0.713). DFS rates at 1 and 3 years for the tumor-targeted TACE group were 67% and 29%, 63% and 27% for the whole-liver TACE group, and 53% and 32% for the control group, respectively. OS rates at 1 and 3 years for the tumor-targeted TACE group were 91% and 80%, 84% and 70% for the whole-liver TACE group, and 83% and 60% in the control group, respectively.

In another RCT, Zhou et al (2009) 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 current 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 retrospective cohort study by Yeh et al (2015) 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 a benefit compared with curative therapy alone in subgroup analysis.

Choi et al (2007) studied 273 patients who underwent curative resection for HCC, 120 of whom received 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.

Zhang et al (2000) 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**

**Systematic Reviews**

Liao et al (2017) reported on the 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 eight RCTs, reported OS and seven reported recurrence-free survival (RFS). The larger and more current 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.

**Randomized Controlled Trials**

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), surgery plus TACE (n=35), or 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 three 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 were no statistical differences 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 and 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, 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 hepatectomy alone (n=59). Three patients were excluded from the final analysis (two from the adjuvant arm, one 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 with 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 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 the 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 a 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 two 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 endpoints). Well-conducted multicentric trials from the U. S. 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**

The purpose of TACE plus RFA is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as surgery alone, in patients with resectable HCC.

The question addressed in this evidence review: Does the use of TACE improves the net health outcome in patients with various resectable and unresectable malignancies confined to or deriving from the liver?

The following PICOs were used to select literature to inform this review.

The relevant population of interest are individuals with resectable HCC.

The therapy being considered is TACE plus RFA.

TACE plus RFA is performed by radiologists, oncologists, and primary care providers in an outpatient clinical setting.

Comparators of interest include TACE plus RFA.

Surgery alone is performed by surgical oncologists in an inpatient clinical setting.

The general outcomes of interest are OS, disease-specific survival, QOL, treatment-related mortality, and treatment-related morbidity.

| Table 7. Outcomes of Interest for Individuals With Resectable HCC Treated with TACE Plus RFA |
|-----------------------------------------------|------------------|------------------|
| Outcomes                                      | Details           | Timing           |
| Overall survival                              |                   | Up to 5 years    |
| Disease-specific survival                      | Recurrence-free   | Up to 5 years    |

HCC: hepatocellular carcinoma; RFA: radiofrequency ablation; TACE: transcatheter arterial chemoembolization.
Randomized Controlled Trials

Liu et al (2016) published an 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 cm, with a median of 3 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 8). 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 were no significant differences in recurrence or OS between the 2 groups for HCC lesions 3 cm or smaller, but there were significant benefits 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 virus DNA and platelet count. Hepatitis B virus 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). It was unclear in this trial whether TACE plus RFA was as effective as a surgical resection for these small tumors.

Table 8. Survival Rates After Surgical Resection or TACE Plus RFA for Resectable HCC

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>1 Year, %</th>
<th>3 Years, %</th>
<th>5 Years, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical resection</td>
<td>97.0</td>
<td>83.7</td>
<td>61.9</td>
</tr>
<tr>
<td>TACE plus RFA</td>
<td>96.0</td>
<td>67.2</td>
<td>45.7</td>
</tr>
<tr>
<td>Recurrence-free survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical resection</td>
<td>94.0</td>
<td>68.2</td>
<td>48.4</td>
</tr>
<tr>
<td>TACE plus RFA</td>
<td>83.0</td>
<td>44.9</td>
<td>35.5</td>
</tr>
</tbody>
</table>

Adapted from Liu et al (2016).

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

Retrospective Studies

Ako et al (2018) published a retrospective analysis of 100 patients with HCC who received TACE followed by RFA 20 or more days later. All patients were treated at a single-center in Japan between 2001 and 2014. Tumor size reduction was observed in 69% of patients (median reduction rate, 16.2%). Tumor size was unchanged in 3% of patients or increased by 28%. In a univariate analysis, the tumor size at first treatment and the time between therapies were both significantly related to tumor reduction (p<0.01 and p=0.02, respectively). The study was limited by its retrospective nature, relatively small population size, potential patient selection bias, and two different modalities used to measure tumors, possibly influencing size perception.

Haochen et al (2018) published a retrospective single-center study of 3.1 to 5 cm HCC nodules treated at a university hospital in China, with TACE followed by imaging-guided RFA 2 to 4 weeks later. Two hundred sixteen nodules (162 patients) treated between 2008 and 2016 were identified. Follow-up was performed at 1, 3, 6, and 12 months after TACE plus RFA. Two hundred seven (95.8%) nodules were completely eliminated after 1 to 3 sessions of TACE plus RFA, and 180 (83.3%) nodules were completely eliminated after one session. Besides its retrospective nature, no study limitations were reported.

Bholee et al (2017) published a retrospective matched case-control study comparing TACE plus RFA and hepatectomy as treatments for HCC within Milan criteria. A total of 222 patients were included; 74 individuals treated with TACE plus RFA between 2006 and 2010 at a university cancer center in China, were matched with 148 controls (ratio 1:2) treated with hepatectomy. The 1-, 3-, and 5-year OS for TACE + RFA was 94.6%, 75.1%, and 55.3%, respectively, and 91.2%, 64.4% and 47.7% respectively, for hepatectomy (p=0.488). The 1-, 3-, and 5-year DFS for TACE plus RFA was 87.8%, 48.3%, and 33.5%, respectively, and 68.9%, 49.2%, 40.9%, respectively, for hepatectomy (p=0.619). The study was limited by possible selection bias due to its...
nonrandomized design, relatively small population size, and the fact that some patients who received TACE plus RFA did not have histological diagnoses.

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 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 a surgical resection for these small tumors. Several retrospective studies have compared TACE with surgical resection; results were inconsistent for which treatment produces better outcomes.

TACE Plus RFA for Unresectable HCC
The purpose of TACE plus RFA is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as RFA alone, in patients with unresectable HCC.

The question addressed in this evidence review: Does the use of TACE improves the net health outcome in patients with various resectable and unresectable malignancies confined to or deriving from the liver?

The following PICOs were used to select literature to inform this review.

The relevant population of interest are individuals with unresectable HCC hepatocellular cancer.

The therapy being considered is TACE plus RFA.

Comparators of interest include RFA alone.

RFA alone is performed by radiologists, oncologists, and primary care providers in an outpatient clinical setting.

The general outcomes of interest are OS, disease-specific survival, QOL, treatment-related mortality, and treatment-related morbidity.

Table 9. Outcomes of Interest for Individuals With Unresectable HCC Treated with TACE Plus RFA

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td>Up to 5 years</td>
</tr>
<tr>
<td>Disease-specific survival</td>
<td>Local tumor</td>
<td>Up to 3 years</td>
</tr>
</tbody>
</table>

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

Systematic Reviews
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 five years of follow-up. While many of these meta-analyses have used standard methodologies to pool estimates, including indirect network analysis as well as an 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 on 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-naïve 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-naïve or -experienced. Two of the five meta-analyses also included results from the first RCT that demonstrated combination treatment was better than RFA alone. However, that article was retracted in 2009 because of questions about data integrity and reporting.
Randomized Controlled Trials
To assess the nature of the evidence that makes the case for combined use of TACE and RFA in HCC, BCBSA reviewed the current 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, trialists reported the results of log-rank testing only, which would indicate whether there were differences between the survival times of the two 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 (MWA; n=47) or RFA or to MWA alone (n=47). The hazard of death was statistically significantly lower in the combined arm vs the RFA or MWA alone arm (HR=0.53; 95% CI, 0.33 to 0.82; p=0.002). The 5-year OS rate was 62% in the combined arm and 45% in the RFA or MWA alone arm. No subgroup analyses stratified by lesion size were 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 was 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, results from this single-center trial conducted in China 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 a difference in survival.

Locoregional Treatment-Experienced Therapy for Tumors Less Than 5 cm
Peng et al (2012) also reported on 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 who were randomized to sequential TACE plus RFA (n=69) or to RFA alone (n=70). A p value of 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 rates were statistically significantly greater in the combined arm compared with 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 and RFS favoring 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, most of which are from China, have reported outcomes favoring 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, therefore, the results might not be generalizable to patients in Western countries.

**TACE as a Bridge to Liver Transplant**

TACE has been explored in various settings as a technique to prevent tumor progression in patients on the liver transplant waiting list, to downstage tumors 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 three treatment settings are discussed further here.

### UNOS Liver Allocation Policy

In 2002, UNOS introduced the Model for End-Stage Liver Disease (MELD) system for allocating new livers to adults awaiting a 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 and 5 cm, or 2 or 3 nodules each 1 cm or greater and up to 3 cm
- **T3:** 1 nodule larger than 5 cm, or 2 or 3 nodules with at least 1 larger than 3 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 with those who had T1 lesions and are an acceptable risk of posttransplant tumor recurrence. Therefore, UNOS criteria, which were updated in 2018, 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 study by Mazzaferro et al (1996) 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 priority on the waiting list. All patients with HCC awaiting transplantation are reassessed at three-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 local-regional 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. In a report from a national conference in the U.S., Pomfret et al (2010) addressed the need to characterize better the long-term outcomes of liver transplantation for patients with HCC and to assess the 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 endpoints for downstaging before transplantation.

Clinical Context and Therapy Purpose

The purpose of pretransplant TACE is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as other locally ablative techniques (e.g., RFA, cryoaablation), and systemic therapy, in patients with 1-3 small HCC tumors seeking to prevent tumor growth and maintain candidacy for liver transplant.

The question addressed in this evidence review: Does the use of TACE improves the net health outcome in patients with various resectable and unresectable malignancies confined to or deriving from the liver?

The following PICOs were used to select literature to inform this review.

The relevant population of interest are individuals with 1-3 small HCC tumors seeking to prevent tumor growth and maintain candidacy for a liver transplant.

The therapy being considered is pretransplant TACE.

Comparators of interest include other locally ablative techniques (e.g., RFA, cryoaablation), and systemic therapy.

Other locally ablative techniques (e.g., RFA, cryoaablation), and systemic therapy are performed by oncologists, radiologists, and primary care providers in an outpatient clinical setting.

The general outcomes of interest are OS, disease-specific survival, QOL, treatment-related mortality, and treatment-related morbidity.

Table 10. Outcomes of Interest for Individuals Awaiting Liver Transplant Who Are Treated with TACE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td>Up to &gt; 7 years</td>
</tr>
<tr>
<td>Disease-specific survival</td>
<td>Tumor recurrence</td>
<td>Up to 5 years</td>
</tr>
</tbody>
</table>

TACE: transcatheter arterial chemoembolization.

Systematic Reviews

Si et al (2017) reported on a meta-analysis evaluating the correlation between preoperative TACE and 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 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 (relative risk, 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 the 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.

Prospective Studies
Graziadei et al (2003) reported on 48 patients with HCC awaiting transplantation; all underwent TACE every 6 to 8 weeks until complete response or a donor organ became available.49 None was removed from the list due to tumor progression after a mean waiting time of 178 days. Of the 48 patients, 41 underwent a 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.50 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.51

TACE to Downstage HCC Prior to Transplant or to Reduce Recurrence in Those With T3 Lesions
Published literature reflects an ongoing discussion of whether the UNOS allocation criteria (see Background) should be expanded to include patients with larger tumors. Some patients with T3 lesions are cured with a liver transplant, although most experience tumor recurrence. For example, in the seminal study by Mazzaferro et al (1996),46 the 4-year RFS rate 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 (2008) at the University of California at San Francisco reported similar RFS rates after transplant in patients with T2 tumors and a subset of those with T3 tumors.52 This T3 subset was defined as a single lesion 6.5 cm or smaller or no more than three 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 T2.53 Patients were treated with yttrium-90 (Y90) 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).

Gabert et al (2017) published a prospective, single-center comparative study analyzing posttransplant outcomes for patients with HCC bridged or downstaged to orthotopic liver transplantation by TACE or Y90 radioembolization.54 One hundred seventy-two patients
(TACE=79, Y90=93) treated between 2003 and 2013 were identified; a classification into the TACE or Y90 group was based on the first liver-directed therapy received. Median posttransplant follow-up was 26.1 months. For TACE, 6 (8%) of 79 patients experienced tumor recurrence and 8 (9%) of 92 for Y90. There were no significant differences in RFS (TACE, 77 months vs Y90, 79 months; p=0.71) and OS (TACE, 87.2 months vs Y90, median not reached at 100 months; p=0.42) between groups. The study was limited by its relatively small sample size, inherent selection bias since transplanted patients usually exhibit more favorable biology and response, and lack of etiology of death for some patients.

Section Summary: TACE as a Bridge to Liver Transplant

There is a lack of comparative trials assessing TACE as a bridge to liver transplantation. Several small prospective studies have demonstrated that TACE can prevent dropouts from the transplant list. The evidence of 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 the 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 list is likely death and, therefore, any strategy that delays progression with an acceptable safety profile is beneficial, 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

As mentioned earlier, an estimated 71990 people in the U. S. lived with HCC or ICC in 2015. Surgical resection represents the only form of curative therapy for ICC. 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 disease progression. 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 benefit over supportive therapy alone, because ICC responds poorly to such existing therapies.[2] Survival prognosis for patients with unresectable ICC is five to eight months.

The purpose of TACE is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as other locally ablative techniques (e.g., RFA, cryoablation), and systemic therapy, in patients with unresectable cholangiocarcinoma.

The question addressed in this evidence review: Does the use of TACE improves the net health outcome in patients with various resectable and unresectable malignancies confined to or deriving from the liver?

The following PICOs were used to select literature to inform this review.

The relevant population of interest are individuals with unresectable cholangiocarcinoma. The therapy being considered is TACE.

Comparators of interest include other locally ablative techniques (e.g., RFA, cryoablation), and systemic therapy.

The general outcomes of interest are OS, disease-specific survival, QOL, treatment-related mortality, and treatment-related morbidity.
Table 11. Outcomes of Interest for Individuals With Unresectable Cholangiocarcinoma Treated with TACE

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<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
<th>Timing</th>
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</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td>&gt; 22 months</td>
</tr>
<tr>
<td>Disease-specific survival</td>
<td></td>
<td>Up to 5 years</td>
</tr>
</tbody>
</table>

TACE: transcatheter arterial chemoembolization.

**Systematic Reviews**

Boehm et al (2015) conducted a meta-analysis of 20 studies (total n=657 patients) on the hepatic artery therapies of TACE, HAI, and Y90 for ICC.\(^{56}\) Median OS was lowest for TACE (12.4 months) and drug-eluting bead TACE (12.3 months) compared with HAI (22.8 months) and Y90 (13.9 months). Complete and partial responses to therapy were also lowest with TACE (17.3%) compared with Y90 (27.4%) and HAI (56.9%). TACE had fewer grade 3 and 4 toxicity incidents (0.26 events per patient) than HAI (0.35 events per patient).

**Nonrandomized Observational Studies**

Knüppel et al (2012) evaluated 195 patients with intrahepatic (57%) or extrahepatic (43%) cholangiocarcinoma. Patients received chemotherapy or a combination of photodynamic therapy or TACE plus chemotherapy.\(^{57}\) 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.

Park et al (2011) reviewed the medical and imaging records of 155 patients with unresectable ICC treated with TACE between 1996 and 2009.\(^{55}\) Patients who had undergone local or systemic therapy were excluded. Seventy-two patients underwent TACE and 83 received supportive care, based on physician and patient preference. Survival was the primary endpoint. Baseline patient and tumor characteristics were well-balanced between groups. Most patients had stage III or IV disease. Tumor multiplicity was single or multiple and 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 the 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).

Shen et al (2011) retrospectively analyzed 53 patients who received TACE after surgical resection of ICC and 73 patients who had surgical resection without TACE.\(^{58}\) 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 the standard of care for patients with unresectable cholangiocarcinoma are lacking. Results from three retrospective studies have
reported a survival benefit with TACE over the standard of care. Although the observational data are consistent, the lack of randomization limits definitive conclusions.

**TACE for Symptomatic Unresectable 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.

The purpose of TACE is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as other locally ablative techniques (e.g., RFA, cryoablation), and systemic therapy, in patients with symptomatic metastatic neuroendocrine tumors despite systemic therapy and are not candidates for surgical resection.

The question addressed in this evidence review: Does the use of TACE improves the net health outcome in patients with various resectable and unresectable malignancies confined to or deriving from the liver?

The following PICOs were used to select literature to inform this review.

The relevant population of interest are individuals with symptomatic metastatic neuroendocrine tumors despite systemic therapy and are not candidates for surgical resection.

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.

The therapy being considered is TACE.

Comparators of interest include other locally ablative techniques (e.g., RFA, cryoablation), and systemic therapy.

The general outcomes of interest are OS, disease-specific survival, QOL, treatment-related mortality, and treatment-related morbidity.

**Table 12. Outcomes of Interest for Individuals With Unresectable Metastatic Neuroendocrine Tumors Treated with TACE**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
<th>Timing</th>
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</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td>Up to 5 years</td>
</tr>
<tr>
<td>Disease-specific survival</td>
<td>Freedom from disease progression</td>
<td>Up to 3 years</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Symptomatic relief</td>
<td>Up to 3 years</td>
</tr>
</tbody>
</table>

TACE: transcatheter arterial chemoembolization.

**Systematic Reviews**

A literature review by Nazario and Gupta (2010) 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.

**Nonrandomized Observational Studies**

Ruutiainen et al (2007) reported on a retrospective study of 67 patients who underwent 219 embolization procedures: 23 patients received primarily bland embolization I, and 44 primarily received TACE. 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% for TACE and 68%, 46%, and 33% for bland embolization (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. Osbome 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 exceed 50% and include 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
Uveal melanoma (also called ocular melanoma) is the most common primary ocular malignancy in adults and shows a strong predilection for liver metastases.

The purpose of TACE is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as other locally ablative techniques (e.g., RFA, cryoablation), in patients with liver-dominant metastatic uveal melanoma.

The question addressed in this evidence review: Does the use of TACE improves the net health outcome in patients with various resectable and unresectable malignancies confined to or deriving from the liver?

The following PICO’s were used to select literature to inform this review.

The relevant population of interest are individuals with liver-dominant metastatic uveal melanoma.

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.

The therapy being considered is TACE.

Comparators of interest include other locally ablative techniques (e.g., RFA, cryoablation).

The general outcomes of interest are OS, disease-specific survival, QOL, treatment-related mortality, and treatment-related morbidity.

<table>
<thead>
<tr>
<th>Table 13. Outcomes of Interest With Liver-Dominated Metastatic Uveal Melanoma Treated with TACE</th>
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<tbody>
<tr>
<td><strong>Outcomes</strong></td>
</tr>
<tr>
<td>Overall survival</td>
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TACE: transcatheter arterial chemoembolization.

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Systematic Reviews
A literature review by Sato (2010) 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.63.

Nonrandomized Observational Studies
Huppert et al (2010) reported on a single-arm prospective study of 14 patients with hepatic metastases from uveal melanoma who underwent TACE.64. Patients received a mean of 2.4 treatments (34 total treatments). 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 2007.65. 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 compared with a 1% response rate to systemic chemotherapy.66.

Patel et al (2005) reported the results of a prospective single cohort study of TACE for treatment of hepatic metastases from uveal melanoma.67. 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 the rarity of this condition. Noncomparative prospective and retrospective case series have reported improvements in tumor response and survival compared with historical controls who received 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
The purpose of TACE is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as other locally ablative techniques (e.g., RFA, cryoablation), and systemic therapy, in patients with unresectable hepatic metastases from other types of primary tumors (e.g., colorectal, breast).
The question addressed in this evidence review: Does the use of TACE improves the net health outcome in patients with various resectable and unresectable malignancies confined to or deriving from the liver?

The following PICOs were used to select literature to inform this review.

The relevant population of interest are individuals with unresectable hepatic metastases from other types of primary tumors (e.g., colorectal, breast).

The therapy being considered is TACE.

Comparators of interest include other locally ablative techniques (e.g., RFA, cryoablation), and systemic therapy.

The general outcomes of interest are OS, disease-specific survival, QOL, treatment-related mortality, and treatment-related morbidity.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
<th>Timing</th>
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<tr>
<td>Overall survival</td>
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<td>Up to 3 years</td>
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<tr>
<td>Disease-specific survival</td>
<td></td>
<td>Up to &gt;15 months</td>
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<td>Progression-free survival</td>
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<tr>
<td>Local tumor control</td>
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Table 14. Outcomes of Interest for Individuals With Other Unresectable Hepatic Metastases

Colorectal Cancer

Systematic Reviews

Zacharias et al (2015) published a meta-analysis evaluating 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 one RCT of TACE. In the 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. The grade 3 or 4 toxicity rates were 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 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.

Riemsma et al (2013) reported on 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 the primary tumor. Only 1 RCT published in 1990 fulfilled inclusion criteria. It randomized 61 patients with colorectal liver metastases to hepatic artery embolization, HAI chemotherapy, and 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.

Table 15 provides a comparative breakdown of studies included in select systematic reviews.

Table 15. Comparison of Trials and Studies Included in the Systematic Reviews

<table>
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<td>Liang et al (2007)</td>
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<td>Eichler et al (2012)</td>
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<td>Martin et al (2012)</td>
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<td>Vogl et al (2012)</td>
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<tr>
<td>Martin et al (2011)</td>
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Randomized Controlled Trials
In the RCT included in the Richardson et al (2013) systematic review, Fiorentini et al (2012) reported on 74 patients randomized to TACE (n=36) or to systemic chemotherapy (n=38). With TACE, 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 TACE group and 4 months (95% CI, 3 to 5 months) in the systemic chemotherapy group (p=0.006). However, the systemic chemotherapy administered in this trial is no longer the current standard, limiting conclusions to be drawn from results.

Subsequent RCTs have shown that the addition of oxaliplatin, bevacizumab, cetuximab, and panitumumab to the FOLFIRI chemotherapy regimen and, more recently, the addition of checkpoint inhibitors increased survival compared with FOLFIRI alone. Martin et al (2015) reported on the results of an RCT in which 30 patients with CRC with metastasis to the liver were randomized to the leucovorin, fluorouracil, and oxaliplatin (FOLFOX) plus TACE or FOLFOX plus bevacizumab arm. The overall response rate was significantly longer in the FOLFOX plus TACE 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 TACE 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
Vogl et al (2009) 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). The 1-year survival rate after TACE was 62% and 28% at 2 years. No differences in survival were observed between the three chemotherapy protocols.

Hong et al (2009) compared salvage therapy for liver-dominant colorectal metastatic adenocarcinoma using TACE or Y90 radioembolization. Mean dominant lesion sizes were 9.3 cm in the chemoembolization group and 8.2 cm radioembolization group. 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 assessing CRC 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 TACE treatments 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 assessesCRC. Multiple RCTs and numerous nonrandomized studies have compared TACE with alternatives. The nonrandomized studies have indicated 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 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**

**Unresectable and Resectable HCC**

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. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. Evidence from a limited number of RCTs has suggested 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. For individuals who have resectable HCC who receive neoadjuvant or adjuvant TACE, the evidence includes several RCTs and systematic reviews. The relevant outcomes are OS, disease-specific survival, QOL, 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 an 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 the U.S. 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.

For individuals who have resectable HCC who receive TACE plus RFA, the evidence includes a single RCT. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. The RCT failed to show the superiority in survival benefit with combination TACE plus RFA treatment compared with surgery for HCC lesions 3 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 a surgical resection for these small tumors. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have unresectable HCC who receive TACE plus RFA, the evidence includes multiple systematic reviews and RCTs. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. Multiple meta-analyses and RCTs have shown a consistent benefit in survival and recurrence-free survival favoring 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, data from a study retracted due to questions about data veracity. A larger well-conducted RCT has reported a relative reduction in the hazard of death by 44% and a 14% difference in 4-year
survival favoring 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 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 until these results have been reproduced in patient populations representative of pathophysiology and clinical stage more commonly found in the U.S. or Europe, the results may not be generalizable. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Bridge to Liver Transplant**
For individuals who have a single HCC tumor less than 5 cm or no more than three 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. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. There is a lack of comparative trials on various locoregional treatments as a bridge therapy for 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.

**Unresectable Cholangiocarcinoma**
For individuals who have unresectable cholangiocarcinoma who receive TACE, the evidence includes several retrospective observational studies and systematic reviews. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. RCTs evaluating the benefit of adding TACE to the standard of care for patients with unresectable cholangiocarcinoma are lacking. Results of three retrospective studies have shown a survival benefit with TACE over the standard of care. These studies lacked matched patient controls. Although the observational data are consistent, the lack of randomization limits definitive conclusions. The evidence is insufficient to determine the effects of the technology on health outcomes.

**TACE for Symptomatic Unresectable Neuroendocrine Tumors**
For individuals who have symptomatic metastatic neuroendocrine tumors despite systemic therapy and are not candidates for surgical resection who receive TACE, the evidence includes retrospective single-cohort studies. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. There is a lack of evidence from RCTs supporting the use of TACE. Uncontrolled trials have suggested that TACE reduces symptoms and tumor burden and improves hormone profiles. Generally, the response rates are over 50% and include 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.

**Liver-Dominant Metastatic Uveal Melanoma**
For individuals who have liver-dominant metastatic uveal melanoma who receive TACE, the evidence includes observational studies and reviews. The relevant outcomes are OS, disease-specific survival, QOL, and treatment-related mortality and morbidity. There is a lack of evidence from RCTs assessing the use of TACE. Noncomparative prospective and retrospective studies have reported improvements 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.
Other Unresectable Hepatic Metastases
For individuals who have unresectable hepatic metastases from any other types of primary
tumors (e.g., colorectal or breast cancer) who receive TACE, the evidence includes multiple
RCTs, observational studies, and systematic reviews. The relevant outcomes are OS, disease-
specific survival, QOL, and treatment-related mortality and morbidity. Multiple RCTs and
numerous nonrandomized studies have compared TACE with alternatives in patients who
have CRC and metastases to the liver. Nonrandomized studies have reported that TACE can
stabilize disease in 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 has resulted in statistically significant improvements
in response rate and progression-free survival. 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 assessed 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.

Supplemental Information
Clinical Input 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 from Blue Cross Blue Shield Association, input was received from 1
specialty medical society (2 reviewers) and 3 academic medical centers in 2012. There was
general agreement that the use of transcatheter arterial chemoembolization (TACE) was
medically necessary for indications in the policy; however, reviewers were split for its 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 hepatocellular carcinoma.
Reviewers were split over the investigational policy statement to treat other liver metastases or
for recurrent hepatocellular carcinoma. Four reviewers provided input on the use of TACE in
unresectable cholangiocarcinoma; two reviewers considered it investigational and two others
considered 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 NCCN (v.2.2019) guidelines on hepatocellular carcinoma lists TACE as an option for
patients, not candidates for surgically curative treatments or as a part of a strategy to bridge
patients for other curative therapies (category 2A). The guidelines also recommend that
patients with tumors size between 3 and 5 cm can be considered for combination therapy with
ablation and arterial embolization and those with unresectable or inoperable tumors greater
than 5 cm be treated using arterial embolcic approaches or systemic therapies. Additionally,
TACE in highly selected patients has been shown to be safe in the presence of limited tumor
invasion of the portal vein.

Intrahepatic Cholangiocarcinoma
The NCCN (v.2.2019) guidelines on intrahepatic cholangiocarcinoma consider arterially directed
therapies, including TACE, to be treatment options for unresectable and metastatic intrahepatic
cholangiocarcinoma.
Neuroendocrine Tumors, Carcinoid, and Islet Cell Tumors
The NCCN (v.1.2019) guidelines on neuroendocrine tumors, carcinoid, and islet cell tumors consider chemoembolization as an effective approach for patients with hepatic-predominant metastatic disease (category 2A).78.

Uveal Cancer
No NCCN guidelines were identified for uveal malignancies as of May 2019.

Colon Cancer
An update discussion is in process to establish the NCCN guidelines on the use of TACE for colorectal liver metastases (v.2.2019). As of this guideline version, the NCCN can recommend TACE only for clinical trials.79.

Breast Cancer
The NCCN (v.1.2019) guidelines on breast cancer do not address TACE as a treatment option for breast cancer metastatic to the liver.80.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 16.

Table 16. 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>Ongoing</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>Jul 2019</td>
</tr>
<tr>
<td>NCT02936388</td>
<td>Transarterial Radioembolisation in Comparison to Transarterial Chemoembolisation in Uveal Melanoma Liver Metastasis (SirTac)</td>
<td>108</td>
<td>Dec 2018</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>Dec 2018</td>
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<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>Unpublished</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>
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<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 (unknown)</td>
</tr>
<tr>
<td>NCT00908752</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>734</td>
<td>Jan 2018 (completed)</td>
</tr>
<tr>
<td>NCT01869088</td>
<td>Phase III Trial of Transcatheter Arterial Chemoembolization (TACE) Plus Recombinant Human Adenovirus Type 5 Injection for Unresectable Hepatocellular Carcinoma (HCC)</td>
<td>266</td>
<td>Jan 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.
2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transcatheter arterial chemoembolization of hepatic tumors. TEC Assessments. 2000;Volume 15;Tab 22.


49. Grazia del IW, Sandmueller H, Waldenberger P, et al. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on
the waiting list and leads to excellent outcome. Liver Transpl. Jun 2003;9(6):557-563. PMID 12783395


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**Documentation for Clinical Review**

**Please provide the following documentation (if/when requested):**

- History and physical and/or consultation notes including:
  - Clinical indications/justification of procedure
  - Child-Pugh score (if applicable)
  - Eastern Cooperative Oncology Group functional status (if applicable)
Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

- Previous treatment(s), duration, and response(s)
- Treatment plan
- Tumor type and description (i.e., resectable or unresectable, primary or metastatic, tumor burden [e.g., liver dominant])
  - Pertinent radiological imaging results (i.e., abdominal CT and/or MRI and/or PET)
  - Pathology report including tumor node metastasis (TNM) classification
  - Current serum chemistry, liver function tests, and tumor marker results

Post Service
- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>37243</td>
<td>Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intra procedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction</td>
</tr>
<tr>
<td></td>
<td>75894</td>
<td>Transcatheter therapy, embolization, any method, radiological supervision and interpretation</td>
</tr>
<tr>
<td>HCPCS</td>
<td>Q0083</td>
<td>Chemotherapy administration by other than infusion technique only (e.g., subcutaneous, intramuscular, push), per visit</td>
</tr>
<tr>
<td>ICD-10</td>
<td>3E05005</td>
<td>Introduction of Other Antineoplastic into Peripheral Artery, Open Approach</td>
</tr>
<tr>
<td>Procedure</td>
<td>3E05305</td>
<td>Introduction of Other Antineoplastic into Peripheral Artery, Percutaneous Approach</td>
</tr>
<tr>
<td></td>
<td>3E06005</td>
<td>Introduction of Other Antineoplastic into Central Artery, Open Approach</td>
</tr>
<tr>
<td></td>
<td>3E06305</td>
<td>Introduction of Other Antineoplastic into Central Artery, Percutaneous Approach</td>
</tr>
</tbody>
</table>

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/27/2015</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>10/01/2016</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>09/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>09/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>09/01/2019</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>
Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.