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Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

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Related Policies (if applicable)
None

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Coverage

Transcatheter arterial chemoembolization of the liver **may be considered medically necessary:**

- 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 individuals with hepatocellular cancer where the intent is to prevent further tumor growth and to maintain an individual's candidacy for liver transplant (see Policy Guidelines section);
- To treat liver metastasis in symptomatic individuals with metastatic neuroendocrine tumor whose symptoms persist despite systemic therapy and who are not candidates for surgical resection;
- To treat liver metastasis in individuals with liver-dominant metastatic uveal melanoma.

Transcatheter arterial chemoembolization of the liver **is considered experimental, investigational and/or unproven:**

- As neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable;
- As part of combination therapy (with radiofrequency ablation) for resectable or unresectable hepatocellular carcinoma;
- To treat unresectable intrahepatic 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

When using transcatheter arterial chemoembolization of the liver as a bridge to transplantation to prevent further tumor growth, the candidate should have the following characteristics:

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

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. Transcatheter arterial chemoembolization combines the infusion of chemotherapeutic drugs with particle embolization. Tumor ischemia secondary to the embolization raises the drug concentration compared with infusion alone, extending the retention of the chemotherapeutic agent and decreasing systemic toxicity. The liver is especially amenable to such an approach, given its distinct lobular anatomy, the existence of 2 independent blood supplies, and the ability of healthy hepatic tissue to grow and thus compensate for tissue mass lost during chemoembolization.

Transcatheter Arterial Chemoembolization

Transcatheter arterial chemoembolization is a minimally invasive procedure performed by interventional radiologists who inject highly concentrated doses of chemotherapeutic agents into the tumor tissues and embolic agent(s) 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%). (1)

The TACE procedure requires hospitalization for placement of a hepatic artery catheter and workup to establish eligibility for chemoembolization. Before the procedure, the patency of the portal vein must be demonstrated to ensure an adequate posttreatment hepatic blood supply. With the patient under local anesthesia and mild sedation, a superselective catheter is inserted via the femoral artery and threaded into the hepatic artery. Angiography is then performed to

delineate the hepatic vasculature, followed by injection of the embolic chemotherapy mixture. Embolic material varies but may include a viscous collagen agent, polyvinyl alcohol particles, or ethiodized oil. Typically, only 1 lobe of the liver is treated during a single session, with subsequent embolization procedures scheduled 5 days to 6 weeks later. In addition, because the embolized vessel recanalizes, chemoembolization can be repeated as many times as necessary.

Adverse Events

Transcatheter arterial chemoembolization of the liver has been associated with potentially life-threatening toxicities and complications, including severe postembolization syndrome, hepatic insufficiency, abscess, or infarction. Transcatheter arterial chemoembolization has been investigated to treat resectable, unresectable, and recurrent hepatocellular carcinoma, intrahepatic cholangiocarcinoma, liver metastases, and in the liver transplant setting. Treatment alternatives include resection when possible, other locally ablative techniques (e.g., radiofrequency ablation, cryoablation), and 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.

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 U.S. Food and Drug Administration approval.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to 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 a technology, 2 domains are examined: the relevance and the 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. Randomized controlled trials 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.

TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION FOR UNRESECTABLE AND RESECTABLE HEPATOCELLULAR CARCINOMA

In 2022, an estimated 113,557 people in the U.S. lived with hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma (ICC). (2) 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 9.4 per 100,000 men and women per year. The number of deaths is estimated at 6.6 per 100,000 men and women per year.

Transcatheter Arterial Chemoembolization for Unresectable Hepatocellular Carcinoma Confined to the Liver and Not Associated with Portal Vein Thrombosis

Clinical Context and Therapy Purpose

The purpose of transcatheter arterial chemoembolization (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 individuals with unresectable HCC confined to the liver and not associated with portal vein thrombosis.

The following PICO was used to select literature to inform this policy.

Populations

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

Interventions

The therapy being considered is TACE.

Transcatheter arterial chemoembolization 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. Transcatheter arterial chemoembolization 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.

Comparators

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

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival, quality of life, treatment-related mortality, and treatment-related morbidity (Table 1).

Table 1. Outcomes of Interest for Individuals With Unresectable Hepatocellular Carcinoma Confined to the Liver and Not Associated with Portal Vein Thrombosis

Outcomes	Details
OS	[Timing: ≥ 5 years]
Disease-specific survival	• Progression-free survival/complete response • Local tumor control • Time to secondary therapy [Timing for disease-specific survival: 14 weeks to 2 years]

OS: overall survival.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Systematic Reviews

Systematic reviews have compared TACE with hepatic resection and concluded that hepatic resection is superior to TACE for eligible patients. (3, 4) For patients with unresectable HCC, the evidence is less but does include some systematic reviews. Table 2 provides a comparative breakdown of 25 studies included in systematic reviews of TACE versus another intervention for unresectable HCC. These studies were published from 1990 to 2011.

A Cochrane review by Oliveri et al. (2011) included 9 trials involving 645 patients treated with TACE or transarterial embolization for unresectable HCC. (5) 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]). (6) Microsphere embolization treatment resulted in statistically significant longer OS (hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.60 to 0.88; p<.001) and time to progression (HR, 0.61; 95% CI, 0.41 to 0.89; p=.01) than chemoembolization. However, this meta-analysis included uncontrolled observational studies, which limits interpretation.

Table 2. Comparison of Trials and Studies Included in the Systematic Reviews

Study	Xie et al. (2012) (6)	Oliveri et al. (2011) (5)
Ahmad et al. (2005) (7)	●	
Akamatsu et al. (2004) (8)		●
Bruix et al. (1998) (9)		●
Cao et al. (2005a) (10)	●	
Cao et al. (2005b) (11)	●	
Carr et al. (2010) (12)	●	
Cheng et al. (2004) (13)		●
Doffoel et al. (2008) (14)		●
Du et al. (2002) (15)	●	
GETCH et al. (1995) (16)		●
Hao et al. (2000) (17)	●	
Hou et al. (2006) (18)	●	
Kirchhoff et al. (2006) (19)	●	
Kooby et al. (2009) (20)	●	
Lee et al. (2008) (21)	●	
Lewandowski et al. (2009) (22)	●	
Li et al. (1995) (23)		●
Li et al. (2006) (24)		●
Liu et al. (2005) (25)	●	
Llovet et al. (2002) (26)		●
Lo et al. (2002) (27)		●
Pelletier et al. (1990) (28)		●
Pelletier et al. (1998) (29)		●
Salem et al. (2011) (30)	●	
Xiao et al. (2003) (31)		●

Randomized Controlled Trials

Two additional RCTs not in the systematic reviews were also identified. Tables 3 and 4 summarize key characteristics and results of these trials, and Tables 5 and 6 summarize limitations in study relevance and design. Bush et al. (2016) published interim results of an RCT comparing TACE with proton beam radiotherapy for patients who had unresectable HCC. (32) 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=.06). The total days of hospitalization in the 30 days posttreatment was significantly lower for the TACE group (24 days vs. 166 days; p<.01). For the outcome of local tumor control, there was a trend toward worse control in the TACE group (45% vs. 88%; p=.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. (33) 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% versus 10% of patients in the chemotherapy arm (p=.007). The probability of tumor progression was significantly lower in patients treated with TACE, who had a median PFS of 32 weeks (range, 16 to 70 weeks) versus 26 weeks (range, 14 to 54 weeks) for patients treated with systemic chemotherapy (p=.03). Median OS did not differ significantly between TACE (38 weeks) and chemotherapy (32 weeks; p=.08), except for patients with a serum albumin greater than 3.3 g/dL (60 weeks vs. 36 weeks; p=.003). Treatment-related mortality was 4% in the TACE arm and 0% in the chemotherapy arm.

Table 3. Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	***Comparator***
Bush et al. (2016) (32)	United States	1	NR	69 patients with clinical or pathologic diagnosis of HCC using either Milan or San Francisco transplant criteria; race or ethnicity of participants were not described	TACE	Proton beam radiotherapy
Mabed et al. (2009) (33)	Egypt	1	2003-2005	100 patients with unresectable HCC; race or ethnicity of participants were not described	TACE	Systemic chemotherapy

HCC: hepatocellular carcinoma; NR: not reported; TACE: transcatheter arterial chemoembolization.

Table 4. Summary of Key Randomized Controlled Trial Results

Study	PFS	Overall Survival (%)	Response Rate, n (%)	TRM, %
Bush et al. (2016) (32)	*PFS at 2 years, %*		*Pathologic complete response after liver transplant*	
TACE	31	30 (59) mo (entire group)	1/10 (10)	
Proton beam therapy	48	30 (59) mo (entire group)	3/12 (32)	
95% CI	NR	20.7 to 39.3 mo		
p	0.06	NR	0.38	
Mabed et al. (2009) (33)	*Median PFS*		*Partial response*[a]	

TACE	32 wks	38 wks	16 (32)	4
Range	16 to 70 wks	22 to 72 wks		
Systemic chemotherapy	26 wks	32 wks	5 (10)	0
Range	14 to 54 wks	26 to 68 wks		
p	0.03	0.08	0.007	NR

CI: confidence interval; mo: months; NR: not reported; PFS: progression-free survival; TACE: transcatheter arterial chemoembolization; TRM: treatment-related mortality; wks: week(s).
[a] defined as a decrease of 50% or more in the product of two perpendicular diameters of the largest tumour nodule for a least 4 weeks without the appearance of new lesions or progression of lesions

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
Bush et al. (2016) (32)	3. Patients required to meet Milan or San Francisco criteria for liver transplant to enroll in the trial, and some patients in each group underwent liver transplant after treatment			3. Treatment-related toxicities were only reported in detail for patients who were hospitalized due to complications, and investigators used days of hospitalization as a surrogate to quantify significant toxicity (reported difficulty adjudicating significant events as treatment-related or not treatment-related)	
Mabed et al. (2009) (33)	2. Study population is unclear		2.Doxorubicin is not a recommended systemic therapy option in current treatment guidelines; appropriate-		

			ness of dosing regimen used in the trial is unclear		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Bush et al. (2016) (32)		1,2. No blinding was reported			3. Power-estimates led investigators to plan enrollment of 110 patients per treatment arm to identify differences of 15% or greater in 2-year PFS; only 69 patients total were included in this interim analysis	
Mabed et al. (2009) (33)		1,2. No blinding was reported				

PFS: progression-free survival.
The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized Observational Studies

Shen et al. (2019) published a retrospective, single-center study comparing stereotactic body radiation therapy (SBRT) and TACE as treatments for unresectable HCC of 3 to 8 cm. (34) One hundred eighty-eight patients received either TACE (n=142) or SBRT (n=46) between 2008 and 2017. Before propensity score matching, the 3-year infield control rates were 63.0% and 73.3% for TACE and SBRT, respectively, while 3-year OS rates were 47.4% and 22.9%. After propensity score matching, 3-year infield control rates were 55.6% and 77.5% (p=.007), and 3-year OS rates were 13.0% and 55.0% (p<.001), both favoring SBRT. This study was limited by its retrospective nature, long look-back period, and possibility for treatment selection bias.

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. (35) 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 (odds ratio [OR], 2.2; 95% CI, 1.4 to 3.3; p<.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=.009); there was no significant difference in OS (p=.29). After matching, radiation segmentectomy still had significantly better results for complete response (p=.005) and time to secondary therapy (p=.001), and there was again no significant difference in OS (p=.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. (36-38) The largest of these studies published in Japan reported results from an 8-year

prospective cohort. (37) 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: Transcatheter Arterial Chemoembolization for Unresectable Hepatocellular Carcinoma Confined to the Liver and Not Associated with Portal Vein Thrombosis
There is evidence from one RCT that survival with TACE is at least as good as with systemic chemotherapy.

Transcatheter Arterial Chemoembolization for Resectable Hepatocellular Carcinoma 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.

Clinical Context and Therapy Purpose
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 following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with resectable HCC.

Interventions
The therapy being considered is neoadjuvant or adjuvant TACE.

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

Outcomes
The general outcomes of interest are OS, disease-specific survival, quality of life, treatment-related mortality, and treatment-related morbidity (Table 7).

Table 7. Outcomes of Interest for Individuals With Resectable Hepatocellular Carcinoma Treated with Neoadjuvant or Adjuvant Transcatheter Arterial Chemoembolization

Outcomes	Details
OS	[Timing: Up to 5 years]
Disease-specific survival	Intra- and extrahepatic recurrence [Timing: Up to 5 years] RFS [Timing: Up to 5 years]

OS: overall survival; RFS: recurrence-free survival.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Neoadjuvant Therapy

Systematic Reviews

Chan et al. (2023) performed a meta-analysis of 12 studies (N=3960) that compared preoperative neoadjuvant TACE with resection in patients with large HCC (≥5 cm). (39) All but 2 of the included studies were retrospective. There was no significant difference in OS between the 2 treatments. Disease-free survival was more common with TACE than resection alone (HR, 0.79; 95% CI, 0.63 to 0.99; p=.04), but operating time and blood loss were also significantly higher with TACE.

Si et al. (2016) reported results of a meta-analysis of RCTs that compared the impact of neoadjuvant TACE with surgery alone. (40) Individually, 2 of the 5 RCTs concluded no effect (no reduction in postoperative recurrence or effect on survival) while 3 suggested an unfavorable effect (higher dropouts from definitive surgery, higher prevalence of intraoperative lesions, delayed definitive surgery). None of the studies were graded as low risk of bias in any of the 5 domains of the Cochrane risk of bias tool. Meta-analysis reported no difference between the 2 groups on OS (HR, 1.25; 95% CI, 0.92 to 1.68), disease-free survival (DFS) rate (HR, 0.95; 95% CI, 0.76 to 1.19), and perioperative mortality rate (OR, 0.70; 95% CI, 0.22 to 2.30).

Zhou et al. (2013) conducted a meta-analysis of 21 studies evaluating preoperative TACE. (41) Included were 4 RCTs and 17 nonrandomized studies (N=3210). 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 57.0% 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 versus controls in 5-year DFS rates (32.1% vs. 30.0%; p=.17) or OS rates (40.2% vs. 45.2%; p=.37). Intra- and extrahepatic recurrence rates also did not differ significantly across pooled analyses for TACE versus controls (51.2% vs. 53.6% and 12.9% vs. 10.3%, respectively; p=.19).

Chua et al. (2010) conducted a systematic review of neoadjuvant TACE for resectable HCC. (42) The authors 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 8 provides a comparative breakdown of RCTs included in select systematic reviews.

Table 8. Comparison of Randomized Controlled Trials Included in Systematic Reviews

Study	Si et al. (2016) (40)	Zhou et al. (2013) (41)	Chua et al. (2010) (42)
Kaibori et al. (2012) (43)	•	•	
Zhou et al. (2009) (44)	•	•	•
Cui et al. (2003) (45)	•		
Yamasaki et al. (1996) (46)	•	•	•
Wu et al. (1995) (47)	•	•	•

Randomized Controlled Trials

The RCTs by Kaibori et al. (2012) and Zhou et al. (2009) were the most recently published RCTs included in the systematic reviews; therefore, their results are described more fully in this section. (43, 44). 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. (43) Race or ethnicity of participants were not described. No statistically significant differences in DFS or OS were reported between the pooled preoperative TACE groups (p=.660) and the control group (p=.412) or between the 3 groups in DFS (p=.830) or OS (p=.713). Disease-free survival 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. Overall survival 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]). (44) Race or ethnicity of participants were not described. 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=.017) and longer operative time (mean, 176.5 minutes vs. 149.3 minutes; p=.042) than the control group. No significant difference was found between the 2 groups in mortality. At a median follow-up of 57 months, 41 (78.8%) of 52 patients in the preoperative TACE group and 51 (91.1%) of 56 patients in the control group had recurrent disease (p=.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=.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=.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. (48) 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=.003), very early stage classification on the Barcelona Clinic Liver Cancer staging system (HR, 2.03; 95% CI, 1.02 to 4.03; p=.043), tumor size less than 5 cm (HR, 1.75; 95% CI, 1.12 to 2.75; p=.015), α-fetoprotein level less than 200 ng/mL (HR, 2.07; 95% CI, 1.35 to 3.18; p=.001), and curative-based therapy (HR, 2.16; 95% CI, 1.44 to 3.22; p<.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=.022) and curative-based therapy (HR, 1.51; 95% CI, 1.13 to 2.03; p=.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 had preoperative TACE. (49) 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.

Subsection Summary: Transcatheter Arterial Chemoembolization for Resectable Hepatocellular Carcinoma as Neoadjuvant Therapy

Randomized and nonrandomized trials have evaluated TACE as neoadjuvant therapy to hepatic resection in HCC. 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

Liang et al. (2020) published a systematic review and meta-analysis that included 9 RCTs and 15 nonrandomized controlled trials (N=6977) that evaluated adjuvant TACE in patients undergoing liver resection with HCC. (50) Overall survival was based on 6 RCTs and 15 nonrandomized controlled trials, while DFS was reported in 7 RCTs and 6 nonrandomized trials. Compared with surgery alone, use of adjuvant TACE resulted in prolonged OS (HR, 0.67; 95% CI, 0.60 to 0.76; p<.001) and DFS (HR, 0.71; 95% CI, 0.61 to 0.84; p<.001). The authors noted that 9 nonrandomized controlled trials were at relatively moderate risk of bias and 6 were at relatively serious risk of bias. Among the RCTs, 4 had unknown risk of bias while 5 had high risk of bias. Key RCTs are discussed in the next section.

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). (51) Five of the 8 RCTs reported OS and 7 reported recurrence-free survival (RFS). A discussion

of key RCTs is presented in the next section. Results showed that adjuvant TACE was associated with improved OS (HR, 0.70; 95% CI, 0.63 to 0.78; p<.001) and RFS (HR, 0.69; 95% CI, 0.63 to 0.76; p<.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). (52) Race or ethnicity of participants were not described. Staging of HCC was not reported. Portal vein thrombus extirpation was performed at the time of surgery. Although the trial was randomized, no details for randomization including allocation concealment were provided for this single-center trial. Power calculations were also not reported. The DFS curve differed significantly across the 3 groups, as estimated using the Kaplan-Meier method (both p<.05). Overall survival 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<.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>.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<.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. (24) 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). (53) Race or ethnicity of participants were not described. Three patients were excluded from the final analysis (2 from the adjuvant arm, 1 from hepatectomy arm). Although the trial was randomized, no details on randomization including allocation concealment were provided in this single-center trial. With a sample size of 56 in each arm, the trial was adequately powered (80%) to detect a 20% difference in 5-year survival. The demographic data were well-matched

between arms. The incremental median OS advantage for adjuvant TACE treatment was 9 months compared with surgery alone (23.0 months vs. 14.0 months, respectively; p=.048). Confidence intervals 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). (54) Race or ethnicity of participants were not described. 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<.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: Transcatheter Arterial Chemoembolization for Resectable Hepatocellular Carcinoma as Adjuvant Therapy

Multiple RCTs and retrospective observational studies, as well as meta-analyses, have evaluated TACE as adjuvant therapy to hepatic resection in HCC. Results of the meta-analyses, which included RCTs and retrospective studies, showed that adjuvant TACE was associated with a 30% to 33% relative reduction in the hazard of death and a 29% and 31% relative reduction in the hazard of DFS and recurrence, respectively. However, the meta-analyses counted the nearly identical RCTs published by Li et al. in 2006 as separate RCTs. Absent any conclusive evidence that these 2 RCTs are distinct trials, the survival estimates of the meta-analyses 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 HEPATOCELLULAR CARCINOMA

Transcatheter Arterial Chemoembolization Plus Radiofrequency Ablation for Resectable Hepatocellular Carcinoma

Clinical Context and Therapy Purpose

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 individuals with resectable HCC.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with resectable HCC.

Interventions
The therapy being considered is TACE plus RFA.

Comparators
Comparators of interest include surgery alone.

Outcomes
The general outcomes of interest are OS, disease-specific survival, quality of life, treatment-related mortality, and treatment-related morbidity (Table 9).

Table 9. Outcomes of Interest for Individuals With Resectable Hepatocellular Carcinoma Treated with Transcatheter Arterial Chemoembolization Plus Radiofrequency Ablation

Outcomes	Details
OS	[Timing: Up to 5 years]
Disease-specific survival	RFS [Timing: Up to 5 years]

OS: overall survival; RFS: recurrence-free survival.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Systematic Reviews
Gui et al. (2020) published a meta-analysis of data from 1 RCT and 8 retrospective studies to compare TACE plus RFA to surgery alone. (55) Key studies from this meta-analysis, including the single RCT, are summarized below. A total of 867 patients were treated with TACE plus RFA and 1025 patients were treated with surgery. Rates of 1-, 3-, and 5-year OS were not significantly different between treatments. At 1 year, DFS was not significantly different between treatments, and surgery alone demonstrated better DFS at 3 years (OR, 0.78; 95% CI, 0.62 to 0.98; p=.03) and 5 years (OR, 0.74; 95% CI, 0.58 to 0.95; p=.02). However, in a subgroup analysis of propensity score-matched studies, 3- and 5-year DFS were not significantly different between treatments. This difference in findings may be due to selection bias in the non-matched studies.

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. (56) Race or ethnicity of participants were not described. 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. Overall survival (p=.007) and RFS (p=.026) were significantly higher in the surgical resection group (see Table 10). Local tumor progression occurred in 1 patient in the surgical resection group and in 18 patients in the TACE plus RFA group (p<.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=.032) and OS (p=.012) in patients with lesions larger than 3 cm. Tumor size was an independent prognostic factor for RFS (HR, 1.76; p=.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=.24). It was unclear in this trial whether TACE plus RFA was as effective as a surgical resection for these small tumors.

Table 10. Survival Rates After Surgical Resection or Transcatheter Arterial Chemoembolization Plus Radiofrequency Ablation for Resectable Hepatocellular Carcinoma

Outcomes	1 Year, %	3 Years, %	5 Years, %
OS			
Surgical resection group	97.0	83.7	61.9
TACE plus RFA group	96.0	67.2	45.7
RFS			
Surgical resection group	94.0	68.2	48.4
TACE plus RFA group	83.0	44.9	35.5

Adapted from Liu et al. (2016). (56)
OS: overall survival; RFA: radiofrequency ablation; RFS: recurrence-free survival; 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. (57) 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<.01 and p=.02, respectively). The study was limited by its retrospective nature, relatively small population size, potential patient selection bias, and 2 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. (58) 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 1 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. (59) 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 plus RFA was 94.6%, 75.1%, and 55.3%, respectively, and 91.2%, 64.4%, and 47.7%, respectively, for hepatectomy (p=.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=.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.

Section Summary: Transcatheter Arterial Chemoembolization Plus Radiofrequency Ablation for Resectable Hepatocellular Carcinoma

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. A meta-analysis of data from retrospective studies and the sole available RCT did not find significant survival benefits with TACE plus RFA compared to surgery alone.

Transcatheter Arterial Chemoembolization Plus Radiofrequency Ablation for Unresectable Hepatocellular Carcinoma

Clinical Context and Therapy Purpose

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 individuals with unresectable HCC.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with unresectable HCC.

Interventions

The therapy being considered is TACE plus RFA.

Comparators

Comparators of interest include RFA alone.

Outcomes

The general outcomes of interest are OS, disease-specific survival, quality of life, treatment-related mortality, and treatment-related morbidity (Table 11).

Table 11. Outcomes of Interest for Individuals With Unresectable Hepatocellular Carcinoma Treated with Transcatheter Arterial Chemoembolization Plus Radiofrequency Ablation

Outcomes	Details
OS	[Timing: Up to 5 years]
Disease-specific survival	Local tumor progression [Timing: Up to 3 years]

OS: overall survival.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

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 5 years of follow-up. (60-63) 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. (60) In addition, Peng et al. (2012) (64) 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) (65) enrolled treatment-naive patients with a solitary tumor measuring 3.1 to 5 cm and Shibata et al. (2009) (66) enrolled patients with tumors smaller than 3 cm without specifying whether they were treatment-naive or -experienced. Two of the 5 meta-analyses also included results from the first RCT that demonstrated combination treatment was better than RFA alone. (67) However, that article was retracted in 2009 because of questions about data integrity and reporting. (68)

Randomized Controlled Trials

To assess the nature of the evidence that makes the case for combined used of TACE and RFA in HCC, the current RCTs (64, 65, 69, 70) published after 2009 (an arbitrary threshold) were reviewed. All trials were conducted in China and all but one were reported in open access journals. (70) 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 2 groups but would not allow other explanatory variables to be taken into account. (64-66) 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 smaller or multiple lesions each measuring less than 3 cm. (69) 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 versus the RFA or MWA alone arm (HR, 0.53; 95% CI, 0.33 to 0.82; p=.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. (70) Patients were randomized to sequential TACE plus RFA (n=94) or to RFA alone (n=95). Overall survival and RFS were longer in the TACE plus RFA group (HR, 0.56; 95% CI, 0.34 to 0.82; p=.002) than in the RFA group alone (HR, 0.58; 95% CI, 0.37 to 0.90; p=.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 59.0% 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). (65) While the rates of local tumor progression at the end of the third year were significantly lower in the combined arm (6%) than in the RFA alone arm (39%; p=.012), there was no difference in the 3-year survival rates (93% vs. 80%, respectively; p=.369). In addition to having the same statistical limitations as Peng et al. (2012), (64) the Morimoto trial had a small sample size with inadequate power to detect a difference in survival. (65)

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). (64) A p-value of less than .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%) versus the RFA alone arm (82%, 47%, and 36%; p=.037) at 1, 2, and 5 years, respectively. The 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=.005). Hazard ratios and CIs were not reported. Further, subgroup analyses showed that OS was longer for the combined arm versus the RFA alone arm among patients with tumors measuring 3.1 to 5.0 cm (p=.002) but not for tumors 3.0 cm or smaller (p=.478).

Section Summary: Transcatheter Arterial Chemoembolization Plus Radiofrequency Ablation for Unresectable Hepatocellular Carcinoma

Multiple meta-analyses and RCTs have shown a consistent benefit in survival and RFS favoring combination treatment with TACE plus RFA versus RFA alone. Results of these meta-analyses are difficult to interpret because the pooled data included heterogeneous patient populations and, in a few cases, included data from a study 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 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; therefore, the results might not be generalizable to patients in Western countries.

TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION AS A BRIDGE TO LIVER TRANSPLANT

Transcatheter arterial chemoembolization has been explored in various settings as a technique to prevent tumor progression in patients on the liver transplant waiting list, to downstage tumors so a patient may be considered a better candidate for liver transplantation, and to decrease the incidence of posttransplant recurrence in patients with larger (T3) tumors. All uses are in part related to the United Network for Organ Sharing (UNOS) liver allocation policy, which prioritizes patients for receiving donor livers. The UNOS policy and the 3 treatment settings are discussed further here.

United Network for Organ Sharing Liver Allocation System

In 2002, UNOS introduced the Model for End-Stage Liver Disease (MELD) system for allocating new livers to adults awaiting a transplant. (71, 72) 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 2022, prioritize only T2 HCC patients who meet specified staging, laboratory, and imaging criteria by awarding exception scores in place of the calculated MELD score. (72) 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. (73) 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 3-month intervals. Those whose tumors have progressed and are no longer T2 tumors lose the additional allocation points.

Additionally, nodules identified through imaging of cirrhotic livers are given an Organ Procurement and Transplantation Network class 5 designation. Class 5B and 5T nodules are eligible for automatic priority. Class 5B criteria consist of a single nodule 2 cm or larger and up to 5 cm (T2 stage) that meets specified imaging criteria. Class 5T nodules have undergone subsequent locoregional treatment after being automatically approved on initial application or extension. A single class 5A nodule (>1 cm and <2 cm) corresponds to T1 HCC and does not qualify for automatic priority. However, combinations of class 5A nodules are eligible for automatic priority if they meet stage T2 criteria. 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. (74) 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. The UNOS criteria specify that certain patients may undergo downstaging with locoregional therapy in order to qualify for a MELD exception score. Downstaging is possible in patients with 1 lesion between 5 and 8 cm; patients with 2 or 3 lesions with at least 1 lesion greater than 3 cm, no lesion greater than 5 cm, and a total diameter of all lesions of 8 cm or less; and patients with 4 or 5 lesions that are less than 3 cm each and less than or equal to 8 cm total. Patients must meet T2 criteria after downstaging in order to qualify for an exception score. Patients with T2 lesions and elevated α

fetoprotein (>1000 ng/mL) may also undergo locoregional therapy in order to qualify for a MELD exception score (α-fetoprotein must be below 500 ng/mL after treatment in order to qualify for an exception score).

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, cryoablation) and systemic therapy, in individuals with 1 to 3 small HCC tumors seeking to prevent tumor growth and maintain candidacy for liver transplant.

The following PICO was used to select literature to inform this policy.

Populations

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

Interventions

The therapy being considered is pretransplant TACE.

Comparators

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

Outcomes

The general outcomes of interest are OS, disease-specific survival, quality of life, treatment-related mortality, and treatment-related morbidity (Table 12).

Table 12. Outcomes of Interest for Individuals Awaiting Liver Transplant Who Are Treated with Transcatheter Arterial Chemoembolization

Outcomes	Details
OS	[Timing: Up to > 7 years]
Disease-specific survival	Tumor recurrence [Timing: Up to 5 years]

OS: overall survival.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Systematic Reviews

Butcher et al. (2022) reported on a meta-analysis evaluating long-term survival and postoperative complications of pre-liver transplantation TACE in HCC. (75) Twenty-one high-quality non-randomized controlled trials (N=8242) were included. In all included studies, patients underwent or did not undergo TACE based on clinical recommendations while on the transplant waiting list. Overall, individuals treated with TACE had similar survival and postoperative outcomes as non-TACE patients; however, they had worse prognostic features at baseline. In terms of baseline characteristics, tumor diameter was significantly larger in TACE patients (3.49 cm vs. 3.15 cm; p=.02) compared to control groups and time on the transplant waiting list was significantly longer in TACE patients (4.87 months vs. 3.46 months; p=.05), while MELD scores were significantly higher in non-TACE patients (10.81 vs. 12.35; p=.005). There were no significant differences in 3-year OS, 5-year OS, or 3-year DFS between those who received TACE and those who did not. Based on the worse prognostic features at baseline, administration of TACE to patients with poorer prognosis while awaiting liver transplantation may lead to comparable survival outcomes between those who do not receive TACE but have better prognosis characteristics. Interpretation of results is limited, as all studies pooled were nonrandomized with considerable heterogeneity among outcomes. Additionally, waitlist dropout rates could not be analyzed due to inadequate data.

Si et al. (2017) reported on a meta-analysis evaluating the correlation between preoperative TACE and liver transplant. (76) 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=.83), but a higher rate of vascular complications (relative risk, 2.01; 95% CI, 1.23 to 3.27; p=.005) and a reduction in DFS (HR, 1.66; 95% CI, 1.02 to 2.70; p=.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) 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. (77) None were 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. (78) During a median waiting time of 211 days (range, 28 to 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. (79)

Transcatheter Arterial Chemoembolization to Downstage Hepatocellular Carcinoma Prior to Transplant or to Reduce Recurrence in Those With T3 Lesions (Bridge to Transplant)

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), (73) 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 (UCSF) reported similar RFS rates after transplant in patients with T2 tumors and a subset of those with T3 tumors. (80) This T3 subset was defined as a single lesion 6.5 cm or smaller or no more than 3 lesions with none greater than 3 cm, with a sum of tumor diameters 8 cm or smaller. These expanded criteria are known as "the UCSF criteria."

Lewandowski et al. (2009) compared the efficacy of radioembolization with chemoembolization in downstaging 86 patients with HCC from stage T3 to T2. (22) 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 ($p<.05$).

Gabr 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. (81) 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 patients who received Y90 experienced tumor recurrence. There were no significant differences in RFS (TACE, 77 months vs. Y90, 79 months; p=.71) and OS

(TACE, 87.2 months vs. Y90, median not reached at 100 months; p=.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: Transcatheter Arterial Chemoembolization 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. Two meta-analyses of these studies have shown no difference in OS among patients who received TACE as a bridging therapy and those who did not prior to transplant. The older meta-analysis did show a higher rate of vascular complications and a reduction in DFS with TACE, but the more recent meta-analysis did not demonstrate a difference in DFS. The more recent meta-analysis (Butcher et al. [2022]) demonstrated no differences between groups despite the TACE group having worse prognostic characteristics at baseline. The significant limitations of the meta-analyses, 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 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.

Transcatheter Arterial Chemoembolization for Unresectable Intrahepatic Cholangiocarcinoma
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. (82) Survival prognosis for patients with unresectable ICC is poor, with a median survival of 3 to 6 months if left untreated. (83)

Clinical Context and Therapy Purpose
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 individuals with unresectable ICC.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with unresectable ICC.

Interventions
The therapy being considered is TACE.

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

Outcomes
The general outcomes of interest are OS, disease-specific survival, quality of life, treatment-related mortality, and treatment-related morbidity (Table 13).

Table 13. Outcomes of Interest for Individuals With Unresectable Intrahepatic Cholangiocarcinoma Treated with Transcatheter Arterial Chemoembolization

Outcomes	Details
OS	[Timing: >22 months]
Disease-specific survival	[Timing: Up to 5 years]

OS: overall survival.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Systematic Reviews
Lv et al. (2022) conducted a systematic review of 11 observational studies that compared TACE versus non-TACE interventions in patients with ICC. (84) Some of the included studies had patients who underwent surgical resection. Among patients who received palliative TACE for nonresectable ICC (N=3 studies), OS was significantly higher than in patients who received supportive treatment (HR, 0.35; 95% CI, 0.25 to 0.47; p<.00001). Survival at 1 year was also significantly higher with palliative TACE versus non-TACE interventions (63.9% vs. 9.2%; p<.00001). Interpreting these results is limited by a lack of information about the non-TACE interventions.

Edeline et al. (2021) conducted a systematic review of nonrandomized studies of locoregional treatments (i.e., TACE, radioembolization, HAI, external beam radiotherapy [EBRT], and ablation) for unresectable ICC. (85)
There were 22 cohorts (n=1145) for TACE, 27 cohorts (n=1232) for radioembolization, 16 cohorts (n=331) for HAI, 18 cohorts (n=541) for EBRT, and 15 cohorts (n=645) for ablation. The

mean weighted OS was 15.9 months (95% CI, 12.9 to 19.0) for TACE, 14.1 months (95% CI, 12.1 to 16.0) for radioembolization, 21.3 months (95% CI, 15.4 to 27.1) for HAI, 18.9 months (95% CI, 14.2 to 23.5) for EBRT, and 30.2 months for ablation (95% CI, 21.8 to 38.6).

Mosconi et al. (2021) conducted a systematic review and meta-analysis of 31 studies (N=1695) with either TACE or transarterial radioembolization for unresectable ICC. (86) Median survival after TACE was 14.2 months (95% CI, 11.6 to 17.6) versus 13.5 months (95% CI, 11.4 to 16.1) after transarterial radioembolization. Radiologic objective response was similar between groups (20.6% vs. 19.3%, respectively). Adverse events were more common with TACE (58.5%) than with transarterial radioembolization (43.0%). Substantial heterogeneity between groups limits interpretation of these results.

Boehm et al. (2015) conducted a meta-analysis of 20 studies (N=657) on the hepatic artery therapies of TACE, HAI, and Y90 for ICC. (87) 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%). Transcatheter arterial chemoembolization 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. (88) 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=.039). Survival was not reported for extrahepatic versus ICC.

Park et al. (2011) reviewed the medical and imaging records of 155 patients with unresectable ICC treated with TACE between 1996 and 2009. (82) 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 and multiple or diffuse in 43% and 57% of the TACE patients, respectively, and in 53% and 47% of the supportive group, respectively. Maximum tumor size in the TACE group was 8.1 cm and 7.8 cm in the supportive group. The median number of sessions per patient in the TACE group was 2.5 (range, 1 to 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 versus 3.3 months in the supportive therapy group (p<.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<.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<.001).

Section Summary: Transcatheter Arterial Chemoembolization for Unresectable Intrahepatic Cholangiocarcinoma

Randomized controlled trials evaluating the benefit of adding TACE to the standard of care for patients with unresectable ICC are lacking. Results from retrospective studies have reported a survival benefit with TACE over the standard of care; however, systematic reviews comparing TACE to other locoregional therapies are conflicting.

Transcatheter Arterial Chemoembolization 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.

Clinical Context and Therapy Purpose

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 individuals with symptomatic metastatic neuroendocrine tumors despite systemic therapy and who are not candidates for surgical resection.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with symptomatic metastatic neuroendocrine tumors despite systemic therapy and who 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.

Interventions

The therapy being considered is TACE.

Comparators

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

Outcomes

The general outcomes of interest are OS, disease-specific survival, symptoms, quality of life, treatment-related mortality, and treatment-related morbidity (Table 14).

Table 14. Outcomes of Interest for Individuals With Unresectable Metastatic Neuroendocrine Tumors Treated with Transcatheter Arterial Chemoembolization

Outcomes	Details
OS	[Timing: Up to 5 years]
Disease-specific survival	Freedom from disease progression [Timing: Up to 3 years]
Quality of Life	Symptomatic relief [Timing: Up to 3 years]

OS: overall survival.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Systematic Reviews

Tai et al. (2020) published a systematic review and meta-analysis comparing TACE to transarterial bland embolization in 8 studies (N=504) in patients with neuroendocrine tumors. (89) Seven of the included studies were retrospective cohort studies, and 1 small RCT was included. No differences between groups were found in OS at 1 year (OR, 0.72; 95% CI, 0.27 to 1.94), 2 years (OR, 0.69; 95% CI, 0.43 to 1.11), or 5 years (OR, 0.91; 95% CI, 0.37 to 2.24). In addition, PFS was not different between groups at 1 year (OR, 0.71; 95% CI, 0.38 to 1.55), 2 years (OR, 0.83; 95% CI, 0.33 to 2.06), or 5 years (OR, 0.91; 95% CI, 0.37 to 2.24). The authors noted that the quality of evidence is limited due to the rarity of neuroendocrine tumors. In addition, other factors (age, sex, performance status, tumor grade, volume of hepatic metastasis) may have influenced OS.

A literature review by Nazario and Gupta (2010) summarized the experience with TACE (and transarterial embolization). (90) 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, and 44 primarily received TACE. (91) 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=.16). Patients treated with chemoembolization also experienced longer symptomatic relief (15 months) than those who received bland embolization (7.5 months; p=.14). Post-therapy survival rates at 1, 3, and 5 years were 86%, 67%, and 50% for TACE and 68%, 46%, and 33% for bland embolization (p=.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. (92) Osborne et al. (2006) reported on a nonrandomized study of 59 patients with neuroendocrine tumors who received cytoreduction or embolization for symptomatic hepatic metastases. (93) Both duration of symptom relief (35 months vs. 22 months) and survival (43 months vs. 24 months) favored the cytoreduction approach.

Section Summary: Transcatheter Arterial Chemoembolization 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 the net health outcome.

Transcatheter Arterial Chemoembolization 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.

Clinical Context and Therapy Purpose

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 individuals with liver-dominant metastatic uveal melanoma.

The following PICO was used to select literature to inform this policy.

Populations

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

Even with successful treatment of the primary tumor, up to 50% of individuals 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.

Interventions
The therapy being considered is TACE.

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

Outcomes
The general outcomes of interest are OS, disease-specific survival, quality of life, treatment-related mortality, and treatment-related morbidity (Table 15).

Table 15. Outcomes of Interest for Individuals With Liver-Dominant Metastatic Uveal Melanoma Treated with Transcatheter Arterial Chemoembolization

Outcomes	Details
OS	[Timing: Up to >2 years]

OS: overall survival.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Systematic Review
A literature review by Rowcroft et al. (2020) summarized published studies on liver-directed therapies in patients with hepatic metastases from uveal melanoma. (94) Median OS with TACE ranged from 5 to 29 months in 17 prospective and retrospective observational studies that included a total of 647 patients.

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. (95) 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 to 35 months), and median survival after the first TACE treatment was 14.5 months in responders and 10 months in nonresponders (p=.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 versus 11 months in the 7 patients with more than 25% involvement of the liver (p=.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. (96) The 20 patients underwent 46 TACE sessions (mean, 2.4 sessions; range, 1 to 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. (97)

Patel et al. (2005) reported the results of a prospective single cohort study of TACE for treatment of hepatic metastasis from uveal melanoma. (98) 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: Transcatheter Arterial Chemoembolization 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.

Transcatheter Arterial Chemoembolization for Other Unresectable Hepatic Metastases

Clinical Context and Therapy Purpose

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 individuals with unresectable hepatic metastases from other types of primary tumors (e.g., colorectal, breast).

The following PICO was used to select literature to inform this policy.

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

Interventions
The therapy being considered is TACE.

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

Outcomes
The general outcomes of interest are OS, disease-specific survival, quality of life, treatment-related mortality, and treatment-related morbidity (Table 16).

Table 16. Outcomes of Interest for Individuals With Other Unresectable Hepatic Metastases

Outcomes	Details
OS	[Timing: Up to 3 years]
Disease-specific survival	PFS [Up to >15 months] Local tumor control [Up to >15 months]

OS: overall survival; PFS: progression-free survival

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Metastatic Colorectal Cancer
Systematic Reviews
Swierz et al. (2024) reported the results of a Cochrane review that compared the efficacy and safety of TACE and systemic chemotherapy for unresectable colorectal cancer liver metastases. (99) Three RCTs were included (N=238 patients), which were all conducted outside the U.S. Compared to systemic chemotherapy, the analysis found that TACE reduced mortality at longest follow-up (risk ratio, 0.86; 95% CI, 0.79 to 0.94; very low certainty evidence), but there was no effect on OS (HR, 0.61; 95% CI, 0.37 to 1.01; very low certainty evidence). No trials reported cancer mortality, proportion of participants dying or surviving with progression of the disease, and recurrence of liver metastases.

Sugumar et al. (2024) conducted a systematic review and meta-analysis of several liver-directed therapies, including TACE, for the treatment of colorectal cancer liver metastases. (100) The authors included 7 articles with TACE plus systemic chemotherapy, and 55 articles with other therapies. At 12 months, OS was 83% with TACE, which decreased to 14% at 36 months. Progression-free survival with TACE was 66% at 6 months, followed by 20% at 12 months, and 3% at 36 months. No statistical comparisons between treatments were reported.

Zacharias et al. (2015) published a meta-analysis evaluating hepatic artery-based therapies for colorectal metastases. (101) Techniques included TACE, HAI chemotherapy, and radioembolization. Ninety studies reported on outcomes of HAI-based therapy. Eight studies were RCTs, including 1 RCT of TACE. In 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. This review included retrospective studies along with prospective studies and RCTs, so interpretation of these combined analyses may be limited.

Richardson et al. (2013) reported on a systematic review (1 RCT, 5 observational studies) of TACE for unresectable colorectal liver metastasis. (102) 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.

Swierz et al. (2020) 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. (103) Only one RCT published in 1990 fulfilled inclusion criteria. The trial 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. Results of the trial with respect to mortality were inconclusive. Reviewers concluded that, in patients with liver metastases, the evidence regarding benefits and harms of TACE versus no active treatment is lacking, and more high-quality RCTs are necessary to draw conclusions about TACE in this setting.

Table 17 provides a comparative breakdown of studies included in the highest quality systematic reviews (e.g., reviews that only considered RCTs and/or prospective trials).

Table 17. Comparison of Trials and Studies Included in Select Systematic Reviews

Study	Swierz et al. (2024) (99)	Swierz et al. (2020) (103)	Richardson et al. (2013) (102)
Hunt et al. (1990) (104)		•	
Eichler et al. (2012) (105)			•
Martin et al. (2012) (106)			•
Vogl et al. (2012) (107)			•

Martin et al. (2011) (108)			•
Aliberti et al. (2011) (109)			•
Fiorentini et al. (2012) (110)	•		•
Zheng et al. (2013) (111)	•		
Du et al. (2017) (112)	•		

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). (110) Race or ethnicity of participants were not described. With TACE, OS was significantly longer, with a median OS of 22 months (95% CI, 21 to 23 months) versus 15 months (95% CI, 12 to 18 months) for the systemic chemotherapy group (p=.031). Progression-free survival 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=.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 colorectal cancer (CRC) with metastasis to the liver were randomized to the leucovorin, fluorouracil, and oxaliplatin (FOLFOX) plus TACE or FOLFOX plus bevacizumab arm. (113) Of the patients included, 15.7% were Black, 82.8% were White, and 1.5% were Asian. 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=.02), 4 (95% vs. 70%; p=.03), and 6 months (76% vs. 60%; p=.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=.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. (114) Of the 463 patients, 67% had 5 or more metastases, 14% had 3 or 4, 10% had 2, and 8% had 1 metastasis. Patients were treated at 4-week intervals, with a total of 2441 chemoembolization procedures performed (mean, 5.3 sessions per patient), using 1 of 3 local chemotherapy protocols. Local tumor control was partial response in 68 (14.7%) patients, stable disease in 223 (48.2%) patients, and progressive disease in 172 (37.1%) patients. Median survival from the start of TACE treatments was 14 months (vs. 7 to 8 months from a 2003 study by the same authors [115]). The 1-year survival rate after TACE was 62% and 28% at 2 years. No differences in survival were observed between the 3 chemotherapy protocols.

Hong et al. (2009) compared salvage therapy for liver-dominant colorectal metastatic adenocarcinoma using TACE or Y90 radioembolization. (116) 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=.27). Survival results were comparable with other studies assessing CRC and TACE (range, 7 to 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.

Metastatic Breast Cancer

Systematic Review

Rivera et al. (2021) published a systematic review of various liver directed therapies, including TACE, for treatment of breast cancer liver metastases. (117) The systematic review included 8 retrospective and prospective studies (N=362) that evaluated TACE; however, no RCTs were identified. Pooled median OS was 19.6 months (based on 6 studies) and 1-year survival ranging from 32% to 88.8% (based on 4 studies) with use of TACE.

Nonrandomized Trial

Vogl et al. (2010) published a study that was not included in the systematic review. The authors reported on the efficacy of repeated TACE treatments in 208 patients with unresectable hepatic metastases from breast cancer. (118) A total of 1068 chemoembolizations were performed (mean, 5.1 sessions per patient; range, 3 to 25). Patients received 1 of the chemotherapeutic agents alone (mitomycin-C or gemcitabine) or in combination. Tumor response was evaluated by magnetic resonance imaging using Response Evaluation Criteria in Solid Tumors (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: Transcatheter Arterial Chemoembolization for Other Unresectable Hepatic Metastases

For other types of hepatic metastases, the largest amount of evidence assesses CRC. 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 Hepatocellular Carcinoma

For individuals who have unresectable hepatocellular carcinoma (HCC) confined to the liver and not associated with portal vein thrombosis who receive transcatheter arterial chemoembolization (TACE), the evidence includes several randomized controlled trials (RCTs), large observational studies, and systematic reviews. Relevant outcomes are overall survival (OS), disease-specific survival, quality of life, and treatment-related mortality and morbidity. Evidence from 1 RCT has suggested that survival with TACE is at least as good as with systemic chemotherapy. One systematic review has highlighted possible biases associated with RCTs that compared TACE with no therapy. The evidence is sufficient to determine that the technology results in an 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. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Studies have shown little to no difference in OS rates with neoadjuvant TACE compared with surgery alone. A meta-analysis found no significant improvements in survival or recurrence with preoperative TACE for resectable HCC. While both RCTs and the meta-analyses that evaluated TACE as adjuvant therapy to hepatic resection in HCC reported positive results, the quality of individual studies and the methodologic issues related to the meta-analyses 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 that the technology results in an improvement in the net health outcome.

For individuals who have resectable HCC who receive TACE plus radiofrequency ablation (RFA), the evidence includes a single RCT and a systematic review. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The RCT failed to show the superiority in survival benefit with combination TACE plus RFA treatment compared 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 systematic review, which included mostly retrospective observational studies, did not find a survival benefit with TACE plus RFA over surgery alone. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable HCC who receive TACE plus RFA, the evidence includes multiple systematic reviews and RCTs. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Multiple meta-analyses and RCTs

have shown a consistent benefit in survival and RFS 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 that the technology results in an improvement in the net health outcome.

Bridge to Liver Transplant

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

Unresectable Intrahepatic Cholangiocarcinoma

For individuals who have unresectable intrahepatic cholangiocarcinoma who receive TACE, the evidence includes several retrospective observational studies and systematic reviews. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Randomized controlled trials evaluating the benefit of adding TACE to the standard of care for patients with unresectable intrahepatic cholangiocarcinoma are lacking. Results of retrospective studies (noncontrolled) have shown a survival benefit with TACE over the standard of care; however, systematic reviews comparing TACE to other locoregional therapies are conflicting. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Transcatheter Arterial Chemoembolization 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. Relevant outcomes are OS, disease-specific survival, symptoms, quality of life, 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 an 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. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. There is a lack of evidence from RCTs assessing 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 an 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. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Multiple RCTs and numerous nonrandomized studies have compared TACE with alternatives in patients who have colorectal cancer 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 (PFS). Whether this translates into a prolonged survival benefit relative to systemic chemotherapy alone is uncertain. For cancers other than colorectal, the evidence is extremely limited, and no conclusions can be made. Studies have 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 that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

Hepatocellular Carcinoma

The National Comprehensive Cancer Network (NCCN) (v2.2025) guidelines on hepatocellular carcinoma list TACE as an option for patients who are not candidates for surgically curative treatments or as a part of a strategy to bridge patients for other curative therapies. (128) Arterially directed therapies, including TACE, are appropriate for patients with unresectable or inoperable tumors that are not amenable to ablation therapy. Additionally, TACE in highly selected patients has been shown to be safe in the presence of limited tumor invasion of the

portal vein. The American Association for the Study of Liver Diseases 2023 guideline on hepatocellular carcinoma state that patients with Barcelona Clinic Liver Cancer Stage B HCC should receive TACE (Level 1, strong recommendation). (120) Both conventional TACE and drug-eluting bead TACE are mentioned, with no preference noted between these 2 modalities. The guideline also suggests using neoadjuvant locoregional therapies (which may include TACE) for bridging to liver transplant in patients with T2 lesions, in order to prevent disease progression and prevent dropouts from the waiting list. The guidelines recommend the use of locoregional therapies, including TACE, in patients with cirrhosis and T2 or T3 disease that is not amenable to resection or transplantation. The American Society of Clinical Oncology (ASCO) 2024 guideline on advanced HCC states that patients with locally advanced disease may be candidates for liver-directed therapies (including TACE); however, the guideline is focused on systemic therapy so there are no recommendations regarding TACE. (121)

Intrahepatic Cholangiocarcinoma

The NCCN (v2.2025) guidelines on biliary tract cancers including intrahepatic cholangiocarcinoma consider arterially directed therapies, including TACE, to be treatment options for unresectable and metastatic intrahepatic cholangiocarcinoma. (119)

Neuroendocrine and Adrenal Tumors

The NCCN (v3.2025) guidelines on neuroendocrine and adrenal tumors recommend hepatic regional therapy, including arterial embolization, chemoembolization, or radioembolization, for locally advanced or unresectable liver disease (category 2B). (122)

Uveal Melanoma Cancer

The NCCN (v1.2025) guidelines on uveal melanoma state that in patients with metastatic disease that is confined to the liver, regional liver-directed therapies such as chemoembolization, radioembolization, or immunoembolization should be considered. (123)

Colon Cancer

The NCCN (v4.2025) guidelines on colon cancer recommend TACE in highly selected cases for which chemotherapy has been ineffective, when liver function is preserved, and hepatic metastases are predominant. (124) The ASCO (2020) resource-stratified guidelines on late-stage colorectal cancer state that patients with unresectable liver metastases may receive TACE (weak recommendation). (125) However, this recommendation should only be implemented in centers with expertise in the technique, after multidisciplinary review, or in the context of a clinical trial. The 2022 guidelines for metastatic colorectal cancer from ASCO do not address TACE. (126)

Breast Cancer

The NCCN (v5.2025) guidelines on breast cancer do not address TACE as a treatment option for breast cancer metastatic to the liver. (127)

Ongoing and Unpublished Clinical Trials

Some currently ongoing and/or unpublished trials that might influence this policy are listed in Table 18.

Table 18. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT06909708	SIRT (Yttrium-90 Carbon Microspheres) Versus cTACE for Unresectable Hepatocellular Carcinoma: A Multicenter, Prospective, Open-label, Phase 3 Trial (CHANCE2506)	108	Jan 2027
NCT06715072	Study on the Efficacy and Safety of Transarterial Chemoembolization Combined with Targeted Immunotherapy in Patients with Unresectable Hepatocellular Carcinoma	70	Dec 2026
NCT06353126	A Prospective, Single Arm, Exploratory Study of Using Drug-eluting Beads Transarterial Chemoembolization Prior to SALT Liver Transplantation in the Treatment of Hepatocellular Carcinoma	40	Jul 2027
NCT04143191	Sorafenib Plus Transarterial Chemoembolization Versus Sorafenib Alone as Postoperative Adjuvant Treatment for Resectable Primary Advanced Hepatocellular Carcinoma: A Phase 3, Multicenter, Randomized Controlled Trial	158	Sep 2023 (unknown status)
NCT04912258	Trans-arterial Chemoembolization With Irinotecan Drug-eluding Beads Before Liver Surgery for Patients With Primary Unresectable Colorectal Liver Metastasis: A Randomized Control Trial	80	Jun 2023 (unknown status)
NCT02724540[a]	Randomized Embolization Trial for NeuroEndocrine Tumor Metastases To The Liver	162	Nov 2024
NCT02936388	A Randomized Phase II Trial of Transarterial Radioembolisation With Yttrium-90 (SIRT) in Comparison to Transarterial Chemoembolisation With Cisplatin (TACE) in Patients With Liver Metastasis From Uveal Melanoma	108	Dec 2024

NCT: national clinical trial.

[a] Denotes an industry sponsored or cosponsored clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	37243, 75894
HCPCS Codes	C1982, Q0083

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/01/2025	Document updated. The following change was made to Coverage: Modified medical necessity criteria specific to use as bridge to transplant, with

	movement of some of the language to the Policy Guidelines section. Added references 99, 111, and 112; others updated. Title changed from: Transcatheter Arterial Chemoembolization (TACE) of the Liver.
02/01/2025	Document updated with literature review. Coverage unchanged. Added references 39, 84-86, 99, 116-118, 123, and 125; others updated.
11/15/2023	Reviewed. No changes.
01/15/2023	Document updated with literature review. Coverage unchanged. References 49, 74, 85 & 109 added, some revised.
10/15/2021	Reviewed. No changes.
03/01/2021	Document updated with literature review. The following change was made to Coverage: Added "as part of combination therapy (with radiofrequency ablation) for resectable or unresectable hepatocellular carcinoma" to the experimental, investigational and/or unproven statement. Added references 8-13, 15-22, 24, 26, 29-32, 35, 54, 70, 81, 88, 95-101 and 108-109; others updated or removed.
09/15/2019	Reviewed. No changes.
02/01/2019	Document updated with literature review. The following changes were made to Coverage: 1) A minor addition was made 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; 2) Added "To treat liver metastases from any other tumors or to treat hepatocellular cancer that does not meet the criteria noted above" to experimental, investigational and/or unproven listing. Added/updated references 1, 3, 5, 17, 21, 29, 31-49, 55, 70, 72, 77-80; multiple references removed.
11/15/2017	Reviewed. No changes.
12/01/2016	Document updated with literature review. Coverage unchanged.
05/15/2015	Reviewed. No changes.
10/15/2014	Document updated with literature review. The following was added to the experimental, investigational and/or unproven indication listing: Treatment of unresectable cholangiocarcinoma. CPT/HCPCS code(s) updated
02/15/2011	Document updated with literature review. The following was added: TACE is considered experimental, investigational and unproven as neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable.
10/01/2008	Revised/updated entire document
04/15/2006	Revised/updated entire document
02/01/2002	Revised/updated entire document
03/01/2000	Revised/updated entire document
04/01/1999	Revised/updated entire document