8.01.11	Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies		
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Section:	8.0 Therapy	**Page:**	Page 1 of 44

Policy Statement

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

  A. 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

  B. As a bridge to transplant in individuals with hepatocellular cancer where **all** of the following are met:

    1. The intent is to prevent further tumor growth and to maintain an individual's candidacy for liver transplant

    2. Presence of hepatic tumor(s) meeting **one** of the following:

      a. Single tumor less than or equal to 5 cm

      b. Presence of no more than 3 tumors each less than 3 cm in size

    3. Absence of extrahepatic disease or vascular invasion

    4. Child-Pugh score of either A or B

  C. To treat liver metastasis in symptomatic individuals (e.g., wheezing, flushing of the skin, abdominal cramps, diarrhea, heart disease) with metastatic neuroendocrine tumor whose symptoms persist despite systemic therapy (e.g., Octreotide therapy) and who are not candidates for surgical resection

  D. To treat liver metastasis in individuals with liver-dominant metastatic uveal melanoma

II. Transcatheter arterial chemoembolization of the liver is considered **investigational**:

  A. As neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable

  B. As part of combination therapy (with radiofrequency ablation) for resectable or unresectable hepatocellular carcinoma

  C. To treat unresectable cholangiocarcinoma

  D. 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

  E. To treat hepatocellular tumors prior to liver transplantation except as noted above

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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

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

Neuroendocrine Tumors

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

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

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

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

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.

Coding

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

- **37243**: Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction
- **75894**: Transcatheter therapy, embolization, any method, radiological supervision and interpretation

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

The following Pass Through code was created as a result of an application by TriSalus Life Sciences for the Surefire® SparkTM Infusion System:

- **C1982**: Catheter, pressure generating, one-way valve, intermittently occlusive

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

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

Description

Transcatheter arterial chemoembolization (TACE) of the liver is a proposed alternative to conventional systemic or intra-arterial chemotherapy and to various nonsurgical ablative techniques

to treat resectable and nonresectable tumors. 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.

Related Policies

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

Benefit Application

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

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

Regulatory Status

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

Rationale

Background
Transcatheter Arterial Chemoembolization
Transcatheter arterial chemoembolization (TACE) is a minimally invasive procedure performed by interventional radiologists who inject highly concentrated doses of chemotherapeutic agents into the tumor tissues and 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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, 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.

Literature Review

This evidence review was informed by a TEC Assessment (2000) that assessed the use of transcatheter arterial chemoembolization (TACE) for hepatic tumors.[2,]

Evidence reviews 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Transcatheter Arterial Chemoembolization for Unresectable and Resectable Hepatocellular Carcinoma

In 2020 , an estimated 105,765 people in the U.S. lived with hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma (ICC).[3,] 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 9.3 per 100,000 men and women per year. The number of deaths are 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 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 review.

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 HCC 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]

HCC: hepatocellular carcinoma; 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.

Review of Evidence
Systematic Reviews
Systematic reviews have compared TACE with hepatic resection and concluded that hepatic resection is superior to TACE for eligible patients.[4,5] 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.[6] 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]).[7] 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)[7]	Oliveri et al (2011)[6]
Ahmad et al (2005)[8]	●	
Akamatsu et al (2004)[9]		●
Bruix et al (1998)[10]		●
Cao et al (2005a)[11]	●	
Cao et al (2005b)[12]	●	
Carr et al (2010)[13]	●	
Cheng et al (2004)[14]		●
Doffoel et al (2008)[15]		●
Du et al (2002)[16]	●	
GETCH et al (1995)[17]		●
Hao et al (2000)[18]	●	
Hou et al (2006)[19]	●	
Kirchhoff et al (2006)[20]	●	
Kooby et al (2009)[21]	●	
Lee et al (2008)[22]	●	
Lewandowski et al (2009)[23]	●	
Li et al (1995)[24]		●

Study	Xie et al (2012)[7,]	Oliveri et al (2011)[6,]
Li et al (2006)[25,]		●
Liu et al (2005)[26,]	●	
Llovet et al (2002) [27,]		●
Lo et al (2002)[28,]		●
Pelletier et al (1990)[29,]		●
Pelletier et al (1998)[30,]		●
Salem et al (2011)[31,]	●	
Xiao et al (2003)[32,]		●

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.[33,] 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.[34,] 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 RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Bush et al (2016)[33,]	U.S.	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)[34,]	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; RCT: randomized controlled trial; TACE: transcatheter arterial chemoembolization.

Table 4. Summary of Key RCT Results

Study	PFS	Overall Survival (%)	Response Rate, n (%)	TRM , %
Bush et al (2016)[33,]	*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 (25)	
95% CI	NR	20.7 to 39.3 mo		
p	.06	NR	.38	
Mabed et al (2009)[34,]	*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	.03	.08	.007	NR

CI: confidence interval; NR: not reported; PFS: progression-free survival; RCT: randomized controlled trial; TACE: transcatheter arterial chemoembolization; TRM: treatment-related mortality.
[a]defined as a decrease of 50% or more in the product of two perpendicular diameters of the largest tumour nodule for at 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)[33,]	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)[34,]	2. Study population is unclear		2. Doxorubicin is not a recommended systemic therapy option in current treatment guidelines; appropriateness 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. Clinical significant difference not prespecified; 6. Clinical 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)[33,]		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)[34,]		1,2. No blinding was reported				

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
PFS: progression-free survival.
[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.[35,] 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.[36,] 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.[37,38,39,] The largest of these studies published in Japan reported results from an 8 year prospective cohort.[38,] 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 1 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 review.

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 HCC Treated with Neoadjuvant or Adjuvant TACE

Outcomes	Details
OS	[Timing: Up to 5 years]

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

HCC: hepatocellular carcinoma; OS: overall survival; RFS: recurrence-free survival; TACE: transcatheter arterial chemoembolization.

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
Review of Evidence

Systematic Reviews

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%, p=.19, respectively).

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 RCTs 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,]	●	●	

Study	Si et al (2016)[40,]	Zhou et al (2013)[41,]	Chua et al (2010)[42,]
Zhou et al (2009)[44,]	●	●	●
Cui et al (2003)[45,]	●		
Yamasaki et al (1996)[46,]	●	●	●
Wu et al (1995)[47,]	●	●	●

RCT: randomized controlled trial.

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). DFS rates at 1 and 3 years for the tumor-targeted TACE group were 67% and 29%, 63% and 27% for the whole-liver TACE group, and 53% and 32% for the control group, respectively. 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
Review of Evidence

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.[25,] 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 HCC
Transcatheter Arterial Chemoembolization Plus Radiofrequency Ablation for Resectable HCC

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 review.

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 HCC Treated with TACE Plus RFA

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

HCC: hepatocellular carcinoma; OS: overall survival; RFA: radiofrequency ablation; RFS: recurrence-free survival; TACE: transcatheter arterial chemoembolization.

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.

Review of Evidence
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 TACE Plus RFA for Resectable HCC

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,]
HCC: hepatocellular carcinoma; 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 review.

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 HCC Treated with TACE Plus RFA

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

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

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.

Review of Evidence
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.[60,61,62,63,] 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, BCBSA reviewed the current RCTs[64,65,69,70,] published after 2009 (an arbitrary threshold). All trials were conducted in China and all but 1 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.[64,65,66,] 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 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 review.

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 TACE

Outcomes	Details
OS	[Timing: Up to >7 years]

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

OS: overall survival; TACE: transcatheter arterial chemoembolization.

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.

Review of Evidence
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 to 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.[23,] 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 for Y90. 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 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 cholangiocarcinoma.

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

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

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 Cholangiocarcinoma Treated with TACE

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

OS: overall survival; TACE: transcatheter arterial chemoembolization.

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.

Review of Evidence
Systematic Reviews
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.[84,] 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.[85,] 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 Cholangiocarcinoma
Randomized controlled trials evaluating the benefit of adding TACE to the standard of care for patients with unresectable cholangiocarcinoma are lacking. Results from retrospective studies have reported a survival benefit with TACE over the standard of care. Although the observational data are consistent, the lack of randomization limits definitive conclusions.

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 review.

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 TACE

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; TACE: transcatheter arterial chemoembolization.

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.

Review of Evidence
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.[86,] 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).[87,] 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.[88,] 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.[89,] Osborne et al (2006) reported on a nonrandomized study of 59 patients with neuroendocrine tumors who received cytoreduction or embolization for symptomatic hepatic metastases.[90,] 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 patients with liver-dominant metastatic uveal melanoma.

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

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 TACE

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

OS: overall survival; TACE: transcatheter arterial chemoembolization.

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.

Review of Evidence
Systematic Reviews
A literature review by Rowcroft et al (2020) summarized published studies on liver-directed therapies in patients with hepatic metastases from uveal melanoma.[91,] 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.[92,] 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.[93,] 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.[94,]

Patel et al (2005) reported the results of a prospective single cohort study of TACE for treatment of hepatic metastasis from uveal melanoma.[95,] 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 review.

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.

Review of Evidence
Metastatic Colorectal Cancer

Systematic Reviews

Zacharias et al (2015) published a meta-analysis evaluating hepatic artery-based therapies for colorectal metastases.[96,] 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.[97,] 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.[98,] Only 1 RCT published in 1990 fulfilled inclusion criteria. It randomized 61 patients with colorectal liver metastases to hepatic artery embolization, HAI chemotherapy, and no active therapeutic intervention. Reviewers judged this trial to have a high risk of bias on the basis of lack of sequence generation and lack of allocation concealment or blinding. 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 (2020)[98,]	Richardson et al (2013)[97,]
Hunt et al (1990)[99,]	●	
Eichler et al (2012)[100,]		●
Martin et al (2012)[101,]		●
Vogl et al (2012)[102,]		●
Martin et al (2011)[103,]		●
Aliberti et al (2011)[104,]		●
Fiorentini et al (2012)[105,]		●

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).[105,] 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.[106,] Of the patients included, 15.7% were African American, 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.[107,] 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[108,]). 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.[109,] 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.[110,] 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.[111,] 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.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2012 Input
In response to requests, input was received from 1 specialty medical society (2 reviewers) and 3 academic medical centers while this policy was under review in 2012. There was general agreement that the use of transcatheter arterial chemoembolization (TACE) was medically necessary for indications in the policy; however, reviewers were split for its use as a bridge to transplant. There was general support for the investigational policy statement for the use of TACE as neoadjuvant or adjuvant therapy in resectable hepatocellular carcinoma. Reviewers were split over the investigational policy statement to treat other liver metastases or for recurrent hepatocellular carcinoma. Four reviewers provided input on the use of TACE in unresectable cholangiocarcinoma; 2 reviewers considered it investigational and 2 others considered it investigational but also medically

necessary, the latter citing data showing a survival benefit of TACE compared with supportive therapy.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Hepatocellular Carcinoma

The National Comprehensive Cancer Network (NCCN) (v. v.1.2023) 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.[112,] 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 2018 guidelines on hepatocellular carcinoma suggest using liver-directed 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.[113,] 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.

Intrahepatic Cholangiocarcinoma

The NCCN (v.2.2023) guidelines on biliary tract cancers including intrahepatic cholangiocarcinoma consider arterially directed therapies, including TACE, to be treatment options for unresectable and metastatic intrahepatic cholangiocarcinoma.[112,]

Neuroendocrine and Adrenal Tumors

The NCCN (v.2.2022) guidelines on neuroendocrine and adrenal tumors recommend hepatic regional therapy, including arterial embolization, chemoembolization, or radioembolization, for unresectable liver metastases (category 2B). [114,]

Uveal Melanoma Cancer

The NCCN (v.1.2023) guidelines on uveal melanoma state that in patients with disease that is confined to the liver, regional liver-directed therapies such as chemoembolization, radioembolization, or immunoembolization should be considered.[115,]

Colon Cancer

The NCCN (v.2.2023) guidelines on colon cancer recommend TACE only for clinical trials.[116,] The American Society of Clinical Oncology (ASCO; 2020) resource-stratified guidelines on late-stage colorectal cancer state that patients with unresectable liver metastases may receive TACE (weak recommendation).[117,] 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.[118,]

Breast Cancer

The NCCN (v.4.2023) guidelines on breast cancer do not address TACE as a treatment option for breast cancer metastatic to the liver.[119,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 18.

Table 18. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03960008[a]	A Randomized Multi-Center Phase III Study of Individualized Stereotactic Body Radiation Therapy (SBRT) Versus Trans-Arterial Chemoemebolization (TACE) as a Bridge to Transplant in Hepatocellular Carcinoma	196	Dec 2024
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
NCT04912258	Trans-arterial Chemoembolization With Irinotecan Drug-eluting Beads Before Liver Surgery for Patients With Primary Unresectable Colorectal Liver Metastasis: A Randomized Control Trial	80	Jun 2023
NCT02724540[a]	Randomized Embolization Trial for NeuroEndocrine Tumor Metastases To The Liver	162	Mar 2024
Unpublished			
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 Metastases From Uveal Melanoma	108	Dec 2022

NCT: national clinical trial.

[a]Denotes an industry sponsored or cosponsored clinical trial

References

1. Marelli L, Stigliano R, Triantos C, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. Cardiovasc Intervent Radiol. 2007; 30(1): 6-25. PMID 17103105
2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transcatheter arterial chemoembolization of hepatic tumors. TEC Assessments. 2000;Volume 15;Tab 22.
3. National Cancer Institute, Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Liver and Intrahepatic Bile Duct Cancer. 2023; https://seer.cancer.gov/statfacts/html/livibd.html. Accessed May 25, 2023.
4. Qi X, Wang D, Su C, et al. Hepatic resection versus transarterial chemoembolization for the initial treatment of hepatocellular carcinoma: A systematic review and meta-analysis. Oncotarget. Jul 30 2015; 6(21): 18715-33. PMID 26243835
5. Tian X, Dai Y, Wang DQ, et al. Transarterial chemoembolization versus hepatic resection in hepatocellular carcinoma treatment: a meta-analysis. Drug Des Devel Ther. 2015; 9: 4431-40. PMID 26309396
6. Oliveri RS, Wetterslev J, Gluud C. Transarterial (chemo)embolisation for unresectable hepatocellular carcinoma. Cochrane Database Syst Rev. Mar 16 2011; (3): CD004787. PMID 21412886
7. Xie F, Zang J, Guo X, et al. Comparison of transcatheter arterial chemoembolization and microsphere embolization for treatment of unresectable hepatocellular carcinoma: a meta-analysis. J Cancer Res Clin Oncol. Mar 2012; 138(3): 455-62. PMID 22179199
8. Ahmad J, Rhee J, Carr BI. The effects of hepatic artery chemotherapy on viral hepatitis in patients with hepatocellular carcinoma. Dig Dis Sci. Feb 2005; 50(2): 331-5. PMID 15745096

9.   Akamatsu M, Yoshida H, Obi S, et al. Evaluation of transcatheter arterial embolization prior to percutaneous tumor ablation in patients with hepatocellular carcinoma: a randomized controlled trial. Liver Int. Dec 2004; 24(6): 625-9. PMID 15566514

10. Bruix J, Llovet JM, Castells A, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. Hepatology. Jun 1998; 27(6): 1578-83. PMID 9620330

11. Cao GW, Hu S, Li G, et al. The clinical and experimental research of transhepatic arterial injection of 32P-glass microsphere therapy for hepatic carcinoma. J Med Imaging. 2005;15(8):678681.

12. Cao XC, Wang X, Tan J, et al. Clinical research of intra-arterial radioembolization with 32P-gass microspheres combined with chemoembolization for treatment of liver cancer. Chin J Radiol. 2005;39(10):10681072.

13. Carr BI, Kondragunta V, Buch SC, et al. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. Cancer. Mar 01 2010; 116(5): 1305-14. PMID 20066715

14. Cheng SQ, Wu MC, Chen H, et al. [Transcatheter hepatic arterial chemoembolization and thymosin alpha1 in postoperative treatment of hepatocellular carcinoma]. Zhonghua Zhong Liu Za Zhi. May 2004; 26(5): 305-7. PMID 15312371

15. Doffoël M, Bonnetain F, Bouché O, et al. Multicentre randomised phase III trial comparing Tamoxifen alone or with Transarterial Lipiodol Chemoembolisation for unresectable hepatocellular carcinoma in cirrhotic patients (Fédération Francophone de Cancérologie Digestive 9402). Eur J Cancer. Mar 2008; 44(4): 528-38. PMID 18242076

16. Du W, Lin S, Luo K, et al. Clinical analysis of TACE plus 32P-GMS in advanced hepatic carcinoma. J Hepatobilia Surg. 2002;10(5):351352.

17. Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med. May 11 1995; 332(19): 1256-61. PMID 7708069

18. Hao N, Xiao X, Han X, et al. Efficacy of intra-arterial chemoembolization using drug microspheres in compare with chemoembolization in the treatment of primary hepatic carcinoma. Tumor (Shanghai). 2000;20(5):375378.

19. Hou P, Guan G, Zhang X, Lu H, Wang S. Effects of intra-advanced 32P glass microspheres for advanced hepatic carcinoma. Academic Journal of Fujian Medical University. 2006;40(1):4850.

20. Kirchhoff TD, Rudolph KL, Layer G, et al. Chemoocclusion vs chemoperfusion for treatment of advanced hepatocellular carcinoma: a randomised trial. Eur J Surg Oncol. Mar 2006; 32(2): 201-7. PMID 16373084

21. Kooby DA, Egnatashvili V, Srinivasan S, et al. Comparison of yttrium-90 radioembolization and transcatheter arterial chemoembolization for the treatment of unresectable hepatocellular carcinoma. J Vasc Interv Radiol. Feb 2010; 21(2): 224-30. PMID 20022765

22. Lee W, Luo J, Yan Z, et al. Hepatic radioembolization with epirubicin mixed microsphere for the treatment of hepatocellular carcinoma. J Nantong Univ (Medical Sciences). 2008;28(4):268270.

23. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant. Aug 2009; 9(8): 1920-8. PMID 19552767

24. Li JQ, Zhang YQ, Zhang WZ, et al. Randomized study of chemoembolization as an adjuvant therapy for primary liver carcinoma after hepatectomy. J Cancer Res Clin Oncol. 1995; 121(6): 364-6. PMID 7541051

25. Li Q, Wang J, Sun Y, et al. Postoperative transhepatic arterial chemoembolization and portal vein chemotherapy for patients with hepatocellular carcinoma: a randomized study with 131 cases. Dig Surg. 2006; 23(4): 235-40. PMID 16943671

26. Liu T, Zu M. Treatment of primary hepatic carcinoma by hepatic arterial chemoembolization with KMG microspheres and chemotherapeutic agents. Acad Med Xuzhou. 2005;25(2):126129.

27. Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. May 18 2002; 359(9319): 1734-9. PMID 12049862

28. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. May 2002; 35(5): 1164-71. PMID 11981766

29. Pelletier G, Roche A, Ink O, et al. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. J Hepatol. Sep 1990; 11(2): 181-4. PMID 2174933

30. Pelletier G, Ducreux M, Gay F, et al. Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. Groupe CHC. J Hepatol. Jul 1998; 29(1): 129-34. PMID 9696501

31. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology. Feb 2011; 140(2): 497-507.e2. PMID 21044630

32. Xiao E, Li D, Shen S, et al. Effect of preoperative transcatheter arterial chemoembolization on apoptosis of hepatocellular carcinoma cells. Chin Med J (Engl). Feb 2003; 116(2): 203-7. PMID 12775230

33. Bush DA, Smith JC, Slater JD, et al. Randomized Clinical Trial Comparing Proton Beam Radiation Therapy with Transarterial Chemoembolization for Hepatocellular Carcinoma: Results of an Interim Analysis. Int J Radiat Oncol Biol Phys. May 01 2016; 95(1): 477-482. PMID 27084661

34. Mabed M, Esmaeel M, El-Khodary T, et al. A randomized controlled trial of transcatheter arterial chemoembolization with lipiodol, doxorubicin and cisplatin versus intravenous doxorubicin for patients with unresectable hepatocellular carcinoma. Eur J Cancer Care (Engl). Sep 2009; 18(5): 492-9. PMID 19453695

35. Shen PC, Chang WC, Lo CH, et al. Comparison of Stereotactic Body Radiation Therapy and Transarterial Chemoembolization for Unresectable Medium-Sized Hepatocellular Carcinoma. Int J Radiat Oncol Biol Phys. Oct 01 2019; 105(2): 307-318. PMID 31175903

36. Biederman DM, Titano JJ, Korff RA, et al. Radiation Segmentectomy versus Selective Chemoembolization in the Treatment of Early-Stage Hepatocellular Carcinoma. J Vasc Interv Radiol. Jan 2018; 29(1): 30-37.e2. PMID 29169782

37. Molinari M, Kachura JR, Dixon E, et al. Transarterial chemoembolisation for advanced hepatocellular carcinoma: results from a North American cancer centre. Clin Oncol (R Coll Radiol). Nov 2006; 18(9): 684-92. PMID 17100154

38. Takayasu K, Arii S, Ikai I, et al. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology. Aug 2006; 131(2): 461-9. PMID 16890600

39. Biselli M, Andreone P, Gramenzi A, et al. Transcatheter arterial chemoembolization therapy for patients with hepatocellular carcinoma: a case-controlled study. Clin Gastroenterol Hepatol. Sep 2005; 3(9): 918-25. PMID 16234031

40. Si T, Chen Y, Ma D, et al. Preoperative transarterial chemoembolization for resectable hepatocellular carcinoma in Asia area: a meta-analysis of random controlled trials. Scand J Gastroenterol. Dec 2016; 51(12): 1512-1519. PMID 27598831

41. Zhou Y, Zhang X, Wu L, et al. Meta-analysis: preoperative transcatheter arterial chemoembolization does not improve prognosis of patients with resectable hepatocellular carcinoma. BMC Gastroenterol. Mar 19 2013; 13: 51. PMID 23509884

42. Chua TC, Liauw W, Saxena A, et al. Systematic review of neoadjuvant transarterial chemoembolization for resectable hepatocellular carcinoma. Liver Int. Feb 2010; 30(2): 166-74. PMID 19912531

43. Kaibori M, Tanigawa N, Kariya S, et al. A prospective randomized controlled trial of preoperative whole-liver chemolipiodolization for hepatocellular carcinoma. Dig Dis Sci. May 2012; 57(5): 1404-12. PMID 22271410

44. Zhou WP, Lai EC, Li AJ, et al. A prospective, randomized, controlled trial of preoperative transarterial chemoembolization for resectable large hepatocellular carcinoma. Ann Surg. Feb 2009; 249(2): 195-202. PMID 19212170

45. Cui H, Gao QQ, Li YY, et al. Influence of preventive effects of transcatheter arterial chemoembolization on primary hepatocellular carcinoma. J Med Forum. 2003;24:13.

46. Yamasaki S, Hasegawa H, Kinoshita H, et al. A prospective randomized trial of the preventive effect of pre-operative transcatheter arterial embolization against recurrence of hepatocellular carcinoma. Jpn J Cancer Res. Feb 1996; 87(2): 206-11. PMID 8609071

47. Wu CC, Ho YZ, Ho WL, et al. Preoperative transcatheter arterial chemoembolization for resectable large hepatocellular carcinoma: a reappraisal. Br J Surg. Jan 1995; 82(1): 122-6. PMID 7881929

48. Yeh ML, Huang CI, Huang CF, et al. Neoadjuvant transcatheter arterial chemoembolization does not provide survival benefit compared to curative therapy alone in single hepatocellular carcinoma. Kaohsiung J Med Sci. Feb 2015; 31(2): 77-82. PMID 25645985

49. Choi GH, Kim DH, Kang CM, et al. Is preoperative transarterial chemoembolization needed for a resectable hepatocellular carcinoma?. World J Surg. Dec 2007; 31(12): 2370-7. PMID 17912587

50. Liang L, Li C, Diao YK, et al. Survival benefits from adjuvant transcatheter arterial chemoembolization in patients undergoing liver resection for hepatocellular carcinoma: a systematic review and meta-analysis. Therap Adv Gastroenterol. 2020; 13: 1756284820977693. PMID 33329759

51. Liao M, Zhu Z, Wang H, et al. Adjuvant transarterial chemoembolization for patients after curative resection of hepatocellular carcinoma: a meta-analysis. Scand J Gastroenterol. 2017; 52(6-7): 624-634. PMID 28276833

52. Li Q, Wang J, Sun Y, et al. Efficacy of postoperative transarterial chemoembolization and portal vein chemotherapy for patients with hepatocellular carcinoma complicated by portal vein tumor thrombosis--a randomized study. World J Surg. Nov 2006; 30(11): 2004-11; discussion 2012-3. PMID 17058027

53. Zhong C, Guo RP, Li JQ, et al. A randomized controlled trial of hepatectomy with adjuvant transcatheter arterial chemoembolization versus hepatectomy alone for Stage III A hepatocellular carcinoma. J Cancer Res Clin Oncol. Oct 2009; 135(10): 1437-45. PMID 19408012

54. Peng BG, He Q, Li JP, et al. Adjuvant transcatheter arterial chemoembolization improves efficacy of hepatectomy for patients with hepatocellular carcinoma and portal vein tumor thrombus. Am J Surg. Sep 2009; 198(3): 313-8. PMID 19285298

55. Gui CH, Baey S, D'cruz RT, et al. Trans-arterial chemoembolization + radiofrequency ablation versus surgical resection in hepatocellular carcinoma - A meta-analysis. Eur J Surg Oncol. May 2020; 46(5): 763-771. PMID 31937433

56. Liu H, Wang ZG, Fu SY, et al. Randomized clinical trial of chemoembolization plus radiofrequency ablation versus partial hepatectomy for hepatocellular carcinoma within the Milan criteria. Br J Surg. Mar 2016; 103(4): 348-56. PMID 26780107

57. Ako S, Nakamura S, Nouso K, et al. Transcatheter Arterial Chemoembolization to Reduce Size of Hepatocellular Carcinoma before Radiofrequency Ablation. Acta Med Okayama. Feb 2018; 72(1): 47-52. PMID 29463938

58. Haochen W, Jian W, Li S, et al. Transarterial chemoembolization plus multi-imaging-guided radiofrequency ablation for elimination of hepatocellular carcinoma nodules measuring 3.1 to 5.0 cm: a single-center study. J Int Med Res. Jul 2018; 46(7): 2650-2657. PMID 29683022

59. Bholee AK, Peng K, Zhou Z, et al. Radiofrequency ablation combined with transarterial chemoembolization versus hepatectomy for patients with hepatocellular carcinoma within Milan criteria: a retrospective case-control study. Clin Transl Oncol. Jul 2017; 19(7): 844-852. PMID 28070766

60. Lan T, Chang L, Mn R, et al. Comparative Efficacy of Interventional Therapies for Early-stage Hepatocellular Carcinoma: A PRISMA-compliant Systematic Review and Network Meta-analysis. Medicine (Baltimore). Apr 2016; 95(15): e3185. PMID 27082558

61. Li L, Tian J, Liu P, et al. Transarterial chemoembolization combination therapy vs monotherapy in unresectable hepatocellular carcinoma: a meta-analysis. Tumori. Jun 02 2016; 2016(3): 301-10. PMID 27002950

62. Lu Z, Wen F, Guo Q, et al. Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: a meta-analysis of randomized-controlled trials. Eur J Gastroenterol Hepatol. Feb 2013; 25(2): 187-94. PMID 23134976

63. Wang X, Hu Y, Ren M, et al. Efficacy and Safety of Radiofrequency Ablation Combined with Transcatheter Arterial Chemoembolization for Hepatocellular Carcinomas Compared with Radiofrequency Ablation Alone: A Time-to-Event Meta-Analysis. Korean J Radiol. 2016; 17(1): 93-102. PMID 26798221

64. Peng ZW, Zhang YJ, Liang HH, et al. Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization and RF ablation versus RF ablation alone: a prospective randomized trial. Radiology. Feb 2012; 262(2): 689-700. PMID 22157201

65. Morimoto M, Numata K, Kondou M, et al. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. Cancer. Dec 01 2010; 116(23): 5452-60. PMID 20672352

66. Shibata T, Isoda H, Hirokawa Y, et al. Small hepatocellular carcinoma: is radiofrequency ablation combined with transcatheter arterial chemoembolization more effective than radiofrequency ablation alone for treatment?. Radiology. Sep 2009; 252(3): 905-13. PMID 19567647

67. Cheng BQ, Jia CQ, Liu CT, et al. Chemoembolization combined with radiofrequency ablation for patients with hepatocellular carcinoma larger than 3 cm: a randomized controlled trial. JAMA. Apr 09 2008; 299(14): 1669-77. PMID 18398079

68. DeAngelis CD, Fontanarosa PB. Retraction: Cheng B-Q, et al. Chemoembolization combined with radiofrequency ablation for patients with hepatocellular carcinoma larger than 3 cm: a randomized controlled trial. JAMA. 2008;299(14):1669-1677. JAMA. May 13 2009; 301(18): 1931. PMID 19380477

69. Yi Y, Zhang Y, Wei Q, et al. Radiofrequency ablation or microwave ablation combined with transcatheter arterial chemoembolization in treatment of hepatocellular carcinoma by comparing with radiofrequency ablation alone. Chin J Cancer Res. Feb 2014; 26(1): 112-8. PMID 24653633

70. Peng ZW, Zhang YJ, Chen MS, et al. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. J Clin Oncol. Feb 01 2013; 31(4): 426-32. PMID 23269991

71. Martin AP, Bartels M, Hauss J, et al. Overview of the MELD score and the UNOS adult liver allocation system. Transplant Proc. Dec 2007; 39(10): 3169-74. PMID 18089345

72. Organ Procurement and Transplantation Network (OPTN). OPTN Policies. Updated March 16, 2023; https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf. Accessed May 25, 2023.

73. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. Mar 14 1996; 334(11): 693-9. PMID 8594428

74. Pomfret EA, Washburn K, Wald C, et al. Report of a national conference on liver allocation in patients with hepatocellular carcinoma in the United States. Liver Transpl. Mar 2010; 16(3): 262-78. PMID 20209641

75. Butcher DA, Brandis KJ, Wang H, et al. Long-term survival and postoperative complications of pre-liver transplantation transarterial chemoembolisation in hepatocellular carcinoma: A systematic review and meta-analysis. Eur J Surg Oncol. Mar 2022; 48(3): 621-631. PMID 34774394

76. Si T, Chen Y, Ma D, et al. Transarterial chemoembolization prior to liver transplantation for patients with hepatocellular carcinoma: A meta-analysis. J Gastroenterol Hepatol. Jul 2017; 32(7): 1286-1294. PMID 28085213

77. Graziadei IW, Sandmueller H, Waldenberger P, et al. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. Liver Transpl. Jun 2003; 9(6): 557-63. PMID 12783395

78. Maddala YK, Stadheim L, Andrews JC, et al. Drop-out rates of patients with hepatocellular cancer listed for liver transplantation: outcome with chemoembolization. Liver Transpl. Mar 2004; 10(3): 449-55. PMID 15004776

79. Obed A, Beham A, Püllmann K, et al. Patients without hepatocellular carcinoma progression after transarterial chemoembolization benefit from liver transplantation. World J Gastroenterol. Feb 07 2007; 13(5): 761-7. PMID 17278200

80. Yao FY. Liver transplantation for hepatocellular carcinoma: beyond the Milan criteria. Am J Transplant. Oct 2008; 8(10): 1982-9. PMID 18727702

81. Gabr A, Abouchaleh N, Ali R, et al. Comparative study of post-transplant outcomes in hepatocellular carcinoma patients treated with chemoembolization or radioembolization. Eur J Radiol. Aug 2017; 93: 100-106. PMID 28668402

82. Park SY, Kim JH, Yoon HJ, et al. Transarterial chemoembolization versus supportive therapy in the palliative treatment of unresectable intrahepatic cholangiocarcinoma. Clin Radiol. Apr 2011; 66(4): 322-8. PMID 21356394

83. Seidensticker R, Seidensticker M, Doegen K, et al. Extensive Use of Interventional Therapies Improves Survival in Unresectable or Recurrent Intrahepatic Cholangiocarcinoma. Gastroenterol Res Pract. 2016; 2016: 8732521. PMID 26966431

84. Boehm LM, Jayakrishnan TT, Miura JT, et al. Comparative effectiveness of hepatic artery based therapies for unresectable intrahepatic cholangiocarcinoma. J Surg Oncol. Feb 2015; 111(2): 213-20. PMID 25176325

85. Knüppel M, Kubicka S, Vogel A, et al. Combination of conservative and interventional therapy strategies for intra- and extrahepatic cholangiocellular carcinoma: a retrospective survival analysis. Gastroenterol Res Pract. 2012; 2012: 190708. PMID 21776251

86. Tai E, Kennedy S, Farrell A, et al. Comparison of transarterial bland and chemoembolization for neuroendocrine tumours: a systematic review and meta-analysis. Curr Oncol. Dec 2020; 27(6): e537-e546. PMID 33380868

87. Nazario J, Gupta S. Transarterial liver-directed therapies of neuroendocrine hepatic metastases. Semin Oncol. Apr 2010; 37(2): 118-26. PMID 20494704

88. Ruutiainen AT, Soulen MC, Tuite CM, et al. Chemoembolization and bland embolization of neuroendocrine tumor metastases to the liver. J Vasc Interv Radiol. Jul 2007; 18(7): 847-55. PMID 17609443

89. Gupta S, Yao JC, Ahrar K, et al. Hepatic artery embolization and chemoembolization for treatment of patients with metastatic carcinoid tumors: the M.D. Anderson experience. Cancer J. 2003; 9(4): 261-7. PMID 12967136

90. Osborne DA, Zervos EE, Strosberg J, et al. Improved outcome with cytoreduction versus embolization for symptomatic hepatic metastases of carcinoid and neuroendocrine tumors. Ann Surg Oncol. Apr 2006; 13(4): 572-81. PMID 16511671

91. Rowcroft A, Loveday BPT, Thomson BNJ, et al. Systematic review of liver directed therapy for uveal melanoma hepatic metastases. HPB (Oxford). Apr 2020; 22(4): 497-505. PMID 31791894

92. Huppert PE, Fierlbeck G, Pereira P, et al. Transarterial chemoembolization of liver metastases in patients with uveal melanoma. Eur J Radiol. Jun 2010; 74(3): e38-44. PMID 19467811

93. Sharma KV, Gould JE, Harbour JW, et al. Hepatic arterial chemoembolization for management of metastatic melanoma. AJR Am J Roentgenol. Jan 2008; 190(1): 99-104. PMID 18094299

94. Bedikian AY, Legha SS, Mavligit G, et al. Treatment of uveal melanoma metastatic to the liver: a review of the M. D. Anderson Cancer Center experience and prognostic factors. Cancer. Nov 01 1995; 76(9): 1665-70. PMID 8635073

95. Patel K, Sullivan K, Berd D, et al. Chemoembolization of the hepatic artery with BCNU for metastatic uveal melanoma: results of a phase II study. Melanoma Res. Aug 2005; 15(4): 297-304. PMID 16034309

96. Zacharias AJ, Jayakrishnan TT, Rajeev R, et al. Comparative Effectiveness of Hepatic Artery Based Therapies for Unresectable Colorectal Liver Metastases: A Meta-Analysis. PLoS One. 2015; 10(10): e0139940. PMID 26448327

97. Richardson AJ, Laurence JM, Lam VW. Transarterial chemoembolization with irinotecan beads in the treatment of colorectal liver metastases: systematic review. J Vasc Interv Radiol. Aug 2013; 24(8): 1209-17. PMID 23885916

98. Swierz MJ, Storman D, Riemsma RP, et al. Transarterial (chemo)embolisation versus no intervention or placebo for liver metastases. Cochrane Database Syst Rev. Mar 12 2020; 3(3): CD009498. PMID 32163181

99. Hunt TM, Flowerdew AD, Birch SJ, et al. Prospective randomized controlled trial of hepatic arterial embolization or infusion chemotherapy with 5-fluorouracil and degradable starch microspheres for colorectal liver metastases. Br J Surg. Jul 1990; 77(7): 779-82. PMID 2200559

100. Eichler K, Zangos S, Mack MG, et al. First human study in treatment of unresectable liver metastases from colorectal cancer with irinotecan-loaded beads (DEBIRI). Int J Oncol. Oct 2012; 41(4): 1213-20. PMID 22842404

101. Martin RC, Scoggins CR, Tomalty D, et al. Irinotecan drug-eluting beads in the treatment of chemo-naive unresectable colorectal liver metastasis with concomitant systemic fluorouracil and oxaliplatin: results of pharmacokinetics and phase I trial. J Gastrointest Surg. Aug 2012; 16(8): 1531-8. PMID 22528576

102. Vogl TJ, Jost A, Nour-Eldin NA, et al. Repeated transarterial chemoembolisation using different chemotherapeutic drug combinations followed by MR-guided laser-induced thermotherapy in patients with liver metastases of colorectal carcinoma. Br J Cancer. Mar 27 2012; 106(7): 1274-9. PMID 22382689

103. Martin RC, Joshi J, Robbins K, et al. Hepatic intra-arterial injection of drug-eluting bead, irinotecan (DEBIRI) in unresectable colorectal liver metastases refractory to systemic chemotherapy: results of multi-institutional study. Ann Surg Oncol. Jan 2011; 18(1): 192-8. PMID 20740319

104. Aliberti C, Fiorentini G, Muzzio PC, et al. Trans-arterial chemoembolization of metastatic colorectal carcinoma to the liver adopting DC Bead®, drug-eluting bead loaded with irinotecan: results of a phase II clinical study. Anticancer Res. Dec 2011; 31(12): 4581-7. PMID 22199334

105. Fiorentini G, Aliberti C, Tilli M, et al. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. Anticancer Res. Apr 2012; 32(4): 1387-95. PMID 22493375

106. Martin RC, Scoggins CR, Schreeder M, et al. Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis. Cancer. Oct 15 2015; 121(20): 3649-58. PMID 26149602

107. Vogl TJ, Gruber T, Balzer JO, et al. Repeated transarterial chemoembolization in the treatment of liver metastases of colorectal cancer: prospective study. Radiology. Jan 2009; 250(1): 281-9. PMID 19092099

108. Vogl TJ, Mack MG, Balzer JO, et al. Liver metastases: neoadjuvant downsizing with transarterial chemoembolization before laser-induced thermotherapy. Radiology. Nov 2003; 229(2): 457-64. PMID 14500854

109. Hong K, McBride JD, Georgiades CS, et al. Salvage therapy for liver-dominant colorectal metastatic adenocarcinoma: comparison between transcatheter arterial chemoembolization versus yttrium-90 radioembolization. J Vasc Interv Radiol. Mar 2009; 20(3): 360-7. PMID 19167245

110. Rivera K, Jeyarajah DR, Washington K. Hepatectomy, RFA, and Other Liver Directed Therapies for Treatment of Breast Cancer Liver Metastasis: A Systematic Review. Front Oncol. 2021; 11: 643383. PMID 33842354

111. Vogl TJ, Naguib NN, Nour-Eldin NE, et al. Transarterial chemoembolization (TACE) with mitomycin C and gemcitabine for liver metastases in breast cancer. Eur Radiol. Jan 2010; 20(1): 173-80. PMID 19657653

112. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Biliary Tract Cancers, Version 2.2023. Updated May 10, 2023. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed May 24, 2023.
113. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. Jan 2018; 67(1): 358-380. PMID 28130846
114. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Neuroendocrine and Adrenal Tumors, Version 2.2022. Updated December 21, 2022. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed May 22, 2023.
115. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Melanoma: Uveal , Version 1.2023. Updated May 4, 2023. https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf. Accessed May 23, 2023.
116. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Colon Cancer, Version 2.2023. Updated April 25, 2023. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed May 25, 2023.
117. Chiorean EG, Nandakumar G, Fadelu T, et al. Treatment of Patients With Late-Stage Colorectal Cancer: ASCO Resource-Stratified Guideline. JCO Glob Oncol. Mar 2020; 6: 414-438. PMID 32150483
118. Morris VK, Kennedy EB, Baxter NN, et al. Treatment of Metastatic Colorectal Cancer: ASCO Guideline. J Clin Oncol. Jan 20 2023; 41(3): 678-700. PMID 36252154
119. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Breast Cancer, Version 4.2023. Updated March 23, 2023. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed May 26, 2023.

Documentation for Clinical Review

Please provide the following documentation:
- History and physical and/or consultation notes including:
  - Clinical indications/justification of procedure
  - Child-Pugh score (if applicable)
  - Eastern Cooperative Oncology Group functional status (if applicable)
  - Previous treatment(s), duration, and response(s)
  - Treatment plan
  - Tumor type and description (i.e., resectable or unresectable, primary or metastatic, tumor burden [e.g., liver dominant])
  - Transplant status if applicable
- Pertinent radiological imaging results (i.e., abdominal CT and/or MRI and/or PET)
- Pathology report including tumor node metastasis (TNM) classification
- Current serum chemistry, liver function tests, and tumor marker results as applicable

Post Service (in addition to the above, please include the following):
- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for

clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction
	75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
HCPCS	C1982	Catheter, pressure generating, one-way valve, intermittently occlusive
	Q0083	Chemotherapy administration by other than infusion technique only (e.g., subcutaneous, intramuscular, push), per visit

Policy History

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

Effective Date	Action
02/27/2015	BCBSA Medical Policy adoption
10/01/2016	Policy revision without position change
09/01/2017	Policy revision without position change
09/01/2018	Policy revision without position change
09/01/2019	Policy revision without position change
03/01/2020	Coding update
09/01/2020	Annual review. Policy statement, guidelines and literature review updated.
09/01/2021	Annual review. Policy statement, guidelines and literature review updated.
09/01/2022	Annual review. Policy statement, guidelines and literature review updated.
09/01/2023	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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

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

effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

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

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**

Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies 8.01.11
 	
Policy Statement:
I. Transcatheter arterial chemoembolization (TACE) of the liver may be considered **medically necessary** for **any** of the following:
  A. 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
  B. As a bridge to transplant in individuals with hepatocellular cancer where **all** of the following are met:
    1. The intent is to prevent further tumor growth and to maintain an individual's candidacy for liver transplant
    2. Presence of hepatic tumor(s) meeting **one** of the following:
      a. Single tumor less than or equal to 5 cm
      b. Presence of no more than 3 tumors each less than 3 cm in size
    3. Absence of extrahepatic disease or vascular invasion
    4. Child-Pugh score of either A or B
  C. To treat liver metastasis in symptomatic individuals (e.g., wheezing, flushing of the skin, abdominal cramps, diarrhea, heart disease) with metastatic neuroendocrine tumor whose symptoms persist despite systemic therapy (e.g., Octreotide therapy) and who are not candidates for surgical resection
  D. To treat liver metastasis in individuals with liver-dominant metastatic uveal melanoma
 	
II. Transcatheter arterial chemoembolization of the liver is considered **investigational**:
  A. As neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable
  B. As part of combination therapy (with radiofrequency ablation) for resectable or unresectable hepatocellular carcinoma
  C. To treat unresectable cholangiocarcinoma
	Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies 8.01.11
	
	Policy Statement:
	I. Transcatheter arterial chemoembolization (TACE) of the liver may be considered **medically necessary** for **any** of the following:
	  A. 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
	  B. As a bridge to transplant in individuals with hepatocellular cancer where **all** of the following are met:
	    1. The intent is to prevent further tumor growth and to maintain an individual's candidacy for liver transplant
	    2. Presence of hepatic tumor(s) meeting **one** of the following:
	      c. Single tumor less than or equal to 5 cm
	      d. Presence of no more than 3 tumors each less than 3 cm in size
	    3. Absence of extrahepatic disease or vascular invasion
	    4. Child-Pugh score of either A or B
	  C. To treat liver metastasis in symptomatic individuals (e.g., wheezing, flushing of the skin, abdominal cramps, diarrhea, heart disease) with metastatic neuroendocrine tumor whose symptoms persist despite systemic therapy (e.g., Octreotide therapy) and who are not candidates for surgical resection
	  D. To treat liver metastasis in individuals with liver-dominant metastatic uveal melanoma
	
	II. Transcatheter arterial chemoembolization of the liver is considered **investigational**:
	  A. As neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable
	  B. As part of combination therapy (with radiofrequency ablation) for resectable or unresectable hepatocellular carcinoma
	  C. To treat unresectable cholangiocarcinoma

POLICY STATEMENT
(No changes)

BEFORE	AFTER
D. 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 E. To treat hepatocellular tumors prior to liver transplantation except as noted above	D. 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 E. To treat hepatocellular tumors prior to liver transplantation except as noted above