Policy Statement

I. Initial radioembolization of tumors of the liver may be considered **medically necessary** for a patient with **all** of the following:
   A. The treatment is NOT a repeat session
   B. Adequate functional status (Eastern Cooperative Oncology Group Performance Status [ECOG] 0 to 2)
   C. Adequate liver function and reserve
   D. Child-Pugh class A or B
   E. Liver-dominant metastases
   F. Documentation of **one or more** of the following:
      1. Primary hepatocellular carcinoma that is unresectable (greater than 3 cm) and limited to the liver
      2. Primary hepatocellular carcinoma as a bridge to liver transplantation
      3. Unresectable primary intrahepatic cholangiocarcinoma
      4. Hepatic metastases from neuroendocrine tumors (carcinoid and noncarcinoid) if **all** of the following are met:
         a. Disease is diffuse and symptomatic
         b. Systemic therapy has failed to control symptoms
      5. Liver dominant unresectable hepatic metastases from colorectal carcinoma, melanoma (ocular or cutaneous), or breast cancer that are progressive, diffuse, and **one or more** of the following:
         a. Refractory to chemotherapy
         b. Not a candidate for chemotherapy or other systemic therapies

II. Radioembolization is considered **investigational** for all other hepatic metastases except as noted above.

III. Radioembolization is considered **investigational** for all other indications not described above.

See Policy Guidelines for allowable codes/number of units.

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

Policy Guidelines

In general, "diffuse" disease is tumor tissue that has spread throughout the affected organ (e.g., diffuse liver disease).

There is little information on the safety or efficacy of repeated radioembolization treatments or on the number of treatments that should be administered.

Eastern Cooperative Oncology Group Performance Status[77]

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

Hepatic Metastases from Neuroendocrine Tumors

Symptomatic disease from metastatic neuroendocrine tumors refers to symptoms related to excess hormone production. Vasoactive peptides that would normally be cleared by the enterohepatic circulation can cause profuse diarrhea, flushing, bronchospasm, damage to heart valves, and myriad other symptoms due to varied peptide hormone secretion.[78] Classically, the carcinoid syndrome is characterized by episodic flushing, tachycardia, diarrhea and bronchospasm.[79]

Examples of neuroendocrine tumors:

- Carcinoid Tumors 74-+
- Islet Cell Tumors (also known as 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)

Neuroendocrine tumors are also referred to by their anatomical location: (e.g., pulmonary neuroendocrine tumors; gastroenteropancreatic neuroendocrine tumors).

Coding

The coding for radioembolization may depend on the medical specialty providing therapy. The following CPT codes might be used:

- **77261:** Therapeutic radiology treatment planning; simple
- **77262:** Therapeutic radiology treatment planning; intermediate
- **77263:** Therapeutic radiology treatment planning; complex
- **77280:** Therapeutic radiology simulation-aided field setting; simple
- **77285**: Therapeutic radiology simulation-aided field setting; intermediate
- **77290**: Therapeutic radiology simulation-aided field setting; complex
- **77295**: 3-dimensional radiotherapy plan, including dose-volume histograms
- **77300**: Basic radiation dosimetry calculation, central axis depth dose calculation, TDF, NSD, gap calculation, off axis factor, tissue inhomogeneity factors, calculation of non-ionizing radiation surface and depth dose, as required during course of treatment, only when prescribed by the treating physician
- **75894**: Transcatheter therapy, embolization, any method, radiological supervision and interpretation
- **77778**: Interstitial radiation source application, complex, includes supervision, handling, loading of radiation source, when performed
- **79445**: Radiopharmaceutical therapy, by intra-arterial particulate administration

The following code is available for the embolization 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

Because this therapy involves radiotherapy, a variety of radiotherapy planning codes may be a component of the overall procedure. For example, CPT code 77399 (unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services) may be used.

The following HCPCS code is also available for radioembolization:

- **S2095**: Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres

Allowable Codes and Frequencies for Brachytherapy

Description	Code	Maximum per course of treatment	Notes
Clinical Treatment Planning	77261, 77262 or 77263	1	When used as standalone or with external beam, only one plan is allowed.
Simulation	77280, 77285, 77290	5	May not be billed with 77301
Verification Simulation	77280	5	May not be billed with 77301
Respiratory Motion Management	77293	0	Not needed for brachytherapy alone
3D CRT Plan	77295	1 per insertion, max 5	May not be billed with 77301 or with 77316/77317/77318
Brachytherapy Isodose Plan	77316, 77317 or 77318	1 per insertion, max 5	cannot be billed along with 77295
Special Radiation Physics Consult	77370	0	May allow x 1; documentation of medical necessity required
Special MD Consultation (Special Tx Procedure)	77470	1	May allow x 1; documentation of medical necessity required for more than 1 unit
Supervision, Handling, Loading of Radiation Source	77790	1	May not be billed with 77761, 77762, 77763, 77770, 77771, 77772 or 77778
Application of Radiation Sources: LDR Brachytherapy	77761, 77762, 77763, 77778	1	May not be billed with 77770, 77771, 77772
Application of Radiation Sources: HDR Brachytherapy	77770, 77771, 77772	4	Only one delivery code allowed per day per course of therapy. May not be billed with 77761, 77762, 77763, 77778, 77790.
High Dose Rate Electronic Brachytherapy, per fraction	0394T-0395T	0	Investigational for the treatment of skin lesions.
Placement of Radiotherapy Afterloading Catheters	19296, 19297, 19298	1	

Description

Radioembolization (RE), also referred to as selective internal radiotherapy, delivers small beads (microspheres) impregnated with yttrium 90 intra-arterially via the hepatic artery. The microspheres, which become permanently embedded, are delivered to tumors preferentially because the hepatic circulation is uniquely organized, whereby tumors greater than 0.5 cm rely on the hepatic artery for blood supply while the normal liver is primarily perfused via the portal vein. Radioembolization has been proposed as a therapy for multiple types of primary and metastatic liver tumors.

Related Policies

- Cryosurgical Ablation of Primary or Metastatic Liver Tumors
- Microwave and Locoregional Laser Tumor Ablation
- Radiation Oncology
- Radiofrequency Ablation of Primary or Metastatic Liver Tumors
- Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

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

Currently, 2 forms of Y90 microspheres have been approved by the FDA.

In 1999, TheraSphere® (Boston Scientific; previously manufactured by Nordion, under license by BTG International), a glass sphere system, was approved by the FDA through the humanitarian drug exemption process for radiotherapy or as a neoadjuvant treatment to surgery or transplantation in patients with unresectable hepatocellular carcinoma who can have placement of appropriately positioned hepatic arterial catheters (H980006).

On March 17, 2021, TheraSpherereceived approval through the premarket approval process for use as selective internal radiation therapy (SIRT) for local tumor control of solitary tumors (1-8 cm in diameter), in patients with unresectable hepatocellular carcinoma, Child-Pugh Score A cirrhosis, well-compensated liver function, no macrovascular invasion, and good performance status (P200029).

In 2002, SIR-Spheres® (ex Medical), a resin sphere system, was approved by the FDA through the premarket approval process for the treatment of inoperable colorectal cancer metastatic to the liver (P990065).

FDA product code: NAW.

Rationale

Background
Treatments for Hepatic and Neuroendocrine Tumors
The use of external-beam radiotherapy and the application of more advanced radiotherapy approaches (e.g., intensity-modulated radiotherapy) may be of limited use in patients with multiple diffuse lesions due to the low tolerance of the normal liver to radiation compared with the higher doses of radiation needed to kill the tumor.

Various nonsurgical ablative techniques have been investigated that seek to cure or palliate unresectable hepatic tumors by improving locoregional control. These techniques rely on extreme temperature changes (cryosurgery or radiofrequency ablation), particle and wave physics (microwave or laser ablation), or arterial embolization therapy including chemo-embolization, bland embolization, or radioembolization.

Radioembolization
Radioembolization (referred to as selective internal radiotherapy in older literature) delivers small beads (microspheres) impregnated with yttrium-90 (Y90) intra-arterially via the hepatic artery. The microspheres, which become permanently embedded, are delivered to tumors preferentially because the hepatic circulation is uniquely organized, whereby tumors greater

than 0.5 cm rely on the hepatic artery for blood supply while the normal liver is primarily perfused via the portal vein. Y90 is a pure beta-emitter with a relatively limited effective range and a short half-life that helps focus the radiation and minimize its spread. Candidates for radioembolization are initially examined by hepatic angiogram to identify and map the hepatic arterial system. At that time, a mixture of technetium 99-labeled albumin particles are delivered via the hepatic artery to simulate microspheres. Single-photon emission computed tomography is used to detect possible shunting of the albumin particles into the gastrointestinal or pulmonary vasculature.

Currently, 2 commercial forms of Y90 microspheres are available: a glass sphere (TheraSphere) and a resin sphere (SIR-Spheres). Noncommercial forms are mostly used outside the U.S. While the commercial products use the same radioisotope (Y90) and have the same target dose (100 gray), they differ in microsphere size profile, base material (i.e., resin vs glass), and size of commercially available doses. The physical characteristics of the active and inactive ingredients affect the flow of microspheres during injection, their retention at the tumor site, spread outside the therapeutic target region, and dosimetry calculations. The U.S. Food and Drug Administration granted premarket approval of SIR-Spheres for use in combination with 5-floxuridine chemotherapy by hepatic arterial infusion to treat unresectable hepatic metastases from colorectal cancer. In contrast, TheraSphere's glass sphere was approved under a humanitarian device exemption for use as monotherapy to treat unresectable hepatocellular carcinoma. In 2007, this humanitarian device exemption was expanded to include patients with hepatocellular carcinoma who have partial or branch portal vein thrombosis. For these reasons, results obtained with a product do not necessarily apply to another commercial (or non-commercial) products (see Regulatory Status section).

Literature Review

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Radioembolization or Radioembolization Plus Liver Transplant for Unresectable Hepatocellular Carcinoma

Clinical Context and Therapy Purpose

The purpose of radioembolization (RE) or RE plus liver transplant in patients who have unresectable hepatocellular carcinoma (HCC) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does RE improve the net health outcome 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 who may or may not need a liver transplant. Most patients with HCC present with unresectable disease and treatment options are limited secondary to the chemoresistance of HCC and the intolerance of normal liver parenchyma to tumoricidal radiation doses.

Interventions
The treatment being considered is RE with or without a liver transplant. RE may also be referred to as selective internal radiation therapy (SIRT) or transarterial radioembolization (TARE).

Comparators
The following are comparators to RE in the treatment of patients with unresectable HCC: standard of care, often palliative. Results of 2 RCTs have shown a survival benefit for transarterial chemoembolization (TACE) therapy compared with supportive care in patients with unresectable HCC.[1,2] One study randomized patients to TACE, transarterial embolization (TAE), or supportive care. One-year survival rates for TACE, TAE, and supportive care were 82%, 75%, and 63%, respectively; 2-year survival rates were 63%, 50%, and 27%, respectively. Targeted therapies have been investigated for HCC. For example, sorafenib was associated with improved overall survival (OS) in a randomized phase 3 trial evaluating 602 patients.[3]

Outcomes
The general outcomes of interest are OS, functional outcomes, quality of life, and treatment-related morbidity.

Table 1. Outcomes of Interest for Individuals with Unresectable Hepatocellular Carcinoma

Outcomes	Details
Treatment-related morbidity	Outcomes of interest include complete remission, partial response, PFS, overall survival and stable disease [Timing: ≥3 months up to 5 years]

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
- Within each category of study design, larger sample size studies and longer duration studies were preferred.
- Studies with duplicative or overlapping populations were excluded.

Radioembolization for Unresectable Hepatocellular Carcinoma
Review of Evidence

Systematic Reviews
Various meta-analyses have been performed to compare the effects of TACE, drug-eluting bead (DEB) plus TACE (DEB-TACE), and RE in patients with unresectable HCC, each of which performed slightly different analyses (e.g., pairwise vs indirect comparisons and assessment of different outcomes or comparator groups). Results of these meta-analyses are summarized below.

Abdel-Rahman et al (2020) conducted a meta-analysis of RCTs comparing RE alone or combined with other systemic or locoregional treatments to placebo, no treatment, or other similar interventions in patients with unresectable HCC.[4] Six RCTs (N =1340) were identified, all of which were assessed by authors as being at high risk of bias. The authors reported the certainty of evidence as low to very low. Meta-analysis was able to be performed using data from more than 1 RCT for few comparisons. Based on meta-analysis of 2 RCTS, disease control rate was not significantly different between RE and sorafenib (relative risk [RR], 0.94; 95% confidence interval [CI], 0.84 to 1.05), though RE was associated with less hand-foot skin reactions (RR, 0.02; 95% CI, 0.00 to 0.06), skin rash (RR, 0.11; 95% CI, 0.04 to 0.34), diarrhea (RR, 0.11, 95% CI, 0.04 to 0.34), and hypertension (RR, 0.10; 95% CI, 0.01 to 0.88). Based on meta-analysis of 3 RCTs, the risk of serious adverse events did not differ between RE and TACE (RR, 1.47; 95% CI, 0.66 to 3.25). Meta-analysis could not be performed for other comparisons; thus, results of other included trials are described individually in the section below on RCTs.[5,6,]

Venerito et al (2020) performed a meta-analysis to assess the noninferiority of as monotherapy or followed by sorafenib versus sorafenib monotherapy on OS.[7,] A noninferiority margin of 1.08 in terms of hazard ratio (HR) was prespecified. Three RCTs were included (N =1,243), and meta-analysis demonstrated with or without sorafenib was noninferior to sorafenib monotherapy in OS (median, 10.2 and 9.2 months; HR, 0.91; 95% CI, 0.78 to 1.05). Treatment-related severe adverse events were reported in 28.9% vs 43.3% of patients treated with and sorafenib monotherapy, respectively (p<.01)

Yang et al (2020) conducted a meta-analysis of RCTs to compare effects of DEB-TACE, TACE, and RE on the primary outcome of OS.[8,] Compared with TACE, RE was associated with similar 1-year OS (RR, 0.91; 95% CI 0.79 to 1.05), but a better OS than TACE at 2 years (RR, 0.87; 95% CI, 0.80 to 0.95) and 3 years (RR, 0.90; 95% CI 0.85 to 0.96). Overall survival was not significantly different between RE and DEB-TACE at 1 year (RR, 0.83, 95% CI, 0.68 to 1.02), but DEB-TACE was associated with better OS at 2 years than RE (RR, 0.40; 95% CI, 0.19 to 0.84). However, pooled HRs indicated that RE was superior to TACE in OS (HR, 0.84; 95% CI, 0.70 to 1.00) and that DEB-TACE was superior to RE in OS (HR, 0.59; 95% CI, 0.38 to 0.91).

Tao et al (2017) reported on a network meta-analysis comparatively evaluating 9 minimally invasive surgeries for treatment of unresectable HCC.[3,] The interventions included were TACE, TACE plus sorafenib, sorafenib, TACE plus high-intensity focused ultrasound, TACE plus percutaneous ethanol injection, DEB-TACE , yttrium-90 (Y90) RE, TACE plus external-beam radiation therapy (EBRT), and ethanol ablation. The network included 17 studies with 2669 patients and 4 studies with 230 patients including Y90 RE. In a pairwise meta-analysis, patients treated with Y90 RE were more likely to achieve complete remission than those who received TACE (odds ratio [OR], 4.5; 95% CI, 1.3 to 15.1). However, in the network meta-analysis, there was no significant difference between the corresponding 8 treatments and TACE with respect to complete remission, partial response, stable disease, and objective response rate. The treatments were ranked for several outcomes using surface under the cumulative ranking curves. TACE plus EBRT had the highest surface under the cumulative ranking curves in complete remission (77%), partial response (89%), progressive disease (95%), and objective response rate (81%).

Ludwig et al (2017) conducted an indirect meta-analysis of studies that compared DEB-TACE with Y90 RE for HCC.[9,] Fourteen studies (N =2065 patients) comparing DEB-TACE or Y90 RE with conventional TACE for primary HCC treatment were included. The pooled estimate of median survival was 23 months for DEB-TACE and 15 months for RE. The estimated 1-year survival was significantly higher for DEB-TACE (79%) than for RE (55%; OR=0.57; 95% CI, 0.36 to 0.92; p=.02). Survival did not differ statistically significantly at 2 or 3 years but did favor DEB-TACE. At 2 years, survival was 61% for DEB-TACE and 34% for RE (OR=0.65; 95% CI, 0.29 to 1.44; p=.29) and at 3 years survival was 56% and 21% (OR=0.71; 95% CI, 0.21 to 2.55; p=.62), respectively.

Two systematic reviews published in 2016 compared RE with TACE for the treatment of unresectable HCC. Lobo et al (2016) selected 5 retrospective observational studies (N =533 patients).[10,] Survival at 1 year did not differ statistically between RE (42%) and TACE (46%; RR, 0.93; 95% CI, 0.81 to 1.08; p=.33). At 2 years, the survival rate was higher for RE (27% vs 18%;

RR=1.36; 95% CI, 1.05 to 1.76; p=.02), but there was no statistically significant difference in survival rates at 3, 4, or 5 years. Postprocedural complications were also similar in the 2 groups. Facciorusso et al (2016) included 10 studies (N =1557 patients), 2 of which were RCTs.[11.] The OR for survival was not statistically significant at 1 year (OR=1.0; 95% CI, 0.8 to 1.3; p=.93) but favored RE in years 2 (OR=1.4; 95% CI, 1.1 to 1.90; p=.01) and 3 (OR=1.5; 1.0 to 2.1; p=.04).

Vente et al (2009) conducted a meta-analysis evaluating tumor response and survival in patients who received a Y90 glass or resin microsphere RE for the treatment of primary HCC or metastases from colorectal cancer (CRC).[12.] (Refer to the Unresectable Metastatic CRC section for the data from the meta-analysis as pertains to that disease.) Selected studies were from 1986 through 2008 and presented tumor response (measured by computed tomography) and data on median survival times. To allow comparability of results for tumor response, the category of "any response" was introduced and included complete remission, partial response, and stable disease. Overall tumor response could only be assessed as any response because response categories were not uniformly defined in the analyzed studies. In 14 articles, clinical data were presented on tumor response and survival for 425 patients with HCC who had received Y90 RE. Treatment with resin microspheres (0.89) was associated with a significantly higher proportion of any response than glass microsphere treatment (0.78; p=.02). Median survival was reported in 7 studies, in which survival time was defined as survival from microsphere treatment or diagnosis or recurrence of HCC. Median survival from microsphere treatment varied between 7.1 months and 21.0 months, and median survival from diagnosis or recurrence ranged from 9.4 to 24.0 months.

Randomized Controlled Trials

Kolligs et al (2015) reported on results for a small pilot RCT (the selective internal radiation therapy vs chemoembolization in unresectable hepatocellular carcinoma study) comparing RE with TACE for the treatment of unresectable HCC.[5.] The trial included 28 subjects with unresectable HCC, preserved liver function, and an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 2 or less, with no vascular invasion or extrahepatic spread, who had 5 or fewer liver lesions or a single lesion of 10 cm or less. Patients were randomized to RE (n=13) or TACE (n=15). Over posttreatment follow-up, partial response rates were 13.3% for TACE and 30.8% for RE, with disease control rates (complete remission, stable disease, partial response) of 73.3% for TACE and 76.9% for RE. Median progression-free survival (PFS) was 3.6 months for TACE and 3.7 months for RE.

Pitton et al (2015) reported on results from a small RCT comparing RE with DEB-TACE for the treatment of unresectable HCC.[6.] The trial included 24 patients, with 12 randomized to each group. No deaths occurred within 30 days of the procedure. There were no statistically significant differences between groups in terms of PFS (180 days for RE vs 216 days for DEB-TACE, p=.619) or OS (592 days for RE vs 788 days for DEB-TACE, p=.927).

Nonrandomized Comparative Studies

Facciorusso et al (2020) performed a retrospective analysis that compared patients with HCC treated with RE plus sorafenib (n=45) with propensity score-matched patients treated with sorafenib alone (n=90).[13.] No significant differences were identified in median OS (10 vs. 10 months; p=.711), median PFS (6 versus 7 months; p=.992), and objective response rate (45.5% versus 42.8%; p=1).

Padia et al (2017) reported on a single-center, retrospective study (2010-2015) comparing segmental RE with segmental chemoembolization in 101 patients with localized, unresectable HCC not amenable to ablation.[14.] Patients receiving chemoembolization had poorer ECOG Performance Status ratings and Child-Pugh class while those receiving RE had larger and more infiltrative tumors. Overall complete remission was 84% with RE and 58% with chemoembolization (p=.001). Median PFS was 564 days and 271 days (p=.002) and median OS was 1198 days and 1043 days (p=.35), respectively, for the RE group and the chemotherapy group.

Soydal et al (2016) retrospectively assessed outcomes for patients receiving RE and TACE for HCC.[15] Each group included 40 patients. RE patients had a mean survival of 39 months vs 31 months for TACE patients (p=.014). There were no significant differences in complication or disease recurrence rates.

Oladeru (2016) retrospectively analyzed Surveillance, Epidemiology, and End Results registry data, comparing survival outcomes for patients with HCC receiving RE with EBRT.[16] A total of 189 patients with unresectable HCC (77 receiving RE, 112 receiving EBRT) were treated between 2004 and 2011. Median OS for RE was 12 months and 14 months for EBRT. Median disease-specific survival was identical for both groups at 14 months. After adjustment for differences between patients, multivariable survival analysis showed no association between treatment and OS or disease-specific survival.

El Fouly et al (2015) reported on results of a nonrandomized study comparing RE with TACE for 86 patients with intermediate stage, nonresectable HCC.[17] Sixty-three patients at a single institution were treated with TACE, while 53 patients at a second institution were treated with RE. Median OS for TACE (18 months) and RE (16.4 months) did not differ significantly between groups; similarly, the median time to progression did not differ significantly between groups (6.8 months for TACE vs 13.3 months for RE). TACE patients had more treatment sessions, lengthier hospital stays, and higher adverse event rates.

Gramenzi et al (2015) conducted a retrospective cohort study comparing RE with the kinase inhibitor sorafenib for intermediate- or advanced-stage HCC.[18] Patients with HCC refractory to other therapies and no metastases or systemic chemotherapy were included, 74 of whom were treated with sorafenib and 63 with RE. Median OS between groups was similar (14.4 months for sorafenib-treated patients vs 13.2 months for RE-treated patients). After propensity-score matching of 32 subjects in each group, there were no significant differences in median OS or 1-, 2-, and 3-year survival rates between groups.

Carr et al (2010) reported on a consecutive series of patients with HCC seen at a single medical center and not candidates for surgical resection.[19] Patients received conventional cisplatin-TACE between the years 1992 and 2000 (n=691), Y90 microspheres between 2000 and 2005 (n=99), or no treatment (n=142). Median OS for the Y90 group was 11.5 months (95% CI, 8 to 16 months) and 8.5 months (95% CI, 8 to 10 months) for the TACE group (p<.05). Untreated patients had a median survival of 2 months. Although the authors detected a slight selection bias toward milder disease in the RE group, they concluded that Y90 and TACE appeared to be equivalent regional therapies for patients with unresectable, nonmetastatic HCC.

Section Summary: Radioembolization for Unresectable Hepatocellular Carcinoma
Radioembolization has been compared with alternative treatments for HCC, including TACE, DEB-TACE, TACE plus EBRT, and sorafenib. Systematic reviews, RCTs, and nonrandomized comparative studies reported varied treatment superiority in tumor response and survival outcomes. Although rigorous comparative RCTs are lacking, if the active comparators are effective treatments for HCC, then these results are consistent with some degree of efficacy for RE in the treatment of HCC. In all studies reviewed, tumor response is observed, which may improve survival.

Radioembolization as a Bridge to Liver Transplantation for Unresectable Hepatocellular Carcinoma

Review of Evidence

Systematic Reviews

Kulik et al (2018) published a systematic review of 18 comparative studies and 31 non-comparative studies that included patients with unresectable HCC who needed a liver transplant and received transplant alone or some type of bridging therapy as well (see Table 2).[20] Of the 18 comparative studies, 2 studies (n=257 patients) reported on the incidence of dropout from transplantation wait-lists, and patients receiving bridging therapy. This group had reduced risk of dropout due to disease progression, compared with those receiving transplantation alone (RR=0.32) (see Table 3). Between-group differences were not statistically significant for mortality (5 comparative studies; n=531 patients) or recurrence rate (10 comparative studies; n=889 patients). Subgroup analysis was conducted for types of bridging therapy: for all-cause mortality after transplantation, the RR was 1.124 with transarterial embolization (TAE) compared with transplantation alone (1 cohort). For disease recurrence, the RR for this bridging therapy type was 2.374 compared with transplantation alone. No RCTs were identified, and most of the selected studies had a high risk of bias on patient selection.

Table 2. Characteristics of Systematic Reviews

Study	Dates	Trials	Participants[a]	Design
Kulik et al (2018)[20]	1996-2016	49	Unresectable hepatocellular carcinoma	• 18 comparative • 31 noncomparative

[a] Patients needed liver transplantation and received transplant alone or bridging therapy in addition to transplant.

Table 3. Results of Systematic Reviews

Study	Dropout From Wait-list	Mortality	Recurrence Rate	Subgroup Analysis by Therapy Type	Comments
Kulik et al (2018)[20]					
Comparative studies (N=18)	2 studies (n=257 patients)	5 studies (n=531 patients)	10 studies (n=889 patients)		
	Reduced risk of dropout in patients with bridging therapy vs transplant alone (RR=0.32; 95% CI, 0.06 to 1.85; I2=0%)	Nonsignificant between-group difference	Nonsignificant between-group difference	• All-cause mortality: TAE vs transplant alone, RR=1.124 (95% CI, 0.675 to 1.873) • Recurrence: TAE vs transplant alone, RR=2.374 (95% CI, 0.609 to 9.252)	No RCTs identified; many studies had high-risk of bias for patient selection.

CI: confidence interval; RCTs: randomized controlled trials; RR: relative risk; TAE: transarterial embolization.

Randomized Controlled Trials

Salem et al (2016) reported on results of a phase 2 RCT comparing conventional TACE with TheraSphere RE (Y90) for treatment of unresectable, unablatable HCC.[21] Twenty-four patients were assigned to Y90 and 21 patients to TACE; the ultimate endpoint of treatment for these patients was liver transplantation. The primary outcome was time to progression using intention-to-treat analysis. Median follow-up was 17 months. In the TACE group, there were 7 transplants at a median of 9 months (range, 3-17 months). In the Y90 group, there were 13 transplants at a median of 9 months (range, 4-15 months). Median time to progression exceeded 26 months in the Y90 group and 6.8 months in the TACE group (hazard ratio, 0.12; 95% CI, 0.03 to 0.56; p=.007). Median survival was 19 months with Y90 and 18 months in TACE (p=0.99). Adverse events were similar between groups, with the exception of more diarrhea (21% vs 0%) and hypoalbuminemia (58% vs 4%) in the conventional TACE group. A limitation of the OS analysis was the censoring of the survival outcome at liver transplantation given that transplantation is related to the treatment effect.

Kulik et al (2014) reported on results of a pilot RCT of Y90 RE with or without sorafenib for patients who had HCC and were awaiting liver transplantation.[22] The trial randomized 23 subjects; after accounting for losses due to self-withdrawal from the trial, failure to confirm HCC, and death, the modified intention-to-treat population included 10 subjects randomized to RE alone and 10 randomized to RE plus sorafenib. Overall, 17 of 20 patients underwent liver transplantation, with no difference in median time-to-transplant between groups. However, the addition of sorafenib was associated with increased peritransplant biliary complications and acute rejection.

Nonrandomized Studies

Salem et al (2021) reported the results of the multicenter, single-arm, retrospective LEGACY trial investigating Y90 RE with TheraSphere for the treatment of solitary, unresectable HCC.[23] The aim of the study was to evaluate the objective response rate (ORR) and the duration of response based on modified RECIST criteria as evaluated by blinded, independent, central review. Eligibility criteria included: solitary HCC ≤8 cm, Child-Pugh A cirrhosis, and ECOG performance status 0-1. Of 162 enrolled patients, 60.5% were ECOG 0 and RE served as neoadjuvant therapy for transplantation or resection in 21% and 6.8% of patients, respectively. Median follow-up duration was 29.9 months. ORR (best response) was 88.3% (95% CI, 82.4 to 92.4) with 62.2% (95% CI, 54.1 to 69.8) exhibiting a duration of response ≥6 months. Three-year OS was 86.6% for all patients and 92.8% for neoadjuvant patients resected or transplanted. This study supported FDA premarket approval of TheraSphere for use in HCC.[24]

Pellegrinelli et al (2021) reported on an 8-year single-center experience utilizing RE for the treatment of patients with unresectable HCC (n=44), metastatic colorectal cancer (n=20), and intrahepatic cholangiocarcinoma (n=6).[25] Treatment with prior chemotherapy was reported in 48.6% of all patients, and RE-related grade 3 or higher adverse events impacted 17.1% of patients. Patients were treated with RE as bridge to transplant (4.3%), for downstaging prior to surgical resection (15.7%), as ablative therapy (1.4%), and for palliative treatment (78.6%). Median follow-up was 32.1 months, during which disease progression occurred in 63 (90%) of all patients. Among patients with HCC at study end, complete and partial responses were achieved in 1 and 2 patients, respectively. Median OS was 16.1 months (range, 1.0 to 72.5 months) with no significant differences in survival among disease groups.

Gabr et al (2020) performed a retrospective review that reported on long-term outcomes of liver transplantation for patients with HCC who were bridged or downstaged with RE.[26] From 2004 to 2018, 207 patients underwent transplant after RE. Median OS from transplant was 12.5 years, with median time to liver transplantation of 7.5 months (interquartile range, 4.4 to 10.3). Overall, 169 patients were bridged and 38 were downstaged to liver transplant. Overall survival rates at 3, 5, and 10 years were 84%, 77%, and 60%, respectively.

Zori et al (2020) performed a retrospective cohort analysis that compared patients with HCC undergoing bridging locoregional therapy with RE (n=28) to TACE (n=37) prior to liver transplant.[27] Three-year survival was not significantly different with RE vs TACE (92.9% vs. 75.7%; p=.052). However, microvascular invasion occurred in 3.6% versus 27% of patients treated with RE versus TACE (p=.013).

In a retrospective review, Tohme et al (2013) reported on 20 consecutive HCC patients awaiting liver transplant who received RE as bridge therapy.[28] When RE began, Milan criteria were met by 14 patients and sustained until transplantation. Of the 6 patients who did not meet Milan criteria initially, RE was able to downstage 2 patients to meet Milan criteria. After RE, the median time to liver transplant was 3.5 months. Complete or partial radiologic response to RE, assessed using modified Response Evaluation Criteria In Solid Tumors (RECIST), occurred in 9 patients. Additionally, on pathologic examination, 5 patients had no evidence of viable tumor whose disease met the Milan criteria.

Ramanathan et al (2014) reported on various therapies, including RE, for 715 HCC patients of whom 231 were intended for transplant.[29] In the intention-to-treat transplantation arm, 60.2% received a transplant. Survival rates posttransplant were 97.1% and 72.5% at 1 and 5 years, respectively. Tumor recurrence rates were 2.4%, 6.2%, and 11.6% at 1, 3, and 5 years, respectively.

Lewandowski et al (2009) compared the efficacy of RE with chemoembolization in downstaging 86 patients with HCC from stage T3 to T2 (potentially making these patients liver transplant candidates).[30] Patients were treated with RE using Y90 microspheres (n=43) or TACE (n=43). Median tumor sizes were similar between treatment groups (5.7 cm for TACE vs 5.6 cm for RE). Partial response rates were 61% for RE and 37% for TACE, with downstaging from T3 to T2 in 58% of patients treated with RE vs 31% with TACE (p<.05).

Section Summary: Radioembolization as a Bridge to Liver Transplantation for Unresectable Hepatocellular Carcinoma

A systematic review, RCTs, and nonrandomized studies have shown that bridging therapy can support patients with unresectable HCC until a liver transplant is available. Radioembolization is among the therapies that can provide a bridge to transplant.

Radioembolization for Unresectable Intrahepatic Cholangiocarcinoma

Clinical Context and Therapy Purpose

The purpose of RE in patients who have unresectable intrahepatic cholangiocarcinoma (ICC) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does RE improve the net health outcome in individuals with unresectable ICC?

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

Populations

The relevant population of interest is individuals with unresectable ICC. Cholangiocarcinomas are tumors that arise from the epithelium of the bile duct and are separated into intrahepatic and extrahepatic types. ICC appear in the hepatic parenchyma and are also known as peripheral cholangiocarcinomas. Approximately 3,000 cases of ICC are diagnosed annually in the U.S., with an estimated incidence of 0.7 cases per 100,000.[31]

Interventions

The treatment being considered is RE. RE may also be referred to as SIRT or TARE.

Comparators

The following are comparators to RE in the treatment of unresectable ICC: standard of care, usually palliative. Resection is the only treatment with potentially curative effect, and 5-year survival rates have ranged from 20% to 43%.[32] Patients with unresectable disease may select among fluoropyrimidine- or gemcitabine-based chemotherapy, fluoropyrimidine chemoradiation, or best supportive care. Arterially directed locoregional therapies for unresectable presentations, including hepatic arterial infusion (HAI), radiofrequency ablation, TACE, or DEB-TACE, may also be considered.

Outcomes

The general outcomes of interest are OS, functional outcomes, quality of life, and treatment-related morbidity. Outcomes of interest for palliative care include quality of life measures and relief of pain, pruritus, jaundice, and biliary obstruction.

Table 4. Outcomes of Interest for Individuals with Unresectable Intrahepatic Cholangiocarcinoma

Outcomes	Details
Treatment-related morbidity	Outcomes of interest include complete remission, partial response, PFS, overall survival and stable disease [Timing: ≥3 months]

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

Systematic Reviews

Al-Adra et al (2015) reported on outcomes in a systematic review of studies on RE for ICC.[33] Reviewers included 12 publications, 7 of which were published in abstract form only. Of the peer-reviewed articles, 3 were described as prospective cohort studies, which are detailed below (Mouli et al [2013][34]; Hoffmann et al [2012][35]; Saxena et al [2010][36]; of note, the Hoffmann study was reported as retrospective). The overall weighted median survival was 15.5 months (range, 7-22.2 months), based on 11 studies. A weighted mean partial response was seen in 28% of patients and stable disease was seen in 54% at 3 months posttreatment.

Boehm et al (2015) conducted a systematic review comparing hepatic artery-based therapies, including HAI, TACE, DEB-TACE, and Y90 RE, for unresectable ICC.[37] Of 20 studies that met inclusion criteria, 5 evaluated Y90 RE. Median OS across studies was 22.8 months for HAI, 13.9 months for RE, 12.4 months for TACE, and 12.3 months for DEB-TACE. Complete remission or partial response occurred in 56.9% of patients treated with HAI compared with 27.4% of those treated with RE and 17.3% of those treated with TACE.

Noncomparative Studies

Edeline et al (2019) published results from the phase 2, MISPHEC trial (Yttrium-90 Microspheres in Cholangiocarcinoma), which included 41 patients with unresectable ICC treated in the first-line setting with cisplatin, gemcitabine, and RE in French centers with experience with glass microspheres.[38] Fifteen (37%) patients underwent >1 RE treatment. The response rate at 3 months according to RECIST version 1.1 criteria was 39% (90% CI, 26% to 53%) according to local review, with a disease control rate of 98%. After a median follow-up of 36 months, median PFS was 14 months (95% CI, 8 to 17 months) and median OS was 22 months (95% CI, 14 to 52 months). Of 41 patients, 29 (71%) experienced grade 3 and 4 toxic events, including neutropenia (51%), thrombocytopenia (24%), asthenia (225), anemia (20%), and abdominal pain (12%). Fourteen patients experienced hepatic failure, including 5 nonreversible cases in patients with cirrhosis who had received whole-liver RE. Nine patients (22%) were downstaged to surgical intervention, with 8 cases achieving an R0 surgical resection. A follow-up phase 3 trial randomizing patients with unresectable ICC to chemotherapy alone or RE followed by chemotherapy in the first-line setting is currently underway.

Case Series

Case series characteristics and results are summarized in Tables 5 and 6.

Table 5. Summary of Case Series Characteristics

Study	Study Size	Study Design	Study Population
Riby et al (2020)[39.]	169; 19 treated with RE combined with chemotherapy	Retrospective review of outcomes in consecutive patients resected for ICC with upfront surgery (n=137) or following downstaging treatment with chemotherapy alone (n=13) or RE plus chemotherapy (n=19)	• WHO score 0-1, 82.3% • Cirrhosis, 21% • Lymph node metastases, 18%
Buettner et al (2020)[40.]	115	Retrospective review of consecutive patients at 6 tertiary treatment centers with unresectable disease treated with glass (n=22) or resin (n=92) microspheres, or their combination (n=1)	• ECOG PS 0-1, 94% • Previous resection, 15% • Prior chemotherapy, 79% • Cirrhosis, 8%
Jia et al (2017)[41.]	24	Retrospective review of unresectable and failed first-line chemotherapy; 2006-2015	• ECOG PS 0-1, 100% • Extrahepatic metastases, 3 (12.5%) • Lymph node metastases, 9 (37.5%)
Mosconi et al (2016)[42.]	23	Retrospective review of patients with unresectable or recurrent ICC	• ECOG PS 0-1, 23 (100%) • No prior treatment, 4 (17%) • No prior surgery, 7 (30%) • Prior systemic chemotherapy, 12 (52%)
Rayar et al (2015)[43.]	45; 10 eligible for resection	Retrospective review of patients with unresectable ICC treated with RE and systemic chemotherapy as palliative treatment; patients were evaluated every 2 months for possible secondary resection	Among 8 patients downstaged for resection: • ECOG PS 0-1, 8 (100%) • Lymph node metastasis, 3 (37.5%) • Bilobar tumor distribution, 5 (62.5%)
Mouli et al (2013)[34.]	46	Retrospective review of prospectively collected data at a single institution from 2008-2013; patients received an average of 2 treatments	• ECOG PS 0-1, 46 (98%) • Extrahepatic metastases, 16 (35%) • Prior chemotherapy, 16 (35%) • Prior liver-directed therapy, 7 (15%) • Infiltrative morphology, 20 (43%)
Hoffmann et al (2012)[35.]	33	Retrospective review of consecutive patients unresectable or	• ECOG PS 0-1, 73% • Prior chemotherapy, 79% • Prior surgery, 37% • Extrahepatic metastases, 24%

Study	Study Size	Study Design	Study Population
		chemotherapy-refractory cholangiocellular carcinoma treated with resin-based RE from 2007-2010	• Infiltrative morphology, 64%
Haug et al (2011)[44.]	26	Consecutive patients with unresectable ICC and Karnofsky Performance Status of 60 or more evaluated at a single center from 2006 to 2009	• Prior chemotherapy, 65% • Prior surgery, 28% • Prior locoregional therapy, 20% • Extrahepatic metastases, 31%
Saxena et al (2010)[36.]	25	Prospective review of patients with unresectable ICC treated with resin-based RE from 2004 to 2009	• ECOG PS 0-1, 88% • Prior surgery, 40% • Prior chemotherapy, 72% • Prior locoregional therapy, 16% • Extrahepatic disease, 48% • Infiltrative morphology, 40%
Ibrahim et al (2008)[45.]	24	Patients with unresectable ICC treated with glass-based RE at a single center	• ECOG PS 0-1, 92% • Prior chemotherapy, 29% • Extrahepatic metastases, 33% • Infiltrative morphology, 29% • Bilobar disease, 67%

ECOG PF: Eastern Cooperative Oncology Group Performance Status; ICC: intrahepatic cholangiocarcinoma; RE: radioembolization; WHO: World Health Organization..

Table 6. Summary of Case Series Results

Study	Median OS, mo (95% CI)	Median PFS, mo (95% CI)	Response Rates	Downstaging	SAE
Riby et al (2020)[39.]	Upfront surgery: 32.3 (23.9 to 40.7) Any downstaging: 45.9 (32.3 to 59.4) Chemotherapy: 36 (0.4 to 71.7) RE + chemotherapy: Median not reached but no significance difference compared to upfront resection	NR	RECIST 1.1 24 (83%) PR 5 (17%) SD	R1 resection: Upfront: 26 (19%) Chemotherapy: 5 (39%) RE + chemotherapy: 2 (12%) p=.174	NR
Buettner et al (2020)[40.]	11 (8 to 13)	5 (3 to 7)	Resin: 2 (3%) PR 54 (69%) SD 20 (26%) PD Glass: 5 (25%) PR	5 patients underwent resection with curative intent	4 patients with grade 3 or higher laboratory toxicities 29 (25%) patients with clinical

Study	Median OS, mo (95% CI)	Median PFS, mo (95% CI)	Response Rates	Downstaging	SAE
			9 (45%) SD 6 (30%) PD	2 patients died from surgical complications	toxicity per Society of Interventional Radiology criteria
Jia et al (2017)[41]	9 (range, 6 to 12); 24 (range, 18 to 30)[a]	NR	mRECIST 8 (36%) PR 10 (46%) SD 6 (18%) PD	NR	5 patients with grade 3 toxicities.
Mosconi et al (2016)[42]	18 (14 to 21)	NR	RECIST 1.1 3 (15%) PR 6 (30%) SD 11 (55%) PD mRECIST 1 (5%) CR 8 (40%) PR 3 (15%) SD 8 (40%) PD	NR	1 case of grade 3 bilirubin increase, which spontaneously resolved 3 months after RE 1 case of cholecystitis requiring medical management 5 cases of mild ascites, resolved with diuretic therapy
Rayar et al (2015)[43]	NR	NR	NR	10 patients eligible for resection 8 resected with R0 margin 5 alive at conclusion of study 2 postoperative deaths 2 recurrences Median follow-up was 15.6 mo (range, 4 to 40.7) after treatment and 7.2 mo (range, 0.13 to 36.4) after resection	No toxicities of grade 3 or higher.
Mouli et al (2013)[34]	15.6 mo versus 6.1 mo for peripheral and infiltrative morphologies, respectively (p=.006) 15% at median follow-up of 29 mo	NR	NR	5 resected with R0 margin 5 alive at conclusion of study (follow up range, 169 to 1412 days)	NR
Hoffmann et al (2012)[35]	22 (7.9 to 29.4)	9.8 (4 to 31.9)	RECIST 12 (36%) PR 17 (52%) SD 5 (15%) PD	NR	NR

Study	Median OS, mo (95% CI)	Median PFS, mo (95% CI)	Response Rates	Downstaging	SAE
Haug et al (2011)[44]	51 weeks (20 to 82 weeks)	NR	RECIST 0% CR 24% PR 48% SD 20% PD	NR	No cases of grade 3 or higher toxicity.
Saxena et al (2010)[36]	9.3 (NR)	NR	RECIST 0% CR 24% PR 48% SD 20% PD	NR	3 cases (12%) of grade 3 toxicity 1 case of duodenal ulcer due to microsphere malperfusion
Ibrahim et al (2008)[45]	Overall: 14.9 ECOG PS 0: 31.8 ECOG PS 1: 6.1 ECOG PS 2: 1.0 Prior chemotherapy: 4.4	NR	WHO 6 (27%) PR 15 (68%) SD 1 (5%) PD EASL/WHO 2 (9%) CR 17 (77%) PR	1 patient downstaged to resection	1 case (4%) of grade 3 toxicity 1 case (4%) of duodenal ulcer

CI: confidence interval; EASL: European Association for the Study of Liver Disease; ECOG PS: Eastern Cooperative Oncology Group Performance Score; mRECIST: modified RECIST; NR: not reported; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; RE: radioembolization; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: severe adverse events; SD: stable disease; WHO: World Health Organization.
[a] From diagnosis.

Riby et al (2020) retrospectively reviewed data from 169 consecutive patients with ICC in a single-center database.[39] Patients were treated with upfront surgery (n=137) or downstaging with chemotherapy alone (n=13) or chemotherapy plus radioembolization (n=19). Chemo-therapy regimens included gemcitabine and oxaliplatin, FOLFIRINOX, and cisplatin-based treatments. Overall survival of patients resected following downstaging treatment was not significantly different compared with patients that were resected upfront. Delivery of RE as a downstaging treatment was associated with a significant benefit in multivariable analysis (HR, 0.34; 95% CI, 0.14 to 0.84; p=.019).

Buettner et al (2020) retrospectively analyzed data from 115 patients with unresectable ICC at 6 tertiary care centers.[40] The majority of patients were treated with resin microspheres (80%). Laboratory toxicity of grade 3 or higher was reported in 4 patients. Clinical toxicity per Society of Interventional Radiology criteria was reported in 29 patients (25%). The partial response rate was 25% (95% CI, 6% to 44%) in patients who underwent RE with glass microspheres versus 3% (95% CI, 0% to 6%) in patients who were treated with resin microspheres (p=.008). Median OS post-treatment was 11 months (95% CI, 8 to 13 months) and was not significantly different between glass and resin microspheres (p=.475). Median PFS was 5 months (95% CI, 3 to 7 months). Five patients were downstaged and underwent resection with curative intent. Two patients died as a result of surgical complications.

Jia et al (2017) retrospectively reviewed all 24 patients who underwent Y90 RE for unresectable and failed first-line chemotherapy for ICC at a single institution.[41] Mean follow-up was 11 months (range, 3-36 months). Median OS from the time of diagnosis was 24 months (range, 18-30 months) and from the RE procedure was 9 months (range, 6-12 months). Survival rates at 6, 12, and 30 months were 70%, 33%, and 20%, respectively.

Mosconi et al (2016) retrospectively analyzed 23 consecutive patients with unresectable or recurrent ICC at a single institution.[42] Overall median survival was 18 months (95% CI, 14 to 21 months). Survival was statistically significantly longer in treatment-naive patients (52 months) than in those who received other treatments before RE (16 months; p=.009).

Rayar et al (2015) reported on successful downstaging of unresectable ICCs after RE in 8 patients with initial unresectability due to the involvement of hepatic veins or portal veins of the future liver remnant.[43] After RE, all patients underwent successful resection.

Mouli et al (2013) reported on 46 patients treated with RE for ICC using a retrospective review of prospectively collected data from a single institution.[34] Survival varied by level of disease (multifocal, infiltrative, bilobar), and ranged from 5.7 to 15.6 months. Five patients achieved a resectable status and underwent curative resection.

A retrospective study by Hoffmann et al (2012) assessing RE with Y90 resin microspheres included 24 patients with nonresectable chemorefractory ICC and no extrahepatic disease.[35] The mean age of the sample was 65.2 years. Tumor response was assessed by RECIST criteria. Complete remission was seen in 0%, partial response in 36.4%, stable disease in 51.5%, and progressive disease in 15.2%. Follow-up ranged from 3.1 to 44 months (median, 10 months). Median OS was 22 months and the median time to progression was 9.8 months. Favorable subgroups with respect to survival included those with ECOG Performance Status score of 0, tumor burden as a percentage of the liver volume of 25% or less, the response by cancer antigen 19-9 criterion, and RECIST partial response. The same subgroups, except those with a cancer antigen 19-9 response, had favorable time to progression results. No toxicity results were reported.

A study by Haug et al (2011) evaluated prognostic factors of RE treatment in 26 consecutive patients with unresectable ICC who underwent RE with Y90 resin microspheres.[44] Tumor response results according to RECIST criteria were: complete remission in 0%; partial response in 22%; stable disease in 65%; and progressive disease in 13%. Median OS was 51 weeks. The authors found no cases of grade 3 toxicity in transaminases or bilirubin.

Saxena et al (2010) prospectively evaluated 25 patients with unresectable ICC who received RE with Y90 resin microspheres.[36] By RECIST tumor response criteria, complete remission was seen in 0%, partial response in 24%, stable disease in 48%, and progressive disease in 20%. Follow-up was collected between 0.4 months and 55 months (median, 8.1 months). In the entire group, the median OS was 9.3 months. Among subgroups, longer survival duration was seen in patients with peripheral tumors and those with ECOG Performance Status score of 0. The proportion of patients with both grade 3 albumin toxicity and grade 3 bilirubin toxicity was 8%. Grade 3 alkaline phosphatase toxicity was observed in 4%. One (4%) patient experienced duodenal ulcer due to malperfusion of Y90 microspheres.

A study by Ibrahim et al (2008) reported on results for RE with Y90 glass microspheres among 24 patients with unresectable ICC.[45] The group was 33% female and had a median age of 68 years. Using World Health Organization tumor response criteria, complete remission was observed in 0%; partial response in 27%; stable disease in 68%; and progressive disease in 5%. Follow-up was collected over a median of 17.7 months and median OS was 14.9 months. Subgroups that had favorable survival results included those with ECOG Performance Status score of 0, no previous chemotherapy, and peripheral tumor. Grade 3 albumin toxicity was found in 17%, grade 3 bilirubin toxicity in 4%, and 1 (4%) patient developed a duodenal ulcer.

Section Summary: Intrahepatic Cholangiocarcinoma

The evidence for RE in ICC primarily consists of retrospective case reviews. Across studies, the median survival in patients treated with RE ranged from 6 to 22 months. Side effects are common but generally mild. Patient populations in these studies were heterogeneous, varying in performance status, prior interventions, presence of extrahepatic disease, and tumor distribution and morphology. Therefore, in the absence of data in well-defined patient populations, it is difficult to ascertain which patients are most likely to derive benefit from RE.A phase 2 study evaluating the use of RE with chemotherapy in the first-line reported a response rate of 39% and a disease control rate of 98%. A RCT investigating the use of RE in the neoadjuvant setting is currently ongoing.

Radioembolization for Unresectable Neuroendocrine Tumors

Clinical Context and Therapy Purpose

The purpose of RE in patients who have unresectable neuroendocrine tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does RE improve the net health outcome in individuals with unresectable neuroendocrine tumors?

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

Populations

The relevant population of interest is individuals with unresectable neuroendocrine tumors. These tumors are an uncommon, heterogeneous group of mostly slow-growing, hormone-secreting malignancies, with an average patient age of 60 years. Primary neuroendocrine tumors vary in location, but most are either carcinoids (which most commonly arise in the midgut area) or pancreatic islet cells. The estimated incidence of neuroendocrine tumors in the U.S. is 12,000 cases per year, with approximately 175,000 individuals living with this diagnosis.[46]

Interventions

The treatment being considered is RE. RE may also be referred to as SIRT or TARE.

Comparators

The following are comparators to RE in the treatment of unresectable neuroendocrine tumors: standard of care, usually palliative. Conventional therapy is generally considered to be palliative supportive care, to control, eradicate, or debulk hepatic metastases, often to palliate carcinoid syndrome or local pain from liver capsular stretching. Therapies for unresectable metastatic neuroendocrine tumors include medical (somatostatin analogues like octreotide), systemic chemotherapy, ablation (radiofrequency or cryotherapy), TAE or TACE, or radiotherapy. Although patients often achieve symptom relief with octreotide, the disease eventually becomes refractory, with a median duration of symptom relief of approximately 13 months, with no known effect on survival. Systemic chemotherapy for these tumors has revealed that: (1) modest response rates are of limited duration; (2) it is more effective for pancreatic neuro-endocrine tumors than carcinoids; and (3) it is frequently associated with significant toxicity. [47] Chemoembolization has shown response rates of nearly 80%, but the effect is of short duration, and a survival benefit has not been demonstrated.[47]

Outcomes

The general outcomes of interest are OS, functional outcomes, quality of life, and treatment-related morbidity. Although considered indolent tumors at the time of diagnosis, up to 75% of patients experienced liver metastases and with metastases to the liver, 5-year survival rates are less than 20%. Surgical resection of the metastases is considered the only curative option; however, less than 10% of patients are eligible for resection, because most patients have multiple diffuse lesions.

Carcinoid tumors, particularly if they metastasize to the liver, can result in excessive vasoactive amine secretion including serotonin and are commonly associated with the carcinoid syndrome (diarrhea, flush, bronchoconstriction, right valvular heart failure).

The timeframe for outcome measures varies from several months to 5 years.

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
Ngo et al (2021) conducted a meta-analysis of 6 retrospective cohort studies with a total of 643 patients treated with TACE (n=422) or RE (n=221).[48] Patients treated with TACE exhibited significantly improved OS (OR 1.92; 95% CI, 1.14 to 3.22; p=.014) compared to those treated with RE. No significant differences in hepatic progression-free survival (p=.96) or overall tumor response (p=.99) were observed. Although the overall proportion of patients with unresectable disease is unclear, the history of resection or ablation in the two groups was not significantly different (OR 1.20; 95% CI, 0.71 to 2.02; p=.49). Patients receiving RE were more likely to have received prior systemic chemotherapy (OR 0.48; 95% CI, 0.27 to 0.83; p=.009) and octreotide therapy (OR, 0.50; 95% CI, 0.30 to 0.84; p=.009).

Frilling et al (2019) reported results from a case series of 24 patients that were then included in a meta-analysis of patients treated with for neuroendocrine liver metastases.[49] Overall, 26 additional studies were included in the meta-analyses, which reported a fixed-effects weighted averages for objective response rate of 51% (95% CI, 47% to 54%) and disease control rate (complete response, partial response, or stable disease) of 88% (95% CI, 85% to 90%).

Devcic et al (2014) conducted a meta-analysis of studies evaluating RE for liver-dominant metastatic neuroendocrine tumors.[50] The analysis included 12 studies that provided RECIST data for hepatic metastatic neuroendocrine tumors treated with RE. For Y90 RE with resin microspheres only, objective radiographic response rates (complete remission or partial response by RECIST) ranged from 12% to 80%, with a random effects weighted average of 50% (95% CI, 38% to 62%). Disease control rates (complete remission, partial response, stable disease) ranged from 62% to 100%, with a random-effects weighted average of 86% (95% CI, 78% to 92%).

Nonrandomized Comparative Studies
Egger et al (2020) performed a retrospective cohort analysis comparing patients with neuroendocrine liver metastases treated with RE (n=51) or TACE (n=197).[51] Between RE and TACE, there were no statistically significant differences in overall morbidity (13.7% vs. 22.6%, respectively; p=.17), grade 3/4 complication (5.9% vs. 9.2%; p=.58), 90-day mortality (9.8% vs 5.2%; p=.21), median OS (35.9 months vs. 50.1 months; p=.3), or progression-free survival (15.9 vs. 19.9 months; p=.37). However, disease control rate was greater for TACE compared with RE (96% vs. 83%, p<.01).

Engelman et al (2014) retrospectively compared transarterial, liver-directed therapies, including RE, hepatic artery embolization (HAE), and hepatic artery chemoembolization (HACE), in 42 patients treated for metastatic neuroendocrine tumors.[52] Treatment decisions were at the discretion of the referring physician and interventional radiologist, but the decision to proceed with therapy was typically based on the progression of symptoms nonresponsive to octreotide therapy or rapid progression of liver tumor burden on imaging. Seventeen patients had HACE, 13 had HAE, and 12 had RE. Among the 27 patients with symptoms related to their liver metastases, there were no statistically significant differences in symptom improvement at 3 months after first liver-directed therapy across treatment modalities (6/13 for HACE; 4/8 for HAE; 5/6 for RE; p=.265). There were no statistically significant differences between treatment modalities in radiographic response at 6 months postprocedure (p=.134), time to progression (p=.968), or OS (p=.30).

Case Series

Rhee et al (2008) reported on the results of a multicenter, open-label, phase 2 study that assessed the safety and efficacy of RE, using glass or resin microspheres, in 42 patients with metastatic neuroendocrine liver disease who had failed prior treatment(s), including medical (e.g., octreotide), surgical resection, bland or chemoembolization, and radiofrequency ablation or cryoablation.[53.] RECIST criteria were used to assess tumor response, which showed 92% of glass patients and 94% of resin patients had a partial response or had a stable disease at 6 months after treatment. Median survival was 22 months for glass and 28 months for resin.

Cao et al (2010) reported on outcomes for 58 patients with unresectable neuroendocrine liver metastases from 2 hospitals who were treated with RE from 2003 to 2008.[54.] Response was assessed with radiographic evidence before and after RE and measured using RECIST guidelines. Systemic chemotherapy was routinely given at a single institution. Mean patient age at the time of RE was 61 years (range, 29-84 years). Primary tumor site varied and included small bowel, pancreas, colon, thyroid, lung, and unknown. Thirty-one patients underwent surgical resection of their primary tumor, which was classified as a low grade in 15, intermediate grade in 7, and high grade in 7. Forty-three percent of patients had extrahepatic metastatic disease at study entry. Median follow-up was 21 months (range, 1-61 months). Fifty-one patients were evaluable, and 6 achieved complete remission, 14 had a partial response, 14 had stable disease, and 17 experienced disease progression. OS rates at 1, 2, and 3 years were 86%, 58%, and 47%, respectively. Median survival was 36 months (range, 1-61 months). Prognostic factors for survival included the extent of tumor involvement of the liver, radiographic response to treatment, the presence of extrahepatic disease at the time of RE, the histologic grade of the tumor, and whether patients responded to RE.

King et al (2008) reported on outcomes for patients treated in a single institution prospective study.[47.] Thirty-four patients with unresectable neuroendocrine liver metastases were given radioactive microspheres (SIR-Spheres) and concomitant 7-day systemic infusion of fluorouracil (5-FU), between 2003 and 2005. Mean patient age was 61 years (range, 32-79 years). Mean follow-up was 35.2 months. Primary tumor sites varied and included bronchus (n=1), thyroid (n=2), gastrointestinal (n=15), pancreas (n=8), and unknown (n=8). Subjective changes from baseline hormone symptoms were reported every 3 months. Twenty-four (71%) patients had, at baseline assessment, symptoms of carcinoid syndrome, including diarrhea, flushing, or rash. At 3 months, 18 (55%) of 33 patients reported improvements in symptoms, as did 16 (50%) of 32 at 6 months. Radiologic tumor response was observed in 50% of patients and included 6 (18%) complete remission and 11 (32%) partial response. Mean OS was 29.4 months.

Kennedy et al (2008) retrospectively reviewed 148 patients from 10 institutions with unresectable hepatic metastases from neuroendocrine tumors.[55.] All patients had completed treatment of the primary tumor and metastatic disease and were not excluded based on prior therapy. The total number of resin microsphere treatments was 185, with retreatment in 22.3% of patients (19.6% received 2 treatments, 2.7% received 3 treatments). All patients were followed using imaging studies at regular intervals to assess tumor response (using either World Health Organization or RECIST criteria) until death, or they were censored if a different type of therapy was given after the microspheres. Median follow-up was 42 months. By imaging, response rates were a stable disease in 22.7%; partial response in 60.5%; complete remission in 2.7%; and progressive disease in 4.9%. Hepatic and extrahepatic metastases contributed to death in most patients, with 7% lost to follow-up. Median survival was 70 months.

Additional case series in patients with treatment-refractory, unresectable neuroendocrine hepatic metastases have shown tumor response and improvement in clinical symptoms with RE.[56,57,58,59,60,]

Section Summary: Unresectable Neuroendocrine Tumors

The available comparative evidence for the use of RE to treat unresectable neuroendocrine tumors primarily consists of nonrandomized retrospective study designs. A 2019 meta-analysis reported fixed-effects weighted averages for objective response rate of 51% (95% CI, 47% to 54%) and disease control rate (complete response, partial response, or stable disease) of 88% (95% CI, 85% to 90%).In a small nonrandomized comparative study of RE, HAE, and HACE, no statistically significant differences in radiographic response, time to progression, and OS were observed, suggesting comparable efficacy.

Radioembolization for Unresectable Intrahepatic Metastases from Colorectal Carcinoma and Prior Treatment Failure

Clinical Context and Therapy Purpose

The purpose of RE in patients who have unresectable intrahepatic metastases from colorectal carcinoma (CRC) and prior treatment failure is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does RE improve the net health outcome in individuals with unresectable intrahepatic metastases from CRC and prior treatment failure?

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

Populations

The relevant population of interest is individuals with unresectable intrahepatic metastases from CRC and prior treatment failure. Fifty to 60 percent of patients with CRC will develop metastases, either synchronously or metachronously. Select patients with liver-only metastases that are surgically resectable can be cured, with some reports showing 5-year survival rates exceeding 50%. The emphasis of treating these patients with the potentially curable disease is complete removal of all tumors with negative surgical margins. Most patients diagnosed with the metastatic colorectal disease are initially classified as having unresectable disease. In some with metastatic disease limited to the liver, preoperative chemotherapy is sometimes used to downstage the metastases from metastatic lesions to resectable lesions (conversion chemotherapy).

Interventions

The treatment being considered is RE. RE may also be referred to as SIRT or TARE.

Comparators

The following are comparators to RE in the treatment of unresectable intrahepatic metastases from CRC and prior treatment failure: standard of care, usually palliative. In patients with unresectable disease, the primary treatment goal is palliative, with a survival benefit shown in both second- and third-line systemic chemotherapy.[61] Recent advances in chemotherapy, including oxaliplatin, irinotecan, and targeted antibodies like cetuximab, have doubled the median survival in this population from less than 1 year to more than 2 years. Palliative chemotherapy using combined systemic and HAI may increase disease-free intervals for patients with unresectable hepatic metastases from CRC.

Outcomes

The general outcomes of interest are OS, functional outcomes, quality of life, and treatment-related morbidity.

Table 7. Outcomes of Interest for Individuals with Unresectable Intrahepatic Metastases from Colorectal Cancer and Prior Treatment Failure

Outcomes	Details
Treatment-related morbidity	Outcomes of interest include complete remission, partial response, PFS, and stable disease [Timing: ≥3 months]

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

Systematic Reviews

In a systematic review, Saxena et al (2014) evaluated 20 experimental and observational studies on RE for chemoresistant, unresectable CRC liver metastasis (N =979 patients).[62] They included 2 RCTs (Gray et al [2001][63]; Hendlisz et al [2010][64]; described below), 5 non-RCTs or well-designed cohort studies, and 13 observational studies. After RE, the average reported complete remissions and partial response rates from 16 studies were 0% (range, 0%-6%) and 31% (range, 0%-73%), respectively. Nine months was the median time to intrahepatic progression (range, 6-16 months). In 11 studies reporting on OS, the median survival time was 12 months (range, 8.3-3.6 months).

Rosenbaum et al (2013) evaluated 13 relevant studies in a systematic review on RE as monotherapy and 13 studies on RE combined with chemotherapy for chemoresistant, unresectable CRC liver metastasis.[65] Complete remission, partial response, and stable disease rates ranged from 29% to 90% with RE only and from 59% to 100% for RE plus chemotherapy. At 12 months, survival rates ranged from 37% to 59% with RE only and from 43% to 74% for RE plus chemotherapy.

Three earlier systematic reviews, published in 2010 and 2009, are briefly noted; all include RCTs by Gray et al (2001)[63] and Van Hazel et al (2004).[66] The 2010 report by the California Technology Assessment Forum assessed 25 studies, including the 2 RCTs, a retrospective comparative study (n=36), and 21 case series.[61] The review concluded that the RCT results were encouraging but not definitive. A Cochrane review by Townsend et al (2009) assessed the efficacy and toxicity of RE, alone or with systemic or regional hepatic artery chemotherapy.[67] Townsend et al (2009) found insufficient evidence to demonstrate that RE improved survival or quality of life.[67] The meta-analysis by Vente et al (2009) included 19 studies with a total of 792 patients. A meta-regression model found a tumor response rate of 80% in the salvage setting and 90% at first-line neoadjuvant therapy. Median survival after RE ranged from 6.7 to 17 months, irrespective of microsphere type, chemotherapy protocol, or use as salvage or first-line therapy.[12]

Randomized Controlled Trials

A phase 3 RCT by van Hazel et al (2016) compared modified FOLFOX chemotherapy and FOLFOX chemotherapy plus RE in 530 patients with previously untreated liver-dominant metastatic disease.[68] The primary endpoint was overall (any site) PFS. Secondary endpoints included liver-specific outcomes such as PFS in the liver, tumor response rate, and liver resection rate. The primary endpoint of PFS at any site showed no difference between groups (10.6 months for RE vs 10.2 months for control; HR, 0.93; p=.43). Secondary endpoints of median PFS in the liver and objective response rate for RE in the liver vs controls were improved in the RE group (liver PFS, 20.5 months vs 12.6 months; liver response rate, 78.7% vs 68.8%), all respectively. Wasan et al (2017) analyzed OS from this study in combination with 2 other studies of chemotherapy with and without RE.[69] Overall, 549 patients were randomly assigned to FOLFOX alone and 554 patients were assigned FOLFOX plus. Overall survival was not significantly different between groups (HR, 1.04; 95% CI, 0.90 to 1.19). Wolstenholme et al (2020) published a follow-up analysis of health-related quality of life (HRQOL) measures as assessed by the three-level EQ-5D, European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30), and EORTC Colorectal Liver Metastases cancer module (EORTC QLQ-LMC21).[70] HRQOL was statistically significantly lower in RE + FOLFOX patients ≤3 months after administration according to all 3 instruments, but these differences were not deemed clinically important. No clinically important differences were observed over the 2-year follow-up period.

The RCT by Gray et al (2001) randomized 74 patients with bilobar unresectable liver metastases to monthly HAI with 5-FU alone or to 5-FU plus a single infusion of Y90 microspheres.[63.] Accrual was halted early, entering 74 patients rather than the planned 95 at the discretion of the investigator rather than by planned data monitoring board oversight. To monitor responses to therapy, investigators serially measured serum levels of carcinoembryonic antigen and estimated tumor cross-sectional area and volume from repeated computerized tomography scans read by physicians blinded to treatment assignment. For HAI plus RE vs HAI, they reported increased overall responses (complete remission plus partial response) measured by area (44% vs 18% p=.01) and volume (50% vs 24%, p=.03), or by serum carcinoembryonic antigen levels (72% vs 47%, p=.004), all respectively. They also reported increased time to progression detected by increased area (9.7 months vs 15.9 months; p=.001) or volume (7.6 months vs 12.0 months; p=.04), both respectively. Treatment-related complications (grades 3-4) included 23 events in each arm (primarily changes in liver function tests). While in this trial, response rate and time to progression after plus HAI appeared superior to the same outcomes after HAI alone, results for the plus HAI group are within the range reported by other randomized trials of HAI in comparable patients.[19,71,]

A phase 2 RCT (2004) by the same research group assessed 21 patients with advanced colorectal liver metastases; a total of 11 patients received systemic chemotherapy (fluorouracil and leucovorin) plus RE, and 10 received systemic chemotherapy alone.[66.] Disease time to progression was greater in those receiving combination therapy (18.6 months vs 3.6 months, respectively; p<.001).

A phase 3 RCT by Hendlisz et al (2010), which assessed 46 patients, compared intravenous 5-FU plus RE (SIR-Spheres) with intravenous 5-FU alone in CRC metastatic to the liver and refractory to standard chemotherapy.[64.] The time to liver progression (the primary outcome) was significantly longer in the group receiving SIR-Spheres (2.1 months vs 5.5 months, respectively; p=.003). After progression, patients received further treatment, including 10 in the 5-FU alone arm who received RE. There was no difference in median survival (7.3 months vs 10.0 months, respectively; p=.80).

Nonrandomized Comparative Studies

Mokkarala et al (2019) performed a propensity score-matched retrospective analysis of patients with colorectal metastases treated with DEB-TACE (n=47) or RE (n=155).[72.] Extra-hepatic metastasis was more frequent with DEB-TACE (68.1% vs. 47.7%; p=.014), as was occurrence of ≥10 liver lesions (42.2% vs. 68.8%; p=.001). Toxicity was not significantly different between DEB-TACE and RE (27% vs. 9.1%, respectively; p=.057). Treatment with DEB-TACE was not a prognostic factor for survival (HR, 0.94; 95% CI, 0.54 to 1.65).

Seidensticker et al (2012) published a retrospective, matched-pair comparison of RE plus best supportive care with best supportive care alone for patients with chemorefractory, liver-dominant colorectal metastases (n=29 in each group).[73.] Patients were matched on tumor burden, prior treatments, and additional clinical criteria. Results showed prolongation of survival in patients who received RE (median survival, 8.3 months vs 3.5 months; p<.001; HR, 0.3; 95% CI, 0.16 to 0.55; p<.001). Adverse events were considered generally mild-to-moderate and manageable.

Section Summary: Unresectable Intrahepatic Metastatic Colorectal Carcinoma

The evidence for the use of RE to treat unresectable intrahepatic metastatic CRC includes systematic reviews, RCTs, and nonrandomized comparative studies. The largest RCT compared chemotherapy to chemotherapy plus RE in 530 patients. Median PFS (20.5 versus 10.2 months) and objective response rates (78.7% versus 68.8%) were higher in the RE arm. When analyzed in combination with 2 other studies comparing chemotherapy with and without RE, OS was not significantly different between groups (HR, 1.04; 95% CI, 0.90 to 1.19).

Radioembolization for Unresectable Intrahepatic Metastases from Other Cancers
Clinical Context and Therapy Purpose
The purpose of RE in patients who have unresectable intrahepatic metastases from other cancers is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does RE improvement the net health outcome in individuals with unresectable intrahepatic metastases from other cancers?

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

Populations
The relevant population of interest is individuals with unresectable intrahepatic metastases from other cancers.

Interventions
The treatment being considered is RE. RE may also be referred to as SIRT or TARE.

Comparators
The comparator of interest is standard of care. Comparators for RE may also include liver-directed therapies such as HAI chemotherapy.

Outcomes
The general outcomes of interest are OS, functional outcomes, quality of life, and treatment-related morbidity.

Table 8. Outcomes of Interest for Individuals with Unresectable Intrahepatic Metastases from Other Cancers (e.g., Breast, Melanoma, Pancreatic)

Outcomes	Details
Treatment-related morbidity	Outcomes of interest include complete remission, partial response, PFS, overall survival and stable disease [Timing: ≥3 months]

PFS: progression-free survival

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

Metastatic Intrahepatic Breast Cancer
Most studies on the use of RE for metastatic breast cancer have evaluated the use of RE alone (i.e., not in combination with chemotherapy) either between lines of chemotherapy or in patients refractory to standard of care chemotherapy.[74]

Review of Evidence
Systematic Review
Feretis et al (2020) performed a systematic review of RE for treatment of metastatic intrahepatic breast cancer.[75] Twelve case series were included (N =452; range, 7 to 81), with a duration of follow-up ranging from 6 to 15.7 months in studies reporting follow-up duration. Overall, 52.2% of patients had breast metastases not confined to the liver. Radioembolization provided disease control in 81% of patients, and OS ranged from 3.6 to 20.9 months, with an estimated mean survival of 11.3 months.

Case Series

Ridouani et al (2021) published the results of a retrospective study reviewing all breast cancer patients undergoing RE of liver metastases from 2011 to 2019 at a single center.[76.] RE was performed with glass (66%) or resin (34%) microspheres based on operator preference. Imaging response assessments were available for 60/64 patients, of which 46 (77%, 95% CI, 64% to 86%) achieved an objective response (OR), demonstrating a 30% or greater reduction in metabolic activity. Patients with OR had a high median dose deliver to the tumor (167 Gy) compared to patients not achieving an OR (54 Gy; p<.001). Eight patients developed grade 3 or higher treatment-related hepatotoxicity.

Davisson et al (2020) retrospectively reviewed 24 patients with chemotherapy-refractory hepatic metastases from breast cancer who underwent RE from 2013 to 2018.[77.] Extrahepatic metastases were reported in 18 and 20 continued to receive concurrent chemotherapy and/or immunotherapy. Median OS was 35.4 months from first RE. Radioembolization within 6 months of hepatic metastasis diagnosis and estrogen receptor-positive status were identified as positive predictors of overall survival.

Metastatic Melanoma

Many studies of metastatic melanoma focus on patients with uveal melanoma, for whom the liver is the most common site of metastatic disease.

Review of Evidence

Systematic Reviews

Rowcroft et al (2020) planned to perform a meta-analysis of studies of patients with liver-only metastases of uveal melanoma treated with systemic therapy, isolated hepatic perfusion, hepatic artery infusion, TACE, and immunoembolization.[78.] However, due to heterogeneity in available data, meta-analysis was not performed. The authors descriptively reported that 6 non-comparative retrospective cohort studies (n=150; range, 8 to 71) evaluated the use of RE, which reported median OS ranged from 9 to 24 months.

Nonrandomized Comparative Studies

Gonsalves et al (2019) performed a prospective study of patients with liver metastases of uveal melanoma treated with RE.[79.] Among patients who were treatment-naive, complete response, partial response, or stable disease was achieved in 20 of 23 patients (87.0%; 95% CI, 66.4%, 97.2%), median PFS from liver metastasis was 8.1 months (95% CI, 6.4, 11.8), and median OS was 18.5 months (95% CI, 11.3 to 23.5). Among patients who progressed after immunoembolization, complete response, partial response, or stable disease was achieved in 14 of 24 patients (58.3%; 95% CI, 36.3%, 77.9%), median PFS from liver metastasis was 5.2 months (95% CI, 3.7 to 9.8), and median OS was 19.2 months (95% CI, 11.5 to 24.0).

Xing et al (2017) conducted a retrospective observational study comparing outcomes for patients who had unresectable melanoma (both uveal and cutaneous) liver metastases refractory with standard chemotherapy treated with Y90 RE (n=28) or best supportive care (n=30).[80.] The groups were similar at baseline in terms of Child-Pugh class, ECOG Performance Status scores, age, sex, and race. Patients treated with RE had larger tumors at baseline (mean, 7.28 cm) than those treated with best supportive care (mean, 4.19 cm; p=.02). Median OS from diagnosis of melanoma liver metastases was longer in RE-treated subjects (19.9 months vs 4.8 months; p<.000), as was median OS from diagnosis of the primary melanoma (119.9 months vs 26.1 months; p<.001), respectively. Pre- and posttreatment imaging studies were available for 24 (85.7%) of 28 of those treated with RE. Of those, no patients had complete remission, 5 (17.9%) patients had a partial response, 9 (32.1%) patients had stable disease, and 10 (35.7%) patients had progressive disease. Two patients receiving RE had major (grade 5) clinical toxicities (ascites and hepatic encephalopathy and eventual death).

Case Series

Eldredge-Hindy et al (2016) retrospectively evaluated outcomes for the use of Y90 RE in 71 patients with biopsy-confirmed uveal melanoma liver metastases.[81.] Median time from the diagnosis of liver metastases to RE was 9.8 months (95% CI, 7.4 to 12.2 months), and 82% of patients had received prior liver-directed therapies. Sixty-one (86%) patients had computed tomography or magnetic resonance imaging evaluation of treatment response at 3 months post-RE. Of those, 5 (8%) patients had a partial response, 32 (52%) patients had stable disease, and 24 (39%) patients had disease progression. Median OS was 12.3 months (range, 1.9-49.3 months).

Several smaller studies published from 2009 to 2020 have reported on the use of RE in patients with hepatic metastases from melanoma.[82,83,84,85.] Three included only patients with ocular melanoma,[82,83,84.] and 2 included patients with ocular or cutaneous melanoma.[85,86.] Sample sizes ranged between 11 patients and 32 patients. Four studies excluded those with poor performance status. Median age was in the 50s for 3 studies and in the 60s for 2 studies. One article did not describe any previous treatment, and another described it incompletely. One study evaluated patients treated with RE and immune checkpoint inhibitors within a 15-month period.[86.] Four studies reported tumor response data, by RECIST criteria. Among 32 patients in the study by Gonsalves et al (2011), 1 (3%) patient had complete remission, 1 (3%) had a partial response; 18 (56%) had stable disease, and 12 (38%) had progressive disease.[82.] In the study of 13 patients by Klingenstein et al (2013), none had complete remission; 8 (62%) had a partial response; 2 (15%) had stable disease, and 3 (23%) had progressive disease.[84.] Nine of 11 patients in Kennedy et al (2009) provided response data: 1 had complete remission; 6 had a partial response; 1 had stable disease, and 1 had progressive disease.[83.] In the study of 22 patients by Ruohoniemi et al (2020), 17 patients had adequate response data: 2 had complete response, 8 had partial response, 6 had stable disease, and 1 had progressive disease. [86.] Median survival in Gonsalves et al (2011), Klingenstein et al (2013), Ruohoniemi et al (2020), and Kennedy et al (2009) were 10.0 months, 19 months, 20 months, and not yet reached, respectively. Gonsalves et al (2011) reported on 4 (12.5%) patients with grade 3 or 4 liver toxicity. Klingenstein et al (2013) observed 1 patient with marked hepatomegaly. Kennedy et al (2009) described 1 patient with a grade 3 gastric ulcer. Piduru et al (2012)[85.] (n=12) did not include any toxicity data. Ruohoniemi et al (2020) described grade 3 hepatobiliary toxicities in 3 patients within 6 months.

Metastatic Pancreatic Cancer

Michl et al (2014) reported on a case series on RE for pancreatic cancer.[87.] A response was seen in 47%, with median local PFS in the liver of 3.4 months (range, 0.9-45.0 months). Median OS was 9.0 months (range, 0.9-53.0 months) and 1-year survival was 24%.

Hepatic Sarcoma

Miller et al (2018) retrospectively reviewed 39 patients with metastatic (n=37) or primary (n=2) liver sarcoma in a multicenter study.[88.] All patients had received at least 1 course of chemotherapy before receiving resin-based (n=17) or glass-based (n=22) Y90 RE (see Table 11). Most toxicities observed (93%) were grade 1 or 2, and the objective response rate (complete and partial responses) was 36% (see Table 8). Six months after treatment, 30 patients showed stable disease or response, and the median OS was 30 months (95% CI, 12 to 43 months).

Section Summary: Unresectable Intrahepatic Metastases From Other Cancers

The evidence for the use of RE to treat metastatic breast cancer consists of case series including 7 to 75 patients, primarily patients who progressed while on chemotherapy. Radioembolization provided disease control in 81% of patients, and OS ranged from 3.6 to 20.9 months, with an estimated mean survival of 11.3 months.

The evidence bases for metastatic melanoma have demonstrated that RE has a significant tumor response; however, improvement in survival has not been demonstrated in controlled comparative studies and some serious adverse events have been reported.

The evidence bases for metastatic pancreatic cancer and hepatic sarcoma are currently insufficient to draw definitive conclusions on treatment efficacy.

Summary of Evidence

For individuals who have unresectable HCC who receive RE or RE with a liver transplant, the evidence includes primarily retrospective and prospective nonrandomized studies, with limited evidence from RCTs. Relevant outcomes are OS) functional outcomes, quality of life, and treatment-related morbidity. Nonrandomized studies have suggested that RE has high response rates compared with historical controls. Two small pilot RCTs have compared RE with alternative therapies for HCC, including TACE and DEB-TACE. Both trials reported similar outcomes for RE compared with alternatives. Evidence from nonrandomized studies has demonstrated that RE can permit successful liver transplantation in certain patients. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable ICC who receive RE, the evidence includes a phase 2 study and case series. Relevant outcomes are OS, functional outcomes, quality of life, and treatment-related morbidity. Comparisons of these case series to case series of alternative treatments have suggested that RE for primary ICC has response rates similar to those seen with standard chemotherapy. Due to high study heterogeneity, it is difficult to identify patients that are most likely to benefit from treatment. A phase 2 study of RE with chemotherapy in the first-line setting reported a response rate of 39% and a disease control rate of 98%. The efficacy of RE in the neoadjuvant setting is being evaluated in an ongoing follow-up RCT. However, at this time, the evidence is not yet sufficiently robust to draw definitive conclusions about treatment efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable neuroendocrine tumors who receive RE, the evidence includes an open-label phase 2 study, retrospective reviews, and case series, some of which have compared RE with other transarterial liver-directed therapies. Relevant outcomes are OS, functional outcomes, quality of life, and treatment-related morbidity. This evidence has suggested that RE provides outcomes similar to standard therapies and historical controls for patients with neuroendocrine tumor-related symptoms or progression of the liver tumor. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable intrahepatic metastases from colorectal cancer and prior treatment failure who receive RE, the evidence includes several small- to moderate-sized RCTs, prospective trials, and retrospective studies using a variety of comparators, as well as systematic reviews of these studies. Relevant outcomes are OS, functional outcomes, quality of life, and treatment-related morbidity. RCTs of patients with prior treatment failure have methodologic problems, do not show definitive superiority of RE compared with alternatives but tend to show greater tumor response with RE. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable intrahepatic metastases from other cancers (e.g., breast, melanoma, pancreatic) who receive RE, the evidence includes nonrandomized studies. Relevant outcomes are OS, functional outcomes, quality of life, and treatment-related morbidity. These studies have shown significant tumor response; however, improvement in survival has not been demonstrated in controlled comparative studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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.

2015 Input

In response to requests from Blue Cross Blue Shield Association, input was received from 3 physician specialty societies (with 5 individual responses) and 1 academic medical center (with 4 individual responses), for a total of 9 respondents in 2015. There was consensus supporting the use of radioembolization (RE) for hepatic metastases from melanoma, particularly ocular melanoma, and breast cancer. There was also consensus supporting the use of RE for treatment of primary intrahepatic cholangiocarcinoma. There was less consensus on the use of RE for hepatic metastases from other specific tumor types, including pancreatic cancer. However, many reviewers supported the use of RE for treatment of other radiosensitive tumors metastatic to the liver with the liver-limited or liver-dominant disease for symptom palliation or prolongation of survival.

2010-2011 Input

In response to requests from Blue Cross Blue Shield Association, input was received from 2 physician specialty societies (with 5 individual responses) and 6 academic medical centers, for a total of 11 respondents in 2010 and again in 2011. For the 2011 review, input was received from 2 physician specialty societies and 3 academic medical centers; all but 1 academic medical center had provided input in 2010. There was strong support for the use of RE in patients with primary hepatocellular carcinoma, as a bridge to liver transplant in hepatocellular carcinoma, and in neuroendocrine tumors. There was also strong support for use of RE in patients with liver metastases from colorectal cancers and support for its use in patients with liver metastases from other cancers but with less consensus than for colorectal metastases. Those providing input were split as to whether RE should be used as monotherapy or in combination with other agents.

The support for the use of RE in patients with chemotherapy-refractory colorectal metastases was primarily to prolong time to tumor progression and subsequent liver failure (a major cause of morbidity and mortality in this patient population), potentially prolonging survival. Additional support for the use of RE in this setting was for the palliation of symptoms from tumor growth and tumor bulk.

Support for the use of RE for liver metastases from tumors other than colorectal or neuroendocrine was generally limited to a number of specific tumor types, in particular, ocular melanoma, cholangiocarcinoma, breast, and pancreas.

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.

National Comprehensive Cancer Network

Primary Hepatobiliary Carcinoma

The National Comprehensive Cancer Network (NCCN) guidelines (v.2.2021) on the treatment of hepatobiliary cancers indicate that the use of arterially directed therapies, including transarterial bland embolization, transarterial chemoembolization, and drug-eluting beads transarterial chemoembolization, and RE with yttrium-90 microspheres may be appropriate provided that the arterial blood supply can be isolated without excessive nontarget treatment. Patients should be considered for locoregional therapy if they are not candidates for potential curative treatments (resection, transplantation, and for small lesions, ablative strategies).[89,]

Metastatic Neuroendocrine Tumors
The NCCN guidelines (v.1.2021) on the treatment of neuroendocrine tumors recommend consideration of RE for lobar or segmental disease distribution and in patients with prior Whipple surgery or biliary tract instrumentation.[90]

Metastatic Colon Cancer
The NCCN guidelines (v.2.2021) on the treatment of colon cancer provides a consensus recommendation that: "...arterial-directed catheter therapy, in particular yttrium-90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases." RE may also be considered when hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume. [91]

Metastatic Uveal Melanoma
The NCCN guidelines (v.1.2021) on the treatment of uveal melanoma state that "further study is required to determine the appropriate patients for and risk and benefits" of selective internal radiation therapy for patients with liver metastases using yttrium-90.[92]

National Institute for Health and Care Excellence
Primary Hepatobiliary Carcinoma
The July 2013 National Institute for Health and Care Excellence (NICE) interventional procedures guidance on selective internal radiation therapy for primary hepatocellular carcinoma states that the evidence for efficacy and safety are adequate for use with normal arrangements. However, "uncertainties remain about its comparative effectiveness, and clinicians are encouraged to enter eligible patients into trials comparing the procedure against other forms of treatment."[93]

Primary Intrahepatic Cholangiocarcinoma
The October 2018 NICE interventional procedures guidance on selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma state that there are "well-recognized, serious but rare safety concerns. Evidence on its efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research."[94]

Metastatic Colon Cancer
The March 2020 NICE interventional procedures guidance on selective internal radiation therapy for unresectable colorectal metastases in the liver states that "in people who cannot tolerate chemotherapy or have liver metastases that are refractory to chemotherapy, there is evidence of efficacy but this is limited, particularly for important outcomes such as quality of life. Therefore, in these people, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research."[95]

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 ongoing and unpublished trials that might influence this review are listed in Table 9.

Table 9. Summary of Key Trials

NCT No.	Name	Planned Enrollment	Completion Date
Hepatocellular Carcinoma			
Ongoing			
NCT01556490[a]	A Phase III Clinical Trial of Intra-arterial TheraSphere® in the Treatment of Patients With Unresectable Hepatocellular Carcinoma (HCC) (STOP-HCC)	526	Sept 2022 (ongoing)
NCT04522544[a]	A Phase II Study of Immunotherapy With Durvalumab (MEDI4736) and Tremelimumab in Combination With Either Y-90 SIRT or TACE for Intermediate Stage HCC With Pick-the-winner Design	84	Sep 2024 (recruiting)
NCT04090645	A Humanitarian Device Exemption Treatment Protocol of TheraSphere for Treatment of Unresectable Primary or Unresectable Secondary Liver Cancer	500	May 2025 (recruiting)
Unpublished			
NCT00846131	A Single-Center Proof of Concept Pilot Study to Evaluate the Safety, Efficacy, and Tolerability of Sorafenib Combined With TheraSphere in Subjects With Hepatocellular Carcinoma Awaiting Liver Transplantation	24	Sep 2016 (completed)
NCT01381211	Transarterial RAdioembolization Versus ChemoEmbolization for the Treatment of HCC: A Multicenter Randomized Controlled Trial (TRACE Trial)	140	Dec 2020 (suspended)
Metastatic Colorectal Cancer			
Unpublished			
NCT01483027[a]	A Phase III Clinical Trial Evaluating TheraSphere® in Patients With Metastatic Colorectal Carcinoma of the Liver Who Have Failed First Line Chemotherapy (EPOCH)	428	August 2020 (completed)
Intrahepatic Cholangiocarcinoma			
Ongoing			
NCT02807181[a]	SIRT Followed by CIS-GEM Chemotherapy Versus CIS-GEM Chemotherapy Alone as 1st Line Treatment of Patients With Unresectable Intrahepatic Cholangiocarcinoma (SIRCCA)	89	June 2021 (ongoing)
Unpublished			
Neuroendocrine Tumors			
NCT04362436[a]	A Phase II Assessment of the Safety and Efficacy of TheraSphere® Selective Internal Radiation Therapy (SIRT) in the Treatment of Metastatic (Liver) Neuroendocrine Tumours (NETs)	24	Sep 2022 (recruiting)
Metastatic Uveal Melanoma			
NCT02936388	Transarterial Radioembolisation in Comparison to Transarterial Chemoembolisation in Uveal Melanoma Liver Metastasis (SirTac)	108	Dec 2021 (recruiting)

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

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Documentation for Clinical Review

Please provide the following documentation:

- (click here >>>) Fax Back Form for Radiation Oncology Services

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®	36245	Selective catheter placement, arterial system; each first order abdominal, pelvic, or lower extremity artery branch, within a vascular family
	36246	Selective catheter placement, arterial system; initial second order abdominal, pelvic, or lower extremity artery branch, within a vascular family
	36247	Selective catheter placement, arterial system; initial third order or more selective abdominal, pelvic, or lower extremity artery branch, within a vascular family
	36248	Selective catheter placement, arterial system; additional second order, third order, and beyond, abdominal, pelvic, or lower extremity artery branch, within a vascular family (List in addition to code for initial second or third order vessel as appropriate)
	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

Type	Code	Description
	75726	Angiography, visceral, selective or supraselective (with or without flush aortogram), radiological supervision and interpretation
	75774	Angiography, selective, each additional vessel studied after basic examination, radiological supervision and interpretation (List separately in addition to code for primary procedure)
	75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
	77014	Computed tomography guidance for placement of radiation therapy fields
	77261	Therapeutic radiology treatment planning; simple
	77262	Therapeutic radiology treatment planning; intermediate
	77263	Therapeutic radiology treatment planning; complex
	77280	Therapeutic radiology simulation-aided field setting; simple
	77285	Therapeutic radiology simulation-aided field setting; intermediate
	77290	Therapeutic radiology simulation-aided field setting; complex
	77295	3-dimensional radiotherapy plan, including dose-volume histograms
	77300	Basic radiation dosimetry calculation, central axis depth dose calculation, TDF, NSD, gap calculation, off axis factor, tissue inhomogeneity factors, calculation of non-ionizing radiation surface and depth dose, as required during course of treatment, only when prescribed by the treating physician
	77370	Special medical radiation physics consultation
	77387	Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
	77399	Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services
	77417	Therapeutic radiology port image(s)
	77470	Special treatment procedure (e.g., total body irradiation, hemibody radiation, per oral or endocavitary irradiation)
	77778	Interstitial radiation source application, complex, includes supervision, handling, loading of radiation source, when performed
	77790	Supervision, handling, loading of radiation source
	79445	Radiopharmaceutical therapy, by intra-arterial particulate administration
HCPCS	C2616	Brachytherapy source, nonstranded, yttrium-90, per source
	G6001	Ultrasonic guidance for placement of radiation therapy fields
	G6002	Stereoscopic x-ray guidance for localization of target volume for the delivery of radiation therapy
	G6017	Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment
	S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres

Policy History

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

Effective Date	Action
12/18/2009	New Policy Adoption

Effective Date	Action
04/01/2011	Policy title change from Selective Internal Radiation Therapy for Primary and Metastatic Hepatic Tumors with position change
09/27/2013	Policy Title Revision, criteria revised
05/02/2014	Policy revision with position change
06/30/2015	Coding update
10/01/2016	Policy revisions without position change
09/01/2017	Policy revisions without position change
09/01/2018	Policy revisions without position change
11/01/2019	Policy revisions without position change
06/01/2020	Administrative update. Policy statement and guidelines updated.
11/20/2020	Annual review. Policy statement, guidelines and literature updated. Coding update.
08/01/2021	Annual review. Policy statement and guidelines updated.
09/01/2021	Administrative update. No change to policy statement. Literature review updated.
12/01/2021	Administrative update. No change to policy statement. Policy guidelines updated.
08/01/2022	Annual review. No change to policy statement.

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 (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.

Appendix A

<table>
<tr><th colspan="2">POLICY STATEMENT</th></tr>
<tr><th>BEFORE
Red font: Verbiage removed</th><th>AFTER
Blue font: Verbiage Changes/Additions</th></tr>
<tr><td>
Radioembolization for Primary and Metastatic Tumors of the Liver 8.01.43

Policy Statement:
Initial radioembolization of tumors of the liver may be considered medically necessary for a patient with all of the following:
I. The treatment is NOT a repeat session
II. Adequate functional status (Eastern Cooperative Oncology Group Performance Status [ECOG] 0 to 2)
III. Adequate liver function and reserve
IV. Child-Pugh class A or B
V. Liver-dominant metastases
VI. Documentation of one or more of the following:
A. Primary hepatocellular carcinoma that is unresectable (greater than 3 cm) and limited to the liver
B. Primary hepatocellular carcinoma as a bridge to liver transplantation
C. Unresectable primary intrahepatic cholangiocarcinoma
D. Hepatic metastases from neuroendocrine tumors (carcinoid and noncarcinoid) if all of the following are met:

1. Disease is diffuse and symptomatic
2. Systemic therapy has failed to control symptoms
E. Liver dominant unresectable hepatic metastases from colorectal carcinoma, melanoma (ocular or cutaneous), or breast cancer that are progressive, diffuse, and one or more of the following:
1. Refractory to chemotherapy
2. Not a candidate for chemotherapy or other systemic therapies

Radioembolization is considered investigational for all other hepatic metastases except as noted above.

Radioembolization is considered investigational for all other indications not described above.
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See Policy Guidelines for allowable codes/number of units.	See Policy Guidelines for allowable codes/number of units.