Policy Number	**RAD601.047**
Policy Effective Date	**11/15/2023**
Policy End Date	**12/31/2024**

Radioembolization for Primary and Metastatic Tumors of the Liver

Table of Contents

Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Primary Hepatocellular Carcinoma
Radioembolization **may be considered medically necessary** to treat primary hepatocellular carcinoma that is unresectable and limited to the liver.

Radioembolization **may be considered medically necessary** in primary hepatocellular carcinoma as a bridge to liver transplantation.

Primary Intrahepatic Cholangiocarcinoma
Radioembolization **may be considered medically necessary** to treat primary intrahepatic cholangiocarcinoma in patients with unresectable tumors.

Metastases from Neuroendocrine Tumors

Radioembolization **may be considered medically necessary** to treat hepatic metastases from neuroendocrine tumors (carcinoid and non-carcinoid) with diffuse and symptomatic disease when systemic therapy has failed to control symptoms.

Unresectable Hepatic Metastases
Radioembolization **may be considered medically necessary** to treat unresectable hepatic metastases from colorectal carcinoma, melanoma (ocular or cutaneous), or breast cancer that are both progressive and diffuse, in patients with liver-dominant disease who are refractory to chemotherapy or are not candidates for chemotherapy or other systemic therapies.

Other Indications
Radioembolization **is considered experimental, investigational and/or unproven** for all other hepatic metastases except as noted above.

Radioembolization **is considered experimental, investigational and/or unproven** for all other indications not described above.

Policy Guidelines

In general, radioembolization is used for unresectable hepatocellular carcinoma that is greater than 3 cm.

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

Radioembolization should be reserved for individuals with adequate functional status (Eastern Cooperative Oncology Group Performance Status 0-2), adequate liver function and reserve, Child-Pugh class A or B, and liver-dominant metastases.

Symptomatic disease from metastatic neuroendocrine tumors refers to symptoms related to excess hormone production.

Description

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 chemoembolization, 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 is 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 United States (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 (FDA) 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).

Regulatory Status

Currently, two 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, TheraSphere received 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® (Sirtex 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

This medical policy was originally created in 2008 and inactivated in 2016. It was reactivated in November 2020 and has been updated regularly since that time with searches of the PubMed database. The most recent literature update was performed through June 22, 2022.

Medical policies 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 medical policy is: Does RE improve the net health outcome in individuals with unresectable HCC?

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

Populations
The relevant population of interest is individuals with unresectable HCC 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 radiotherapy (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 trans-arterial chemoembolization (TACE) therapy compared with supportive care in patients with unresectable HCC. (1, 2) One study randomized patients to TACE, trans-arterial 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

Systematic Reviews

Various meta-analyses have been performed to compare the effects of trans-arterial chemoembolization (TACE), drug-eluting bead (DEB) plus TACE (DEB-TACE), and radioembolization (RE) in patients with unresectable hepatocellular carcinoma (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.

Pollock et al. (2021) conducted a systematic review and network meta-analysis of first-line treatments for unresectable HCC in TACE-ineligible patients. (4) Two RCTs comparing sorafenib to resin microspheres were analyzed, finding no significant differences in overall survival (hazard ratio [HR], 0.92; 95% CI, 0.79 to 1.08).

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. (5) Six RCTs (total 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. (6, 7)

Venerito et al. (2020) performed a meta-analysis to assess the noninferiority of RE as monotherapy or followed by sorafenib versus sorafenib monotherapy on OS. (8) 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 SIRT and sorafenib monotherapy, respectively ($p<0.01$)

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. (9) 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. (10) 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=0.02). 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=0.29) and at 3 years survival was 56% and 21% (OR=0.71; 95% CI, 0.21 to 2.55; p=0.62), 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 (total n=533 patients). (11) 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=0.33). At 2 years, the survival rate was higher for RE (27% vs 18%; RR=1.36; 95% CI, 1.05 to 1.76; p=0.02), 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 (total n=1557 patients), 2 of which were RCTs. (12) The OR for survival was not statistically significant at 1 year (OR=1.0; 95% CI, 0.8 to 1.3; p=0.93)

but favored RE in years 2 (OR=1.4; 95% CI, 1.1 to 1.90; p=0.01) and 3 (OR=1.5; 1.0 to 2.1; p=0.04).

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). (13) (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=0.02). 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

Dhondt et al. (2022) reported on results from the Transarterial Radioembolization versus Chemoembolization for the Treatment of Hepatocellular Carcinoma (TRACE), an open-label, single-center, superiority RCT. (14) The primary endpoint was time to overall tumor progression, with study sample size calculations assuming a 20% improvement with RE. A planned interim analysis for efficacy was performed when 45 disease progression events were observed, at which point the null hypothesis would be rejected when the hazard ratio (HR) was greater than 2.60 or less than 0.39 or when the p value was less than.0024. Patients with unresectable Barcelona Clinic Liver Cancer stage A and B HCC were randomized to treatment with glass microsphere-based RE (n=38) or DEB-TACE (n=34). The median time to progression was 17.1 months and 9.5 months for RE and DEB-TACE groups, respectively (HR 0.36; p=.002). With HR <0.39 for the primary end point in favor of RE at interim analysis, the null hypothesis was rejected, and the study was terminated on ethical grounds. Median PFS was 11.8 months in the RE arm and 9.1 months in the DEB-TACE arm (HR 0.40; 95% CI, 0.24 to 0.67; p<.001). Downstaging led to transplant in 10 patients treated with RE and 4 patients treated with DEB-TACE. Median OS in RE and DEB-TACE groups was 30.2 months and 15.6 months, respectively (HR 0.48; 95% CI, 0.28 to 0.82; p=.006).

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. (6) 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, (7) 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=0.619) or OS (592 days for RE vs 788 days for DEB-TACE, p=0.927).

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). (15) No significant differences were identified in median OS (10 vs. 10 months; p=0.711), median PFS (6 versus 7 months; p=0.992), 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. (16) 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=0.001). Median PFS was 564 days and 271 days (p=0.002) and median OS was 1198 days and 1043 days (p=0.35), respectively, for the RE group and the chemotherapy group.

Soydal et al. (2016) retrospectively assessed outcomes for patients receiving RE and TACE for HCC. (17) Each group included 40 patients. RE patients had a mean survival of 39 months vs. 31 months for TACE patients (p=0.014). There were no significant differences in complication or disease recurrence rates.

Oladeru et al. (2016) retrospectively analyzed Surveillance, Epidemiology, and End Results registry data, comparing survival outcomes for patients with HCC receiving RE with EBRT. (18) 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. (19) 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. (20) 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. (21) 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 ($p<0.05$). 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.

Subsection 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, randomized controlled trials (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 hepatocellular carcinoma (HCC), then these results are consistent with some degree of efficacy for RE in the treatment of HCC. In all studies, tumor response is observed, which may improve survival.

Radioembolization as a Bridge to Liver Transplantation for Unresectable Hepatocellular Carcinoma (HCC)

Systematic Reviews

Kulik et al. (2018) published a systematic review of 18 comparative studies and 31 noncomparative 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). (22) 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 trans-arterial

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) (22)	1996-2016	49	Unresectable hepatocellular cardinoma	• 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)					
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. (23) 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=0.007). 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. (24) 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 peri-transplant 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. (25) 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. (26)

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). (27) 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. (28) 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. OS 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. (29) Three-year survival was not significantly different with RE vs. TACE (92.9% vs. 75.7%; p=0.052). However, microvascular invasion occurred in 3.6% versus 27% of patients treated with RE versus TACE (p=0.013).

In a retrospective review, Tohme et al. (2013) reported on 20 consecutive HCC patients awaiting liver transplant who received RE as bridge therapy. (30) 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. (31) 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). (32) 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 ($p<0.05$).

Subsection 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 medical policy is: Does RE improve the net health outcome in individuals with unresectable ICC?

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

Populations
The relevant population of interest is individuals with unresectable ICC. 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 individuals. (33)

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%. (34) 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

Schartz et al. (2022) reported on the efficacy and survival profile of RE for unresectable ICC. (35) Twenty-one studies representing 921 patients with follow-up duration from 3 to 36 months were evaluated, finding an overall disease control rate of 82.3% (95% CI, 76.7% to 87.8%; I^2 = 81%), median PFS of 7.8 months (95% CI, 4.2 to 11.3; I^2 = 94%), and median overall survival (OS) of 12.7 months (95% CI, 10.6 to 14.8; I^2 = 62%). Patients were downstaged for surgical resection in 11% of cases (95% CI, 6.1% to 15.9%; I^2 = 78%). The analysis is limited by inclusion of primarily retrospective study designs and considerable clinical and methodologic heterogeneity.

Edeline et al. (2021) conducted a systematic review and pooled analysis of locoregional therapies in patients with unresectable ICC. (36) Ninety-three studies were pooled for analysis, representing 15 cohorts (n=645) for ablation, 18 cohorts (n=541) for external beam radiation therapy (EBRT), 27 cohorts (n=1232) for RE, 22 cohorts for trans-arterial chemoembolization (TACE), and 16 cohorts (n=331) for hepatic arterial infusion (HAI). Pooled weighted mean PFS was 15.6, 7.8, 15.0, and 10.1 months for EBRT, RE, TACE, and HAI, respectively. Pooled weighted mean overall survival was 30.2, 18.9, 14.1, 15.9, and 21.3 months for ablation, EBRT, RE, TACE, and HAI, respectively. The authors noted that the quality of the studies was insufficient to derive strong recommendations, with the exception of consistently good outcomes for ablation. Instead, the pooled results are presented to establish benchmarks for the design of future clinical trials.

Yu et al. (2021) reported on outcomes in a systematic review and meta-analysis of RE compared to external beam radiation therapy (EBRT) in the treatment of unresectable ICC. (37) Between 2000 and 2020, 29 and 20 studies representing 732 and 443 patients were identified for RE and EBRT groups, respectively. From initial treatment, median overall survival for RE and EBRT was 12.0 months (95% CI, 10.8 to 14.6) and 13.6 months (95% CI, 11.1 to 16.0), respectively. As first-line therapy, median overall survival for RE was 36.1 months (95% CI, 20.6 to 39.5) compared to 11.0 months (95% CI, 9.3 to 13.6) for EBRT. Downstaging to surgery among treatment-naive patients was reported in 30.5% and 18.3% of RE and EBRT groups, respectively. Patients treated with RE experienced higher rates of postembolization abdominal pain, ulcer, nausea, anorexia, thrombocytopenia, hyperbilirubinemia, and hypoalbuminemia. In contrast, EBRT was associated with higher rates of anemia and neutropenia. The authors noted that comparison between groups is limited due to significant population and treatment heterogeneity.

Mosconi et al. (2021) published a systematic review and meta-analysis comparing the treatment efficacy of RE (18 studies; n=789) and trans-arterial chemoembolization (13 studies; TACE; n=906). (38) The median survival was 13.5 months (95% CI, 11.4 to 16.1) and 14.2

months (95% CI, 11.6 to 17.6) for RE and TACE groups, respectively. The survival difference between groups was negligible at 2 and 3 years. Clinical adverse events occurred at a higher frequency in patients treated with TACE (58.5%) compared to RE (43.0%).

Boehm et al. (2015) conducted a systematic review comparing hepatic artery-based therapies, including HAI, TACE, DEB-TACE, and Y90 RE, for unresectable ICC. (39) 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. (40) 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 down-staged 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 (NCT02807181).

Case Series

Numerous small case series (range, 19-115 patients) evaluating RE for unresectable ICC have been published. (41-52) Predominantly retrospective case reviews have assessed heterogeneous populations, making it difficult to ascertain which patients may benefit most from RE. Populations within and between studies have differed in terms of performance status, tumor distribution (e.g., unilobar versus bilobar) (45, 50), morphology (e.g., infiltrative), metastatic disease (e.g., lymph node or extrahepatic metastases), prior treatments (e.g., chemotherapy, [43, 47] surgery, and other liver-directed therapies), treatment setting (e.g., neoadjuvant, [52] palliative [45]), and comorbidities (e.g., cirrhosis [42]). Several studies have reported on resection outcomes following downstaging treatment with RE alone (42, 46, 50, 52) or in combination with chemotherapy. (41, 45) One study compared outcomes with glass versus resin microspheres, finding no significant difference in overall survival between groups. (42) Across series, the median survival in patients treated with RE ranged from 6 to 22 months. Several studies identified favorable subgroups with respect to overall survival, reporting prolonged outcomes in treatment-naive patients, (44) and for tumor burden ≤25%, (47, 51) peripheral tumor type, (49, 50) and an ECOG performance score of 0. (47, 49, 50).

Section Summary: Intrahepatic Cholangiocarcinoma

The evidence for radioembolization (RE) in intrahepatic cholangiocarcinoma (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 medical policy 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 policy.

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. (53)

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), trans-arterial embolization (TAE) or trans-arterial chemoembolization (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 neuroendocrine tumors than carcinoids; and 3) it is frequently associated with significant toxicity. (54) Chemoembolization has shown response rates of nearly 80%, but the effect is of short duration, and a survival benefit has not been demonstrated. (54)

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). (55) 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 SIRT for neuroendocrine liver metastases. (56) 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. (57) 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). (58) Between RE and TACE, there were no differences in overall morbidity (13.7% vs. 22.6%, respectively; p=0.17), grade 3/4 complication (5.9% vs. 9.2%; p=0.58), 90-day mortality (9.8% vs. 5.2%; p=0.21), median OS (35.9 months vs. 50.1 months; p=0.3), or PFS (15.9 vs. 19.9 months; p=0.37). However, disease control rate was greater for TACE compared with RE (96% vs. 83%, p<0.01).

Engelman et al. (2014) retrospectively compared trans-arterial, liver-directed therapies, including RE, hepatic artery embolization (HAE), and hepatic artery chemoembolization (HACE), in 42 patients treated for metastatic neuroendocrine tumors. (59) 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=0.265). There were no statistically significant differences between treatment modalities in radiographic response at 6 months post-procedure (p=0.134), time to progression (p=0.968), or OS (p=0.30).

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. (60) 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. (61) 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. (54) 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. (62) 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. (63-67)

Section Summary: Unresectable Neuroendocrine Tumors

The available comparative evidence for the use of radioembolization (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 radioembolization (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 medical policy 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 policy.

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. (68) 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 5. 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 chemo-resistant, unresectable CRC liver metastasis (total n=979 patients). (69) They included 2 RCTs: (Gray et al. [2001] (70); Hendlisz et al. [2010] (71); 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 chemo-resistant, unresectable CRC liver metastasis. (72) 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) (70) and Van Hazel et al. (2004). (73) 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. (68) 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. (74) Townsend et al. (2009) found insufficient evidence to demonstrate that RE improved survival or quality of life. (74) 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. (13)

Randomized Controlled Trials

Mulcahy et al. (2021) reported on outcomes from the Efficacy Evaluation of TheraSphere Following Failed First Line Chemotherapy in Metastatic Colorectal Cancer (EPOCH) trial, an open-label phase 3 trial studying the impact of RE with TheraSphere in combination with second-line systemic chemotherapy for colorectal liver metastases in 428 patients from 95 centers in North America, Europe, and Asia. (75) Patients who had progressed on first-line chemotherapy were randomized 1:1 to receive second-line oxaliplatin- or irinotecan-based chemotherapy with (n=215) or without RE (n=213). The study was designed to detect a HR of 0.71 for PFS and 0.65 for hPFS favoring RE plus chemotherapy. The median PFS was 8.0 months (95% CI, 7.2 to 9.2) and 7.2 months (95% CI, 5.7 to 7.6), respectively, with a corresponding hazard ratio of 0.69 (95% CI, 0.54 to 0.88; p=.0013) favoring RE. The median hepatic PFS was 9.1 months (95% CI, 7.8 to 9.7) and 7.2 months (95% CI, 5.7 to 7.6) for patients treated with and without RE, respectively (HR = 0.59; 95% CI, 0.46 to 0.77; p<.0001). Delayed progression was also observed for tumors with *KRAS* mutation, left-sided primary tumor, hepatic tumor burden of 10-25%, ≤3 lesions, the addition of a biologic agent, and resected primary. Median overall survival was 14.0 months (95% CI, 11.8 to 15.5) and 14.4 months (95% CI, 12.8 to 16.1; p=.7229) for the RE and chemotherapy groups, respectively (HR = 1.07; 95% CI, 0.86 to 1.32). However, it was noted that the study was not designed or powered for overall survival and the outcome may be confounded by subsequent locoregional therapies including RE in the control arm. The frequency of grade 3 adverse events was higher with the addition of RE to chemotherapy (68.4% versus 49.3%). Overall, the investigators noted that the addition of RE to chemotherapy resulted in a statistically significant delay of disease progression. However, further research will be pursued to better identify patients who might benefit most from treatment, as well as dosimetric considerations to optimize the risk-benefit profile.

A phase 3 RCT by van Hazel et al. (2016) compared modified fluorouracil, leucovorin, and oxaliplatin (FOLFOX) chemotherapy and FOLFOX chemotherapy plus SIR-Spheres in 530 patients with chemotherapy-naive liver-dominant metastatic disease. (76) The use of Bevacizumab was allowed with FOLFOX chemotherapy, at the investigator's discretion. 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=0.43). 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. This finding was consistent irrespective of tumor burden, bevacizumab therapy, or performance status. Wasan et al. (2017) analyzed OS from this study in combination with 2 other studies of chemotherapy with and without RE in the first-line setting (77). Overall, 549 patients were randomly assigned to FOLFOX alone and 554 patients were assigned FOLFOX plus RE. 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 Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30), and EORTC Colorectal Liver Metastases cancer module (EORTC QLQ-LMC21) (78). 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. (70) Accrual was halted early, entering 74 patients rather than the planned at the discretion of the investigator rather than by planned data monitoring board oversight.T o 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=0.01) and volume (50% vs. 24%, p=0.03), or by serum carcinoembryonic antigen levels (72% vs. 47%, p=0.004), all respectively. They also reported increased time to progression detected by increased area (9.7 months vs. 15.9 months; p=0.001) or volume (7.6 months vs. 12.0 months; p=0.04), 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 RE 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. (21, 79)

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. (73) Disease time to progression was greater in those receiving combination therapy (18.6 months vs 3.6 months, respectively; p<0.001).

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. (71) 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=0.003). 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=0.80).

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). (80) Extra-hepatic metastasis was more frequent with DEB-TACE (68.1% vs. 47.7%; p=0.014), as was occurrence of ≥10 liver lesions (42.2% vs. 68.8%; p=0.001). Toxicity was not significantly different between DEB-TACE and RE (27% vs. 9.1%, respectively; p=0.057). 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 chemo-refractory, liver-dominant colorectal metastases (n=29 in each group). (81) 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<0.001; HR, 0.3; 95% CI, 0.16 to 0.55; p<0.001). Adverse events were considered generally mild-to-moderate and manageable.

Section Summary: Unresectable Intrahepatic Metastatic Colorectal Carcinoma
The evidence for the use of radioembolization (RE) to treat unresectable intrahepatic metastatic colorectal carcinoma (CRC) includes systematic reviews, randomized controlled trials (RCTs), and nonrandomized comparative studies. The EPOCH RCT compared chemotherapy with or without RE in 428 patients who had progressed on first-line chemotherapy, finding that the addition of RE significantly prolonged the primary endpoints of PFS (HR, 0.69; 95% CI, 0.54 to 0.88) and hepatic PFS (HR, 0.59; 95% CI, 0.46 to 0.77) in the second-line setting. While studies of patients with prior chemotherapy failure have not shown definitive superiority of RE compared with alternatives in terms of survival benefit, they tend to show greater tumor response and significantly delayed disease progression, particularly with the combined use of RE with chemotherapy.

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 medical policy is: Does RE improve the net health outcome in individuals with unresectable intrahepatic metastases from other cancers?

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

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 6. 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. (82)

Systematic Review
Aarts et al. (2021) published a systematic review and meta-analysis assessing the evidence for intra-arterial therapies in liver metastatic breast cancer. (83) A total of 26 studies representing 1266 individuals were identified, including 11 articles on RE, 10 articles on transarterial chemoembolization (TACE), 4 articles on chemo-infusion, and 1 article comparing RE to TACE. Pooled response rates were 49% (95% CI, 32% to 67%), 34% (95% CI, 22% to 50%), and 19% (95% CI, 14% to 25%) for RE, TACE, and chemo-infusion, respectively. Pooled median survival

was 9.2 months (range, 6.1 to 35.4) for RE, 17.8 months (range, 4.6 to 47.0) for TACE, and 7.9 months (range, 7.0 to 14.2) for chemo-infusion. Overall survival rates could not be compared due to missing data at specific time points and large study heterogeneity.

Feretis et al. (2020) performed a systematic review of RE for treatment of metastatic intrahepatic breast cancer. (84) Twelve case series were included (total 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. (85) 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 delivered 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. (86) 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.

<u>Metastatic Melanoma</u>

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

Systematic Reviews

Alexander et al. (2022) published a systematic review of RE for hepatic metastases of uveal melanoma. (87) Eleven studies representing 268 individuals were identified for review. Most studies were retrospective (n=9; 82%). The disease control rate was 67.5% and the median overall survival was 12.3 months. Median hepatic PFS was 5.4 months.

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. (88) 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. (89) 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 immuno-embolization, 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). (90) 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=0.02). Median OS from diagnosis of melanoma liver metastases was longer in RE-treated subjects (19.9 months vs. 4.8 months;
p<0.000), as was median OS from diagnosis of the primary melanoma (119.9 months vs. 26.1 months; p<0.001), respectively. Pre- and post-treatment 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. (91) 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 2013 have reported on the use of RE in patients with hepatic metastases from melanoma. (92-95) Three included only patients with ocular melanoma, (92-94), and two included patients with ocular or cutaneous melanoma. (95, 96) 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. (96) Four studies reported tumor response data, by RECIST criteria. 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. (92) 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. (94) 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. (93) 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. (96) 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) (95) (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. (97) 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. (98) All patients had received at least 1 course of chemotherapy before receiving resin-based (n=17) or glass-based (n=22) Y90 RE. Most toxicities observed (93%) were grade 1 or 2, and the objective response rate (complete and partial responses) was 36%. Six months after treatment, 30 patients showed stable disease or response, and the overall 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 81 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 hepatocellular carcinoma (HCC) who receive radioembolization (RE) or RE with a liver transplant, the evidence includes primarily retrospective and prospective observational studies, with limited evidence from randomized controlled trials (RCTs). Relevant outcomes are overall survival (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 trans-arterial chemoembolization (TACE) and trans-arterial chemoembolization with drug-eluting beads (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 intrahepatic cholangiocarcinoma (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 trans-arterial 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 (CRC) 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. While studies of patients with prior chemotherapy failure have methodologic problems and do not show definitive superiority of RE compared with alternatives in terms of survival benefits, they tend to show greater tumor response and significantly delayed disease progression, particularly with combined use of RE and chemotherapy. For example, the EPOCH RCT found significantly prolonged primary endpoints of PFS (HR, 0.69; 95% CI, 0.54 to 0.88) and hepatic PFS (HR, 0.59; 95% CI, 0.46 to 0.77) with

combined RE and chemotherapy in patients who had progressed on first-line chemotherapy. 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.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

Primary Hepatobiliary Carcinoma

The NCCN guidelines (v.3.2022) on the treatment of hepatobiliary carcinoma indicate that the use of arterially directed therapies, including trans-arterial bland embolization, trans-arterial chemoembolization, and drug-eluting beads trans-arterial 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). RE with yttrium-90 microspheres has an increased risk of radiation-induced liver disease in patients with bilirubin levels greater than 2 mg/dL. Delivery of 205 Gy or more to the tumor may be associated with increased overall survival. RE may be more appropriate in some patients with advanced HCC, specifically patients with segmental or lobar portal vein, rather than main portal vein, thrombosis. (34)

Metastatic Neuroendocrine Tumors

The NCCN guidelines (v.1.2022) 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. (99)

Metastatic Colon Cancer

The NCCN guidelines (v.3.2022) 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. The guidelines also note that further investigation is necessary to identify the role of radioembolization at earlier stages of disease, particularly in patients with right-sided primary origin. (100)

Metastatic Uveal Melanoma

The NCCN guidelines (v.2.2022) 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. (101)

American College of Radiology et al.

In 2021, the American College of Radiology issued a practice parameter jointly developed with the American Brachytherapy Society, the American College of Nuclear Medicine, the American Society for Radiation Oncology, the Society of Interventional Radiology, and the Society of Nuclear Medicine and Molecular Imaging addressing the use of RE for the treatment of liver malignancies with glass- or resin-based yttrium-90 microspheres. (102) The guidelines provided indications and contraindications for treatment as follows:

- "Indications for both agents include but are not limited to the following:
    1. The presence of unresectable or inoperable primary or secondary liver malignancies (particularly colorectal cancer and neuroendocrine tumor metastases). The tumor burden should be liver dominant, not necessarily exclusive to the liver. Patients should also have a performance status that will allow them to benefit from such therapy.
    2. A life expectancy of at least 3 months."
- "Absolute contraindications include the following:
    1. Inability to catheterize the hepatic artery.
    2. Fulminant liver failure.
    3. Initial mapping angiography and/or technetium-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy demonstrating nontarget deposition to the gastrointestinal organs that cannot be corrected by angiographic techniques.
    4. Pretreatment hepatic arterial administration with technetium-99m MAA demonstrative of unfavorable (or unacceptable) shunt function between the liver and the pulmonary parenchyma. This shunt fraction must not be greater than acceptable limits specific to each brachytherapy device.
    5. Active hepatic infection.
    6. Therapy during pregnancy may possibly be an option in extraordinary circumstances and with multidisciplinary consult and considerations."
- "Relative contraindications include the following:
    1. Excessive tumor burden in the liver with great than 50-70% of the parenchyma replaced by tumor. In the setting of more extensive tumor burden, treatment can be considered if synthetic hepatic function is preserved.
    2. Total bilirubin greater than 2 mg/dL (in the absence of obstructive cause), which indicates severe liver function impairment. Nonobstructive bilirubin elevations may indicate that liver metastases have caused liver impairment to the degree that risks outweigh benefits for this therapy. In contrast, patients with HCC and elevated bilirubin may be treated with radioembolization if a segmental or subsegmental infusion can be performed.
    3. Prior radiation therapy to the liver or upper abdomen that included a significant volume of the liver (clinical judgment by the [authorized user] required).

4. Care must be employed when patients are on systemic therapies that may potentiate or may alter the impact of radioembolization and should use caution when combining therapies."

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." (103)

In March 2021, a NICE technology appraisal guidance on selective internal radiation therapies (SIRTs) for treating hepatocellular carcinoma was published, providing specific evidence-based recommendations for the use of SIR-Spheres (Sirtex), TheraSphere (Boston Scientific), and QuiremSpheres (Quirem Medical). (104) The guidance states that RE with SIR-Spheres or TheraSphere is recommended as an option for treating unresectable advanced hepatocellular carcinoma in adults only if "used for people with Child-Pugh grade A liver impairment when conventional transarterial therapies are inappropriate, and the company provides [the microspheres] according to the commercial arrangement." The guidance also stated that "clinical trial data for these SIRTs compared with other treatment options are limited. But, compared with sorafenib, SIRTs may have fewer and more manageable adverse effects, which can improve quality of life." The use of QuiremSpheres, imageable holmium-166 microspheres, was not recommended due to reduced clinical efficacy compared to sorafenib and higher cost. QuiremSpheres received its CE mark in April 2015 in Europe and is not commercially available in the U.S.

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." (105)

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." (106)

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 7.

Table 7. Summary of Key Trials

NCT. No.	Name	Planned Enrollment	Completion Date
Hepatocellular Carcinoma			
Ongoing			
NCT01176604	Protocol for Use of TheraSphere® for Treatment of Unresectable Hepatocellular Carcinoma	305	Aug 2022 (recruiting)
NCT01556490[a]	A Phase III Clinical Trial of Intra-arterial TheraSphere® in the Treatment of Patients With Unresectable Hepatocellular Carcinoma (HCC) (STOP-HCC)	526	Sep 2022 (ongoing)
NCT04736121[a]	A Prospective, Multicenter, Open-label Single Arm Study Evaluating the Safety & Efficacy of Selective Internal Radiation Therapy Using SIR-Spheres® Y-90 Resin Microspheres on DoR & ORR in Unresectable Hepatocellular Carcinoma Patients (DOORwaY90)	100	Mar 2024 (recruiting)
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 Pickthe-winner Design	84	Sep 2024 (recruiting)
NCT04069468[a]	A Prospective, Post Approval, Multiple Centre, Open-Label, Non-Interventional, Registry Study to Evaluate Effectiveness of TheraSphere® in Clinical Practice in France (PROACTIF)	500	Jan 2025 (recruiting)
NCT05377034[a]	A Multinational, Double-blind, Placebo-Controlled, Parallel Randomized Arms, Phase II Trial to Compare Safety and Efficacy of Selective Internal Radiation Therapy (Y-90 Resin Microspheres) Followed by Atezolizumab Plus Bevacizumab) Versus Selective Internal Radiation Therapy (SIRT-Y90) Followed by Placebo in Patients With	176	Nov 2025 (not yet recruiting)

	Locally Advanced Hepatocellular Carcinoma (HCC) (STRATUM)		
NCT05063565[a]	An Open-Label, Prospective, Multi-Center, Randomized Clinical Trial to Evaluate The Efficacy and Safety Of TheraSphere Followed by Durvalumab (Imfinzi®) With Tremelimumab, Versus TheraSphere Alone For Hepatocellular Carcinoma (HCC) (ROWAN)	150	Apr 2026 (recruiting)
NCT02072356	A Humanitarian Device Exemption Treatment Protocol of TheraSphere® For Treatment of Unresectable Hepatocellular Carcinoma	800	Aug 2027 (recruiting)
Unpublished			
NCT04090645	A Humanitarian Device Exemption Treatment Protocol of TheraSphere for Treatment of Unresectable Primary or Unresectable Secondary Liver Cancer	187	Apr 2021 (completed)
Metastatic Colorectal Cancer			
NCT05195710[a]	Preoperative Y-90 Radioembolization for Tumor Control and Future Liver Remnant Hypertrophy in Patients With Colorectal Liver Metastases	50	Mar 2024 (not yet recruiting)
Intrahepatic Cholangiocarcinoma			
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	Oct 2022 (ongoing)
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) (ArTisaN)	24	Sep 2024 (recruiting)
Metastatic Uveal Melanoma			
NCT02936388	Transarterial Radioembolisation in Comparison to Transarterial Chemoembolisation in Uveal Melanoma Liver Metastasis (SirTac)	108	Dec 2022 (recruiting)
Metastatic Breast Cancer			

NCT05315687[a]	Safety and Efficacy of Radioembolization of Metastatic Breast Cancer to the Liver as a 2nd/3rd Line Therapy	50	Jul 2025 (not yet recruiting)
Various Metastatic Cancers			
NCT00532740	A Humanitarian Device Exemption Compassionate Use Protocol of TheraSphere for Treatment of Unresectable Metastatic Cancer to the Liver	2000	Apr 2025 (ongoing)

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

Coding

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

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

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

CPT Codes	37243, 75894, 77399, 77778, 79445
HCPCS Codes	C2616, S2095

*Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.

References

1. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial. Lancet. May 18 2002; 359(9319):1734-1739. PMID 12049862
2. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. May 2002; 35(5):1164-1171. PMID 11981766
3. Tao R, Li X, Ran R, et al. A mixed analysis comparing nine minimally invasive surgeries for unresectable hepatocellular carcinoma patients. Oncotarget. Jan 17 2017; 8(3):5460-5473. PMID 27705924
4. Pollock RF, Brennan VK, Shergill S, et al. A systematic literature review and network meta-analysis of first-line treatments for unresectable hepatocellular carcinoma based on data from randomized controlled trials. Expert Rev Anticancer Ther. Mar 2021; 21(3):341-349. PMID 33131346

5. Abdel-Rahman O, Elsayed Z. Yttrium-90 microsphere radioembolisation for unresectable hepatocellular carcinoma. Cochrane Database Syst Rev. Jan 24 2020; 1:CD011313. PMID 31978267
6. Kolligs FT, Bilbao JI, Jakobs T, et al. Pilot randomized trial of selective internal radiation therapy vs. chemoembolization in unresectable hepatocellular carcinoma. Liver Int. Jun 2015; 35(6):1715-1721. PMID 25443863
7. Pitton MB, Kloeckner R, Ruckes C, et al. Randomized comparison of selective internal radiotherapy (SIRT) versus drug-eluting bead transarterial chemoembolization (DEB-TACE) for the treatment of hepatocellular carcinoma. Cardiovasc Intervent Radiol. Apr 2015; 38(2):352-360. PMID 25373796
8. Venerito M, Pech M, Canbay A, et al. NEMESIS: Non-inferiority, individual patient meta-analysis of selective internal radiation therapy with yttrium-90 resin microspheres versus sorafenib in advanced hepatocellular carcinoma. J Nucl Med. Dec 2020; 61(12):1736-1742. PMID 32358087
9. Yang B, Liang J, Qu Z, et al. Transarterial strategies for the treatment of unresectable hepatocellular carcinoma: A systematic review. PLoS ONE. 2020; 15(2):e0227475. PMID 32074102
10. Ludwig JM, Zhang D, Xing M, et al. Meta-analysis: Adjusted indirect comparison of drug-eluting bead transarterial chemoembolization versus 90 Y-radioembolization for hepatocellular carcinoma. Eur Radiol. May 2017; 27(5):2031-2041. PMID 27562480
11. Lobo L, Yakoub D, Picado O, et al. Unresectable hepatocellular carcinoma: radioembolization versus chemoembolization: A systematic review and meta-analysis. Cardiovasc Intervent Radiol. Nov 2016; 39(11):1580-1588. PMID 27586657
12. Facciorusso A, Serviddio G, Muscatiello N. Transarterial radioembolization vs chemoembolization for hepatocarcinoma patients: A systematic review and meta-analysis. World J Hepatol. Jun 28 2016; 8(18):770-778. PMID 27366304
13. Vente MA, Wondergem M, van der Tweel I, et al. Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: A structured meta-analysis. Eur Radiol. Apr 2009; 19(4):951-959. PMID 18989675
14. Dhondt E, Lambert B, Hermie L, et al. 90 Y radioembolization versus drug-eluting bead chemoembolization for unresectable hepatocellular carcinoma: Results from the TRACE phase ii randomized controlled trial. Radiology. Jun 2022; 303(3):699-710. PMID 35258371
15. Facciorusso A, Bargellini I, Cela M, et al. Comparison between Y90 radioembolization plus sorafenib and Y90 radioembolization alone in the treatment of hepatocellular carcinoma: A propensity score analysis. Cancers (Basel). Apr 07 2020; 12(4):897. PMID 32272656
16. Padia SA, Johnson GE, Horton KJ, et al. Segmental Yttrium-90 radioembolization versus segmental chemoembolization for localized hepatocellular carcinoma: results of a single-center, retrospective, propensity score-matched study. J Vasc Interv Radiol. Jun 2017; 28(6):777-785.e1. PMID 28365172
17. Soydal C, Arslan MF, Kucuk ON, et al. Comparison of survival, safety, and efficacy after transarterial chemoembolization and radioembolization of Barcelona Clinic liver cancer stage B-C hepatocellular cancer patients. Nucl Med Commun. Jun 2016; 37(6):646-649. PMID 26905317

18. Oladeru OT, Miccio JA, Yang J, et al. Conformal external beam radiation or selective internal radiation therapy-a comparison of treatment outcomes for hepatocellular carcinoma. J Gastrointest Oncol. Jun 2016; 7(3):433-440. PMID 27284477
19. El Fouly A, Ertle J, El Dorry A, et al. In intermediate stage hepatocellular carcinoma: radioembolization with yttrium 90 or chemoembolization? Liver Int. Feb 2015; 35(2):627-635. PMID 25040497
20. Gramenzi A, Golfieri R, Mosconi C, et al. Yttrium-90 radioembolization vs sorafenib for intermediate-locally advanced hepatocellular carcinoma: A cohort study with propensity score analysis. Liver Int. Mar 2015; 35(3):1036-1047. PMID 24750853
21. Carr BI, Kondragunta V, Buch SC, et al. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: A two-cohort study. Cancer. Mar 01 2010; 116(5):1305-1314. PMID 20066715
22. Kulik L, Heimbach JK, Zaiem F, et al. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis. Hepatology. Jan 2018; 67(1):381-400. PMID 28859222
23. Salem R, Gordon AC, Mouli S, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology. Dec 2016; 151(6):1155-1163.e2. PMID 27575820
24. Kulik L, Vouche M, Koppe S, et al. Prospective randomized pilot study of Y90+/-sorafenib as bridge to transplantation in hepatocellular carcinoma. J Hepatol. Aug 2014; 61(2):309-317. PMID 24681342
25. Salem R, Johnson GE, Kim E, et al. Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable HCC: The LEGACY Study. Hepatology. Nov 2021; 74(5):2342-2352. PMID 33739462
26. U.S. Food and Drug Administration. Summary of Safety and Effectiveness Data (SSED): TheraSphere. Available at: <https://www.accessdata.fda.gov> (accessed June 22, 2022)
27. Pellegrinelli J, Chevallier O, Manfredi S, et al. Transarterial radioembolization of hepatocellular carcinoma, liver-dominant hepatic colorectal cancer metastases, and cholangiocarcinoma using Yttrium90 microspheres: eight-year single-center real-life experience. Diagnostics (Basel). Jan 14 2021; 11(1):122. PMID 33466706
28. Gabr A, Kulik L, Mouli S, et al. Liver Transplantation Following Yttrium-90 Radioembolization: 15-year Experience in 207- Patient Cohort. Hepatology. March 2021; 73(3):998-1010. PMID 32416631
29. Zori AG, Ismael MN, Limaye AR, et al. Locoregional therapy protocols with and without radioembolization for hepatocellular carcinoma as bridge to liver transplantation. Am J Clin Oncol. May 2020; 43(5):325-333. PMID 32079854
30. Tohme S, Sukato D, Chen HW, et al. Yttrium-90 radioembolization as a bridge to liver transplantation: A single-institution experience. J Vasc Interv Radiol. Nov 2013; 24(11):1632-1638. PMID 24160821
31. Ramanathan R, Sharma A, Lee DD, et al. Multimodality therapy and liver transplantation for hepatocellular carcinoma: A 14- year prospective analysis of outcomes. Transplantation. Jul 15 2014; 98(1):100-106. PMID 24503764

32. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: Chemoembolization versus radioembolization. Am J Transplant. Aug 2009; 9(8):1920-1928. PMID 19552767
33. National Organization for Rare Disorders. Rare Disease Database: Cholangiocarcinoma. 2020; Available at: <https://rarediseases.org> (accessed June 22, 2022).
34. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Hepatobiliary Cancers. Version 3.2022. Available at: <https://www.nccn.org> (accessed November 9, 2022)
35. Schartz DA, Porter M, Schartz E, et al. Transarterial yttrium-90 radioembolization for unresectable intrahepatic cholangiocarcinoma: A systematic review and meta-analysis. J Vasc Interv Radiol. Jun 2022; 33(6):679-686. PMID 35219834
36. Edeline J, Lamarca A, McNamara MG, et al. Locoregional therapies in patients with intrahepatic cholangiocarcinoma: A systematic review and pooled analysis. Cancer Treat Rev. Sep 2021; 99:102258. PMID 34252720
37. Yu Q, Liu C, Pillai A, et al. Twenty years of radiation therapy of unresectable intrahepatic cholangiocarinoma: Internal or external? A systematic review and meta-analysis. Liver Cancer. Sep 2021; 10(5):433-450. PMID 34721506
38. Mosconi C, Solaini L, Vara G, et al. Transarterial chemoembolization and radioembolization for unresectable intrahepatic cholangiocarcinoma - A systemic review and meta-analysis. Cardiovasc Intervent Radiol. May 2021; 44(5):728-738. PMID 33709272
39. Boehm LM, Jayakrishnan TT, Miura JT, et al. Comparative effectiveness of hepatic artery based therapies for unresectable intrahepatic cholangiocarcinoma. J Surg Oncol. Feb 2015; 111(2):213-220. PMID 25176325
40. Edeline J, Touchefeu Y, Guiu B, et al. Radioembolization plus chemotherapy for first-line treatment of locally advanced intrahepatic cholangiocarcinoma: A phase 2 clinical trial. JAMA Oncol. Jan 01 2020; 6(1):51-59. PMID 31670746
41. Riby D, Mazzotta AD, Bergeat D, et al. Downstaging with radioembolization or chemotherapy for initially unresectable intrahepatic cholangiocarcinoma. Ann Surg Oncol. Oct 2020; 27(10):3729-3737. PMID 32472411
42. Buettner S, Braat AJAT, Margonis GA, et al. Yttrium-90 radioembolization in intrahepatic cholangiocarcinoma: A multicenter retrospective analysis. J Vasc Interv Radiol. Jul 2020; 31(7):1035-1043.e2. PMID 32473757
43. Jia Z, Paz-Fumagalli R, Frey G, et al. Resin-based Yttrium-90 microspheres for unresectable and failed first-line chemotherapy intrahepatic cholangiocarcinoma: preliminary results. J Cancer Res Clin Oncol. Mar 2017; 143(3):481-489. PMID 27826686
44. Mosconi C, Gramenzi A, Ascanio S, et al. Yttrium-90 radioembolization for unresectable/recurrent intrahepatic cholangiocarcinoma: A survival, efficacy and safety study. Br J Cancer. Jul 26 2016; 115(3):297-302. PMID 27336601
45. Rayar M, Sulpice L, Edeline J, et al. Intra-arterial yttrium-90 radioembolization combined with systemic chemotherapy is a promising method for downstaging unresectable huge intrahepatic cholangiocarcinoma to surgical treatment. Ann Surg Oncol. Sep 2015; 22(9):3102-3108. PMID 25623598

46. Mouli S, Memon K, Baker T, et al. Yttrium-90 radioembolization for intrahepatic cholangiocarcinoma: safety, response, and survival analysis. J Vasc Interv Radiol. Aug 2013; 24(8):1227-1234. PMID 23602420
47. Hoffmann RT, Paprottka PM, Schon A, et al. Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: Factors associated with prolonged survival. Cardiovasc Intervent Radiol. Feb 2012; 35(1):105-116. PMID 21431970
48. Haug AR, Heinemann V, Bruns CJ, et al. 18F-FDG PET independently predicts survival in patients with cholangiocellular carcinoma treated with 90Y microspheres. Eur J Nucl Med Mol Imaging. Jun 2011; 38(6):1037-1045. PMID 21308371
49. Saxena A, Bester L, Chua TC, et al. Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. Ann Surg Oncol. Feb 2010; 17(2):484-491. PMID 19876691
50. Ibrahim SM, Mulcahy MF, Lewandowski RJ, et al. Treatment of unresectable cholangiocarcinoma using yttrium-90 microspheres: Results from a pilot study. Cancer. Oct 15 2008; 113(8):2119-2128. PMID 18759346
51. Paprottka KJ, Galie F, Ingrisch M, et al. Outcome and safety after 103 radioembolizations with yttrium-90 resin microspheres in 73 patients with unresectable intrahepatic cholangiocarcinoma - An evaluation of predictors. Cancers (Basel). Oct 27 2021; 13(21):5399. PMID 34771563
52. Sarwar A, Ali A, Ljuboja D, et al. Neoadjuvant yttrium-90 transarterial radioembolization with resin microspheres prescribed using the medical internal radiation dose model for intrahepatic cholangiocarcinoma. J Vasc Interv Radiol. Nov 2021; 32(11):1560-1568. PMID 34454031
53. Cancer.Net. Neuroendocrine Tumors: Statistics. February 2022; Available at: <https://www.cancer.net> (accessed June 22, 2022).
54. King J, Quinn R, Glenn DM, et al. Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. Cancer. Sep 01 2008; 113(5):921-929. PMID 18618495
55. Ngo L, Elnahla A, Attia AS, et al. Chemoembolization versus radioembolization for neuroendocrine liver metastases: A meta-analysis comparing clinical outcomes. Ann Surg Oncol. Apr 2021; 28(4):1950-1958. PMID 33393019
56. Frilling A, Clift AK, Braat AJAT, et al. Radioembolisation with 90Y microspheres for neuroendocrine liver metastases: an institutional case series, systematic review and meta-analysis. HPB (Oxford). Jul 2019; 21(7):773-783. PMID 30733049
57. Devcic Z, Rosenberg J, Braat AJ, et al. The efficacy of hepatic 90Y resin radioembolization for metastatic neuroendocrine tumors: A meta-analysis. J Nucl Med. Sep 2014; 55(9):1404-1410. PMID 25012459
58. Egger ME, Armstrong E, Martin RC, et al. Transarterial chemoembolization vs radioembolization for neuroendocrine liver metastases: A multi-institutional analysis. J Am Coll Surg. Apr 2020; 230(4):363-370. PMID 32032719
59. Engelman ES, Leon-Ferre R, Naraev BG, et al. Comparison of transarterial liver-directed therapies for low-grade metastatic neuroendocrine tumors in a single institution. Pancreas. Mar 2014; 43(2):219-225. PMID 24518499

60. Rhee TK, Lewandowski RJ, Liu DM, et al. 90Y Radioembolization for metastatic neuroendocrine liver tumors: preliminary results from a multi-institutional experience. Ann Surg. Jun 2008; 247(6):1029-1035. PMID 18520231
61. Cao CQ, Yan TD, Bester L, et al. Radioembolization with yttrium microspheres for neuroendocrine tumour liver metastases. Br J Surg. Apr 2010; 97(4):537-543. PMID 20205229
62. Kennedy AS, Dezarn WA, McNeillie P, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: Early results in 148 patients. Am J Clin Oncol. Jun 2008; 31(3):271-279. PMID 18525307
63. Memon K, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for neuroendocrine liver metastases: Safety, imaging, and long-term outcomes. Int J Radiat Oncol Biol Phys. Jul 01 2012; 83(3):887-894. PMID 22137020
64. Paprottka PM, Hoffmann RT, Haug A, et al. Radioembolization of symptomatic, unresectable neuroendocrine hepatic metastases using yttrium-90 microspheres. Cardiovasc Intervent Radiol. Apr 2012; 35(2):334-342. PMID 21847708
65. Peker A, Cicek O, Soydal C, et al. Radioembolization with yttrium-90 resin microspheres for neuroendocrine tumor liver metastases. Diagn Interv Radiol. Jan-Feb 2015; 21(1):54-59. PMID 25430526
66. Jia Z, Paz-Fumagalli R, Frey G, et al. Single-institution experience of radioembolization with yttrium-90 microspheres for unresectable metastatic neuroendocrine liver tumors. J Gastroenterol Hepatol. Sep 2017; 32(9):1617-1623. PMID 28132407
67. Fan KY, Wild AT, Halappa VG, et al. Neuroendocrine tumor liver metastases treated with yttrium-90 radioembolization. Contemp Clin Trials. Sep 2016; 50:143-149. PMID 27520932
68. Tice J. Selective internal radiation therapy or radioembolization for inoperable liver metastases from colorectal cancer San Francisco, CA: California Technology Assessment Forum; 2010.
69. Saxena A, Bester L, Shan L, et al. A systematic review on the safety and efficacy of yttrium-90 radioembolization for unresectable, chemorefractory colorectal cancer liver metastases. J Cancer Res Clin Oncol. Apr 2014; 140(4):537-547. PMID 24318568
70. Gray B, Van Hazel G, Hope M, et al. Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol. Dec 2001; 12(12):1711-1720. PMID 11843249
71. Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol. Aug 10 2010; 28(23):3687-3694. PMID 20567019
72. Rosenbaum CE, Verkooijen HM, Lam MG, et al. Radioembolization for treatment of salvage patients with colorectal cancer liver metastases: a systematic review. J Nucl Med. Nov 2013; 54(11):1890-1895. PMID 24071510
73. Van Hazel G, Blackwell A, Anderson J, et al. Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer. J Surg Oncol. Nov 01 2004; 88(2):78-85. PMID 15499601

74. Townsend A, Price T, Karapetis C. Selective internal radiation therapy for liver metastases from colorectal cancer. Cochrane Database Syst Rev. Oct 07 2009; (4):CD007045. PMID 19821394
75. Mulcahy MF, Mahvash A, Pracht M, et al. Radioembolization with chemotherapy for colorectal liver metastases: A randomized, open-label, international, multicenter, phase III trial. J Clin Oncol. Dec 10 2021; 39(35):3897-3907. PMID 34541864
76. van Hazel GA, Heinemann V, Sharma NK, et al. SIRFLOX: Randomized phase III trial comparing first-line mFOLFOX6 (Plus or Minus Bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. J Clin Oncol. May 20 2016; 34(15):723-1731. PMID 26903575
77. Wasan HS, Gibbs P, Sharma NK, et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIREGlobal): A combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol. Sep 2017; 18(9):1159-1171. PMID 28781171
78. Wolstenholme J, Fusco F, Gray AM, et al. Quality of life in the FOXFIRE, SIRFLOX and FOXFIRE-global randomised trials of selective internal radiotherapy for metastatic colorectal cancer. Int J Cancer. Aug 15 2020; 147(4):1078-1085. PMID 31840815
79. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology. Jan 2010; 138(1):52-64. PMID 19766639
80. Mokkarala M, Noda C, Malone C, et al. Comparison of response and outcomes of drug-eluting bead chemoembolization (DEB-TACE) versus radioembolization (TARE) for patients with colorectal cancer liver metastases. Anticancer Res. Jun 2019; 39(6):3071-3077. PMID 31177151
81. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc Intervent Radiol. Oct 2012; 35(5):1066-1073. PMID 21800231
82. Kennedy AS, Salem R. Radioembolization (yttrium-90 microspheres) for primary and metastatic hepatic malignancies. Cancer J. Mar-Apr 2010; 16(2):163-175. PMID 20404614
83. Aarts BM, Munoz FMG, Wildiers H, et al. Intra-arterial therapies for liver metastatic breast cancer: A systematic review and meta-analysis. Cardiovasc Intervent Radiol. Dec 2021; 44(12):1868-1882. PMID 34322751
84. Feretis M, Solodkyy A. Yttrium-90 radioembolization for unresectable hepatic metastases of breast cancer: A systematic review. World J Gastrointest Oncol. Feb 15 2020; 12(2):228-236. PMID 32104553
85. Ridouani F, Soliman MM, England RW, et al. Relationship of radiation dose to efficacy of radioembolization of liver metastasis from breast cancer. Eur J Radiol. Mar 2021; 136:109539. PMID 33476965
86. Davisson NA, Bercu ZL, Friend SC, et al. Predictors of survival after yttrium-90 radioembolization of chemotherapy-refractory hepatic metastases from breast cancer. J Vasc Interv Radiol. Jun 2020; 31(6):925-933. PMID 32307310

87. Alexander H, Wen D, Chu M, et al. Selective internal radiation therapy for hepatic metastases of uveal melanoma: A systematic review. Br J Radiol. Jan 01 2022; 95(1129):20210200. PMID 34757824
88. Rowcroft A, Loveday BPT, Thomson BNJ, et al. Systematic review of liver directed therapy for uveal melanoma hepatic metastases. HPB (Oxford). Apr 2020; 22(4):497-505. PMID 31791894
89. Gonsalves CF, Eschelman DJ, Adamo RD, et al. A prospective phase II trial of radioembolization for treatment of uveal melanoma hepatic metastasis. Radiology. Oct 2019; 293(1):223-231. PMID 31453767
90. Xing M, Prajapati HJ, Dhanasekaran R, et al. Selective internal yttrium-90 radioembolization therapy (90y-sirt) versus best supportive care in patients with unresectable metastatic melanoma to the liver refractory to systemic therapy: Safety and efficacy cohort study. Am J Clin Oncol. Feb 2017; 40(1):27-34. PMID 25089529
91. Eldredge-Hindy H, Ohri N, Anne PR, et al. Yttrium-90 microsphere brachytherapy for liver metastases from uveal melanoma: Clinical outcomes and the predictive value of fluorodeoxyglucose positron emission tomography. Am J Clin Oncol. Apr 2016; 39(2):189-195. PMID 24441583
92. Gonsalves CF, Eschelman DJ, Sullivan KL, et al. Radioembolization as salvage therapy for hepatic metastasis of uveal melanoma: A single-institution experience. AJR Am J Roentgenol. Feb 2011; 196(2):468-473. PMID 21257902
93. Kennedy AS, Nutting C, Jakobs T, et al. A first report of radioembolization for hepatic metastases from ocular melanoma. Cancer Invest. Jul 2009; 27(6):682-690. PMID 19219675
94. Klingenstein A, Haug AR, Zech CJ, et al. Radioembolization as locoregional therapy of hepatic metastases in uveal melanoma patients. Cardiovasc Intervent Radiol. Feb 2013; 36(1):158-165. PMID 22526099
95. Piduru SM, Schuster DM, Barron BJ, et al. Prognostic value of 18f-fluorodeoxyglucose positron emission tomography-computed tomography in predicting survival in patients with unresectable metastatic melanoma to the liver undergoing yttrium-90 radioembolization. J Vasc Interv Radiol. Jul 2012; 23(7):943-948. PMID 22609292
96. Ruohoniemi DM, Zhan C, Wei J, et al. Safety and effectiveness of yttrium-90 radioembolization around the time of immune checkpoint inhibitors for unresectable hepatic metastases. J Vasc Interv Radiol. Aug 2020; 31(8):1233-1241. PMID 32741550
97. Michl M, Haug AR, Jakobs TF, et al. Radioembolization with yttrium-90 microspheres (SIRT) in pancreatic cancer patients with liver metastases: Efficacy, safety and prognostic factors. Oncology. 2014; 86(1):24-32. PMID 24401529
98. Miller MD, Sze DY, Padia SA, et al. Response and overall survival for yttrium-90 radioembolization of hepatic sarcoma: A multicenter retrospective study. J Vasc Interv Radiol. Jun 2018; 29(6):867-873. PMID 29724518
99. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors. Version 1.2022. Available at: <https://www.nccn.org> (accessed November 9, 2022).

100. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. Version 3.2022. Available at: <https://www.nccn.org> (accessed November 9, 2022).
101. National Comprehensive Cancer Network. Melanoma: Uveal. Version 2.2022. Available at: <https://www.nccn.org> (accessed June 19, 2022).
102. Hong K, Akinwande O, Bodei L, et al. ACR-ABS-ACNM-ASTRO-SIR-SNMMI practice parameter for selective internal radiation therapy or radioembolization for treatment of liver malignancies. Brachytherapy. May-Jun 2021; 20(3):497-511. PMID 33824051
103. National Institute for Health and Care Excellence. Selective internal radiation therapy for primary hepatocellular carcinoma Interventional procedures guidance [IPG460]. July, 2013. Available at: <https://www.nice.org.uk> (accessed June 22, 2022).
104. National Institute for Health and Care Excellence. Selective internal radiation therapies for treating hepatocellular carcinoma. Technology appraisal guidance [TA688]. March 2021. Available at: <https://www.nice.org.uk> (accessed June 19, 2022).
105. National Institute for Health and Care Excellence. Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma Interventional procedures guidance [IPG630]. October 2018. Available at: <https://www.nice.org.uk> (accessed June 21, 2022).
106. National Institute for Health and Care Excellence. Selective internal radiation therapy for unresectable colorectal metastases in the liver Interventional procedures guidance [IPG672]. March 2020. Available at: <https://www.nice.org.uk> (accessed June 22, 2022).

Centers for Medicare and Medicaid Services (CMS)

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

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

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

Policy History/Revision

Date	Description of Change
11/15/2023	Reviewed. No changes.
01/01/2023	Document updated with literature review. Coverage unchanged. New/Updated References include: 4, 14, 25-27, 33, 35-38, 40-42, 51-53, 55, 57, 75, 78, 83, 85-87, 96, 99-106.
11/01/2021	Reviewed. No changes.
04/15/2021	Policy reactivated. Document updated with literature review. Radioembolization may be considered medically necessary to treat primary

	hepatocellular carcinoma that is unresectable and limited to the liver. Radioembolization may be considered medically necessary in primary hepatocellular carcinoma as a bridge to liver transplantation. Radioembolization may be considered medically necessary to treat primary intrahepatic cholangiocarcinoma in patients with unresectable tumors. Radioembolization may be considered medically necessary to treat hepatic metastases from neuroendocrine tumors (carcinoid and non-carcinoid) with diffuse and symptomatic disease when systemic therapy has failed to control symptoms. Radioembolization may be considered medically necessary to treat unresectable hepatic metastases from colorectal carcinoma, melanoma (ocular or cutaneous), or breast cancer that are both progressive and diffuse, in patients with liver-dominant disease who are refractory to chemotherapy or are not candidates for chemotherapy or other systemic therapies. Radioembolization is considered experimental, investigational and/or unproven for all other hepatic metastases except as noted above. Radioembolization is considered experimental, investigational and/or unproven for all other indications not described above.
10/02/2016	Document became inactive.
05/01/2015	Document updated with literature review. The following was added to the experimental, investigational and/or unproven coverage statement: "Including, but not limited to primary intrahepatic cholangiocarcinoma".
03/01/2013	Document updated with literature review. Coverage unchanged. Title changed from "Selective Internal Radiation Therapy (Radioembolization) for Primary and Metastatic Tumors of the Liver".
08/01/2010	Document updated with literature review. The following was added: SIRT (radioembolization) may be considered medically necessary as palliative treatment for individuals with (1) neuroendocrine tumors (e.g. carcinoid tumors, pancreatic islet cell tumors, parathyroid, pituitary angiomas) with hepatic metastases, when systemic therapy has failed to control symptoms such as carcinoid syndrome (e.g. debilitating flushing, wheezing, and diarrhea); or (2) symptoms from non-carcinoid neuroendocrine tumors with hepatic metastases (e.g. hypoglycemia, severe diabetes, Zollinger-Ellison Syndrome). In addition the following was added: SIRT for primary and metastatic tumors of the liver not addressed above, are considered experimental, investigational and unproven.
02/01/2008	New medical document