
Medical Policy



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(See policy history boxes for previous effective dates)

Title: Radioembolization for Primary and Metastatic Tumors of the Liver

Description/Background

TREATMENTS FOR HEPATIC AND NEUROENDOCRINE TUMORS

The use of external-beam radiotherapy and the application of more advanced radiotherapy approaches (eg, 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 [RFA]), 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 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. Yttrium 90 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 yttrium-90 microspheres are available: a glass sphere (TheraSphere) and a resin sphere (SIR-Spheres). Noncommercial forms are mostly used

outside the United States. While the commercial products use the same radioisotope (yttrium 90) and have the same target dose (100 gray), they differ in microsphere size profile, base material (ie, 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 Food and Drug Administration (FDA) granted premarket approval of SIR-Spheres for use in combination with 5-fluorouracil 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 (HCC). In 2007, this humanitarian device exemption was expanded to include patients with HCC who have partial or branch portal vein thrombosis. For these reasons, results obtained with a product do not necessarily apply to another commercial (or noncommercial) products (see Regulatory Status section).

Regulatory Status

Currently 2 forms of yttrium-90 microspheres approved by FDA.

In 1999, TheraSphere® (manufactured by Nordion, Ontario, under license by BTG International), a glass sphere system, was approved by FDA through the humanitarian drug exemption process for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable HCC 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 to 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, Lake Forest, IL), a resin sphere system, was approved by the FDA through the premarket approval process for the treatment of inoperable CRC metastatic to the liver.

FDA product code: NAW.

Medical Policy Statement

The safety and effectiveness of radioembolization for primary and metastatic tumors of the liver are established. It may be considered a useful therapeutic option when indicated.

Inclusionary and Exclusionary Guidelines

Inclusions:

Radioembolization referred to as Selective internal radiation therapy (SIRT), using radioactive Yttrium-90 (⁹⁰Y) microspheres, is considered medically necessary when **ALL** of the following criteria are met:

- Unresectable and/or medically inoperable primary or metastatic liver malignancies from **ANY** of the following:
 - Unresectable liver only or liver dominant metastases from neuroendocrine tumors (eg, carcinoids, pancreatic islet cell tumors, endocrine tumors).
 - Unresectable primary hepatocellular carcinoma (HCC) as a bridge to liver transplantation.
 - Unresectable metastatic liver tumors from primary colorectal cancer.
 - Treatment of unresectable liver metastases from breast carcinoma, ocular melanoma, cutaneous melanoma, or intrahepatic cholangiocarcinoma in the absence of available systemic or liver-directed treatment options to relieve symptoms and/or possibly extend life expectancy.
 - Treatment of other radiosensitive tumors metastatic to the liver with liver-limited or liver-dominant disease for symptom palliation or prolongation of survival.
- The tumor burden should be liver dominant, not necessarily exclusive to the liver.
- Life expectancy should be at least 3 months.
- Radioactive Yttrium-90 (⁹⁰Y) microspheres treatment is allowed only in the outpatient setting unless the documentation supports the medical necessity of inpatient treatment.

Repeat radioembolization is considered medically necessary for new or progressive primary or metastatic liver cancers when **ALL** of the following criteria are met:

- The individual has had a previous satisfactory response to an initial radioembolization treatment as evidenced on results of a computed tomography (CT) scan or positron emission tomography (PET)/CT scan performed 3 months following the previous procedure. Response should be graded according to the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline.
- The disease still must be liver dominant.
- Life expectancy of at least 3 months
- There are no other effective systemic or liver-directed treatment options.
- An individual has compensated liver function tests (LFTs) .
- Estimated lung dose and combined lung dose from previous embolizations are within acceptable dose volume constraints. Exclude an individual with lung shunting in which the lung radiation dose is greater than 25 to 30 Gy per treatment or greater than 50 Gy cumulatively for all treatments.
- Treatment should be given to a targeted tumor volume.

Exclusions:

- Used to treat previously untreated, or unresectable hepatic metastases from colorectal carcinoma.
- Repeat whole liver irradiation is considered experimental, investigational, and/or unproven (EIU) and will not be certified.
- A third radioembolization treatment is considered not medically necessary.
- For all other hepatic metastases not described above.
- For all other indications not described above.

Yttrium-90 is contraindicated for patients who have:

- Had previous external beam radiation therapy of the liver
- Bleeding diathesis not correctable using standard medical means
- Severe pulmonary insufficiency
- Treatment that would result in greater than 25 to 30 Gy dose to the lung in one session or 50 Gy cumulative as assessed by Technetium MAA scan
- Pre-assessment angiogram that demonstrates vascular anatomy abnormalities that would result in significant reflux of hepatic arterial blood to the stomach, pancreas or bowel
- Disseminated and significant extrahepatic malignant disease
- History of treatment with capecitabine within two previous months, or who will be treated with capecitabine at any time following treatment with SIR-Spheres®
- Portal vein thrombosis (relative)

Radioembolization is not recommended in pregnant women, nursing mothers or children.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

Q3001 S2095 37243 79445

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. 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 radioembolization plus liver transplant in individuals who have unresectable hepatocellular carcinoma (HCC) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations

The relevant population of interest is individuals with unresectable HCC who may or may not need a liver transplant. Most patients with HCC present with unresectable disease and treatment options are limited secondary to the chemoresistance of HCC and the intolerance of normal liver parenchyma to tumoricidal radiation doses.

Interventions

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

Comparators

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

Outcomes

The general outcomes of interest are OS, functional outcomes, quality of life, and treatment-related morbidity (Table 1).

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, OS, and stable disease |

OS: overall survival; PFS: progression-free survival.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Radioembolization for Unresectable Hepatocellular Carcinoma

Review of Evidence

Systematic Reviews

Various meta-analyses have been performed to compare the effects of TACE, drug-eluting bead (DEB) plus TACE (DEB-TACE), and RE in patients with unresectable HCC, each of which performed slightly different analyses (eg, pairwise vs indirect comparisons and assessment of different outcomes or comparator groups). The 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% confidence interval [CI], 0.79 to 1.08).

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.(5) 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 that RE 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 RE as monotherapy or followed by sorafenib versus and sorafenib monotherapy, respectively (p<.01).

Yang et al (2020) conducted a meta-analysis of RCTs to compare the effects of DEB-TACE, TACE, and RE on the primary outcome of overall survival.(6) Compared with TACE, RE was associated with similar one-year OS (relative risk [RR], 0.91; 95% CI 0.79 to 1.05), but a better OS than TACE at two years (RR, 0.87; 95% CI, 0.80 to 0.95) and three years (RR, 0.90; 95% CI 0.85 to 0.96). The overall survival was not significantly different between RE and DEB-TACE at one year (RR, 0.83, 95% CI, 0.68 to 1.02), but DEB-TACE was associated with better OS at two years than RE (RR, 0.40; 95% CI, 0.19 to 0.84). However, pooled HRs indicated that RE was superior to TACE in overall survival (HR, 0.84; 95% CI, 0.70 to 1.00) and that DEB-TACE was superior to RE in overall survival (HR, 0.59; 95% CI, 0.38 to 0.91).

Tao et al (2017) reported on a network meta-analysis comparatively evaluating nine 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, drug-eluting bead (DEB) plus TACE (DEB-TACE), yttrium-90 RE (90Y RE), TACE plus external-beam radiation therapy (EBRT), and ethanol ablation. The network meta-analysis included 17 studies with 2669 patients and 4 studies with 230 patients including 90Y RE. In a pairwise meta-analysis, patients treated with 90Y RE were more likely to achieve complete remission than those who received TACE (odds ratio [OR], 4.5; 95% confidence interval [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 (SUCRA). TACE plus EBRT had the highest SUCRA ranking 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 90Y RE for HCC.(7) Fourteen studies (total n=2065) comparing DEB-TACE or 90Y 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 two 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 three 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 (N=533). (8) Survival at 1 year did not differ statistically between RE (42%) and TACE (46%; RR, 0.93; 95% CI, 0.81 to 1.08; p=.33). At 2 years, the survival rate was higher for RE (27% vs 18%; RR, 1.36; 95% CI, 1.05 to 1.76; p=.02), but there was no statistically significant difference in survival rates at 3, 4, or 5 years. Postprocedural complications were also similar in the 2 groups. Facciorusso et al (2016) included 10 studies (N=1557), 2 of which were RCTs.(9) The OR for survival was not statistically significant at 1 year (OR, 1.0; 95% CI, 0.8 to 1.3; p=.93) but favored RE in years 2 (OR, 1.4; 95% CI, 1.1 to 1.90; p=.01) and 3 (OR, 1.5; 1.0 to 2.1; p=.04).

Vente et al (2009) conducted a meta-analysis evaluating tumor response and survival in patients who received yttrium-90 glass or resin microsphere radioembolization (RE) for the treatment of primary HCC or metastases from colorectal cancer (CRC).(10) (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 90Y 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 seven 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.(11) 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 progression-free survival (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).

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).(12) 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 a single-center, retrospective study (2010-2015) comparing segmental RE with segmental chemoembolization in 101 patients with localized, unresectable HCC not amenable to ablation.(13) Patients receiving chemoembolization had poorer Eastern Cooperative Oncology Group (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=.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 of patients receiving RE and TACE for HCC.(14) Each group included 40 patients. RE patients had a mean survival of 39 months versus 31 months for TACE (p=.014). There were no significant differences in complication or disease recurrence rates.

Oladeru (2016) retrospectively analyzed SEER registry data, comparing survival outcomes for patients with HCC receiving RE with EBRT.(15) 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.

Gramenzi et al (2015) conducted a retrospective cohort study to compare RE with the kinase inhibitor sorafenib for intermediate- or advanced-stage HCC.(16) 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.

Section Summary: Radioembolization for Unresectable Hepatocellular Carcinoma

Radioembolization has been compared with alternative treatments for HCC, including transarterial chemoembolization (TACE), drug-eluting beads (DEB) plus TACE, TACE plus external beam radiotherapy (EBRT), and sorafenib. Systematic reviews, RCTs, and nonrandomized comparative studies reported varied treatment superiority in tumor response and survival outcomes. Although rigorous comparative RCTs are lacking, if the active comparators are effective treatments for HCC, then these results are consistent with some degree of efficacy for RE in the treatment of HCC. In all studies reviewed, tumor response is observed, which may improve survival.

RADIOEMBOLIZATION AS A BRIDGE TO LIVER TRANSPLANTATION FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA

Review of Evidence

Systematic Reviews

Kulik et al (2018) published a systematic review of 18 comparative studies and 31 noncomparative studies that included patients with unresectable HCC who needed liver transplant and received transplant alone or some type of bridging therapy as well (see Table 2).(17) Of the 18 comparative studies, two studies (n=257) reported on the incidence of dropout from transplantation wait-lists, and patients receiving bridging therapy. This group had a reduced risk of dropout due to disease progression, compared with those receiving transplantation alone (RR=.32) (see Table 3). Between-group differences were not statistically significant for mortality (five comparative studies; n=531) or recurrence rate (10 comparative studies; n=889). Subgroup analysis was conducted for types of bridging therapy: for all-cause mortality after transplantation, the RR was 1.124 with transarterial embolization (TAE) compared with transplantation alone (1 cohort). For disease recurrence, the RR for this bridging therapy type was 2.374 compared with transplantation alone. No RCTs were identified, and most of the selected studies had a high risk of bias on patient selection.

Table 2. Characteristics of Systematic Reviews

| Study | Dates | Trials | Participants ^a | Design |
|----------------------------------|-----------|--------|---------------------------------------|---|
| Kulik et al (2018) ¹⁷ | 1996-2016 | 49 | Unresectable hepatocellular carcinoma | <ul style="list-style-type: none"> • 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) ¹⁷ | | | | | |
| Comparative studies (n=18) | 2 studies (n=257) | 5 studies (n=531) | 10 studies (n=889) | | |
| | Reduced risk of dropout in patients with bridging therapy vs transplant alone (RR=0.32; 95% CI, 0.06 to 1.85; $I^2=0\%$) | Nonsignificant between-group difference | Nonsignificant between-group difference | <ul style="list-style-type: none"> 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; RR: relative risk; TAE: transarterial embolization.

Randomized Controlled Trials

Salem et al (2016) reported results of a Phase II RCT comparing conventional TACE with TheraSphere RE (Y90) for treatment of unresectable, unablatable HCC.(18) Twenty-four patients were assigned to Y90 and 21 patients to TACE; the ultimate end point 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 to 17 months). In the Y90 group, there were 13 transplants at a median of 9 months (range, 4 to 15 months). Median time to progression exceeded 26 months in the Y90 group and 6.8 months in the TACE group (hazard ratio, 0.12; 95% CI, 0.03 to 0.56; $p=.007$). Median survival was 19 months with Y90 and 18 months in TACE ($p=.99$). 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 the results of a pilot RCT of Y90 RE with or without sorafenib for patients who had HCC awaiting liver transplantation.(19) 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 yttrium-90radioembolization with TheraSphere for the treatment of solitary, unresectable HCC.(20) The aim of the study was to evaluate the objective response rate (ORR) and the duration of response (DOR) based on modified RECIST criteria as evaluated

by a blinded, independent, central review. Eligibility criteria included: solitary HCC ≤ 8 cm, Child-Pugh A cirrhosis, and ECOG performance status 0 to 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. The median follow-up duration was 29.9 months. The 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 of 6 months or greater. Three-year OS was 86.6% for all patients and 92.8% for neoadjuvant patients resected or transplanted. This study supported U.S. Food and Drug Administration (FDA) premarket approval of TheraSphere for use in HCC.(21)

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).(22) 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%), for 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 down staged with RE.(23) From 2004 to 2018, 207 patients underwent transplant after RE. The 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 down staged to liver transplant. The overall survival rates at 3, 5, and 10 years were 84%, 77%, and 60%, respectively.

Zori et al (2020) performed a retrospective cohort analysis that compared patients with HCC undergoing bridging locoregional therapy with RE (n=28) to TACE (n=37) prior to liver transplant.(24) Three-year survival was not significantly different with RE vs TACE (92.9% vs. 75.7%; p=.052). However, microvascular invasion occurred in 3.6% versus 27% of patients treated with RE versus TACE (p=.013).

In a retrospective review, Tome et al (2013) reported on 20 consecutive HCC patients awaiting liver transplant who received RE as bridge therapy.(25) When RE began, Milan criteria were met by 14 patients and sustained until transplantation. Of the six patients who did not meet Milan criteria initially, RE was able to downstage two patients to meet Milan criteria. After onset of RE, median time to liver transplant was 3.5 months. Complete or partial radiologic response to RE on modified Response Evaluation Criteria In Solid Tumors (RECIST) occurred in nine patients. Additionally, on pathologic examination, five 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.(26) In the intent-to-treat with transplantation arm, 60.2% were able to receive a transplant. Survival rates post-transplant 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 down staging 86 patients with HCC from stage T3 to T2 (potentially making patients liver transplant candidates).(27) 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 down staging from T3 to T2 in 58% of patients treated with RE vs 31% with TACE (p<0.05).

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

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

RADIOEMBOLIZATION FOR UNRESECTABLE INTRAHEPATIC CHOLANGIOCARCINOMA

Clinical Context and Therapy Purpose

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

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

Populations

The relevant population of interest is individuals with unresectable ICC. Cholangiocarcinomas are tumors that arise from the epithelium of the bile duct and are separated into intrahepatic and extrahepatic types. ICC appears 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.(33)

Interventions

The treatment being considered is RE. RE may also be referred to as selective internal radiation therapy (SIRT) or transarterial radioembolization (TARE).

Comparators

The following are comparators to RE in the treatment of 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, transarterial chemoembolization(TACE), or drug-eluting bead transarterial chemoembolization (DEB-TACE), may also be considered.

Outcomes

The general outcomes of interest are OS, functional outcomes, quality of life, and treatment-related morbidity (see Table 4). 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 |
|----------|---------|
|----------|---------|

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.(30) 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%; I₂ = 81%), median PFS of 7.8 months (95% CI, 4.2 to 11.3; I₂ = 94%), and median overall survival (OS) of 12.7 months (95% CI, 10.6 to 14.8; I₂ = 62%). Patients were downstaged for surgical resection in 11% of cases (95% CI, 6.1% to 15.9%; I₂ = 78%). The analysis is limited by the 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.(31) 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.(32) 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, the 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-naïve patients was reported in 30.5% and 18.3% of RE and EBRT groups, respectively. Patients treated with RE experienced higher rates of post-embolization 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 (TACE) (13 studies; n=906).⁽³³⁾ 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 hepatic arterial infusion (HAI), TACE, DEB-TACE, and Y90 RE, for unresectable ICC.⁽³⁴⁾ Of 20 studies that met inclusion criteria were included, five 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. CR or PR 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

Robinson et al (2023) reported outcomes for 95 patients with unresectable ICC who were treated with Y90 RE.⁽³⁵⁾ Data were obtained from the Radiation-Emitting SIR-Spheres in Non-resectable (RESiN) liver tumor registry; patient demographic information was not summarized in this publication. Multifocal tumors were present in 60% of patients and 27% had extrahepatic tumors. The median OS was 14 months (95% CI, 12 to 22) and the OS at 3, 6, 12, and 24 months was 94%, 80%, 63%, and 34%, respectively. Imaging response at 6 months predicted OS (HR, 0.39; p=.008). Grade 3/4 bilirubin toxicities and Grade 3 albumin toxicity were noted in 7% and 1.4% of patients, respectively.

Chan et al (2022) published results from a phase 2, multicenter (China, Singapore, and Thailand) study evaluating the efficacy and safety of Y90 SIRT followed by chemotherapy with gemcitabine and cisplatin in patients with unresectable ICC without prior treatment with chemotherapy or radiation.⁽³⁶⁾ The median age of patients was 64 years and 63% were male. A total of 24 patients completed SIRT and 16 of them underwent subsequent chemotherapy. The median OS was 13.6 months (95% CI, 5.4 to 21.6) in the intention-to-treat (ITT) population (ie, patients receiving at least 1 cycle of SIRT regardless of receiving chemotherapy or not; n=24) and 21.6 months (95% CI, 7.3 to 25.2) among the 16 patients who underwent subsequent chemotherapy. In the ITT population, the overall response rate was 16.7% (95% CI, 1.8 to 31.6) and the disease control rate was 58.3% (95% CI, 38.6 to 78.1). Among the 16 patients who received subsequent chemotherapy, the overall response rate was 25% (95% CI, 3.8 to 46.2) and the disease control rate was 75% (95% CI, 53.8 to 96.2).

A few studies have evaluated RE with chemotherapy in the first-line setting.

Kis et al (2023) published results from a prospective feasibility study evaluating the efficacy and safety of Y90 RE in the first-line setting in 24 patients with unresectable ICC without extrahepatic metastasis, and who never received chemotherapy, liver embolization, or radiation therapy.⁽³⁷⁾ The mean age of patients was 72 years, 50% were male, and all but 1 were White. Results demonstrated that the median liver PFS was 5.5 months (95% CI, 3.9 to 7.0) and the median OS from the RE treatment was 19.4 months (95% CI, 5.0 to 33.7).

Edeline et al (2019) published results from the phase 2, MISPHEC trial (Yttrium-90 Microspheres in Cholangiocarcinoma), which included 41 patients with unresectable ICC treated in the first-line setting with cisplatin, gemcitabine, and RE in French centers with experience with glass microspheres.(38) The mean age of included patients ranged from 67 to 71 years and 60% were male. Fifteen (37%) patients underwent more than 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, the 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 (22%), 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.

Case Series

Numerous small case series (range, 19 to 115 patients) evaluating RE for unresectable ICC have been published.(39-51) 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 (eg, unilobar versus bilobar [43,48]), morphology (eg, infiltrative), metastatic disease (eg, lymph node or extrahepatic metastases), prior treatments (eg, chemotherapy,[41,45] surgery, and other liver-directed therapies), treatment setting (eg, neoadjuvant, [50] palliative [43]), and comorbidities (eg, cirrhosis [40]). Several studies have reported on resection outcomes following downstaging treatment with RE alone (40,44,48,50) or in combination with chemotherapy.(39,43) One study compared outcomes with glass versus resin microspheres, finding no significant difference in overall survival between groups.(40) 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-naïve patients,(42) and for tumor burden 25% or less,(45,49) peripheral tumor type,(47,48) and an ECOG performance score of 0.(45,47,48)

Section Summary: Intrahepatic Cholangiocarcinoma

The evidence for RE in ICC primarily consists of retrospective case reviews. Across studies, the median survival in patients treated with RE ranged from 6 to 22 months. Side effects are common but generally mild. Patient populations in these studies were heterogeneous, varying in performance status, prior interventions, presence of extrahepatic disease, and tumor distribution and morphology. Therefore, in the absence of data in well-defined patient populations, it is difficult to ascertain which patients are most likely to derive benefit from RE. A phase 2 study evaluating the use of RE with chemotherapy in the first-line setting reported a response rate of 39% and a disease control rate of 98%. Another phase 2 study evaluating RE with or without subsequent chemotherapy in patients without prior treatment with chemotherapy or radiation found overall response rates of 25% and 16.7% in those who received RE with and without chemotherapy, respectively; the disease control rates were 75% and 58.3% amongst those who received RE with and without chemotherapy, respectively. 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 individuals who have unresectable neuroendocrine tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations

The relevant population of interest is individuals with unresectable neuroendocrine tumors. These tumors are an uncommon, heterogeneous group of mostly slow-growing, hormone-secreting malignancies, with an average patient age of 60 years. Primary neuroendocrine tumors vary in location, but most are either carcinoids (which most commonly arise in the midgut area) or pancreatic islet cells. The estimated incidence of neuroendocrine tumors in the U.S. is 12,000 cases per year, with approximately 175,000 individuals living with this diagnosis.(52)

Interventions

The treatment being considered is RE. RE may also be referred to as selective internal radiation therapy (SIRT) or transarterial radioembolization (TARE).

Comparators

The following are comparators to RE in the treatment of unresectable neuroendocrine tumors: standard of care, usually palliative. Conventional therapy is generally considered to be palliative supportive care, to control, eradicate, or debulk hepatic metastases, often to palliate carcinoid syndrome or local pain from liver capsular stretching. Therapies for unresectable metastatic neuroendocrine tumors include medical (somatostatin analogues like octreotide), systemic chemotherapy, ablation (radiofrequency or cryotherapy), TAE or TACE, or radiotherapy. Although patients often achieve symptom relief with octreotide, the disease eventually becomes refractory, with a median duration of symptom relief of approximately 13 months, with no known effect on survival. Systemic chemotherapy for these tumors has revealed that: (1) modest response rates are of limited duration; (2) it is more effective for pancreatic neuroendocrine tumors than carcinoids; and (3) it is frequently associated with significant toxicity.(53) Chemoembolization has shown response rates of nearly 80%, but the effect is of short duration, and a survival benefit has not been demonstrated.(53)

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, five-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 diffuse multiple 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 time frame for outcomes 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).(54) 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.(55) 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%).

Devicic et al (2014) conducted a meta-analysis of studies evaluating RE for liver-dominant metastatic neuroendocrine tumors.(56) 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).(57) Between RE and TACE, there were no statically significant differences in overall morbidity (13.7%vs. 22.6%, respectively; p=0.17), grade 3/4 complication (5.9% vs. 9.2%; p=.58), 90-day mortality (9.8% vs 5.2%;p=.21), median OS (35.9 months vs. 50.1 months; p=.3), or progression-free survival (15.9 vs. 19.9 months; p=.37).However, disease control rate was greater for TACE compared with RE (96% vs. 83%, p<.01).

Engelman et al (2014) retrospectively compared transarterial, liver-directed therapies, including RE, hepatic artery embolization (HAE), and hepatic artery chemoembolization (HACE), in 42 patients treated for metastatic neuroendocrine tumors.(58) Treatment decisions were at the discretion of the referring physician and interventional radiologist, but the decision to proceed with therapy was typically based on 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 II 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 (eg, octreotide), surgical resection, bland or chemoembolization, and RFA or cryoablation.(59) 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 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 of 58 patients with unresectable neuroendocrine liver metastases from 2 hospitals who were treated RE from 2003 to 2008.(60) Response was assessed with radiographic evidence before and after RE and measured RECIST guidelines. Systemic chemotherapy was routinely given at 1 institution. Mean patient age at the time of RE was 61 (range, 29-84 years). Primary tumor site was variable and included small bowel, pancreas, colon, thyroid, lung, and unknown. Thirty-one patients underwent surgical resection of their primary tumor, which was classified as 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 a CR, 14 a PR, 14 had SD, and 17 had 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 extent of tumor involvement of the liver, radiographic response to treatment, presence of extrahepatic disease at the time of RE, the histologic grade of tumor, and whether patients responded to RE.

King et al (2008) reported outcomes in patients treated in a single-institution prospective study.(53) Thirty-four patients with unresectable neuroendocrine liver metastases were given radioactive microspheres [SIR-Spheres] and concomitant 7-day systemic infusion of 5-FU, between 2003 and 2005. Mean patient age was 61 years (range, 32 to 79 years). Mean follow-up was 35.2 ± 3.2 months. The mean interval from diagnosis of hepatic metastases and treatment with SIR therapy was 36.6 ± 6.7 months. Primary tumor sites were variable 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 three months. Twenty-four patients (71%) had at baseline assessment, symptoms of carcinoid syndrome, including diarrhea, flushing, or rash. At 3 months, 18 of 33 patients (55%) reported improvement of symptoms, as did 16 of 32 (50%) at 6 months. Radiologic tumor response was

observed in 50% of patients and included 6 CR (18%), and 11 PR (32%). Mean OS was 29.4 months.

Kennedy et al (2008) retrospectively reviewed 148 patients from 10 institutions with unresectable hepatic metastases from neuroendocrine tumors.(61) 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 WHO 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 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.(62-66)

Section Summary: Unresectable Neuroendocrine Tumors

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

RADIOEMBOLIZATION FOR UNRESECTABLE INTRAHEPATIC METASTASES FROM COLORECTAL CARCINOMA AND PRIOR TREATMENT FAILURE

Clinical Context and Therapy Purpose

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

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

Populations

The relevant population of interest is individuals with unresectable intrahepatic metastases from CRC and prior treatment failure. Fifty to 60 percent of patients with CRC will develop metastases, either synchronously or metachronously. Select patients with liver-only metastases that are surgically resectable can be cured, with some reports showing 5-year survival rates exceeding 50%. The emphasis of treating these patients, with potentially curable disease, is on complete removal of all tumors with negative surgical margins. Most patients diagnosed with 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 selective internal radiation therapy (SIRT) or transarterial radioembolization (TARE).

Comparators

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

Outcomes

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

Table 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 systemic review, Saxena et al (2014) evaluated 20 experimental and observational studies on RE for chemo resistant, unresectable CRC liver metastasis (total n=979).(68) They included two RCTs (Gray et al [2001],(69) Hendlisz et al [2010],(70) 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% to 6%) and 31% (range, 0% to 73%), respectively. Nine months was the median time to intrahepatic progression (range, 6 to 16 months). In 11 studies reporting on OS, the median survival time was 12 months (range, 8.3 to 3.6 months).

Rosenbaum et al (2013) evaluated 13 relevant articles on RE as monotherapy and 13 studies on RE combined with chemotherapy for chemo resistant, unresectable CRC liver metastasis.(71) Complete remission, partial response, and stable disease rates ranged from 29% to 90% with only RE and from 59% to 100% for RE with chemotherapy At 12 months, survival ranged from 37% to 59% with only RE and from 43% to 74% for RE combined plus chemotherapy.

Three earlier systematic reviews, published in 2010 and 2009, are briefly noted; all include RCTs by Gray et al (2001),(69) and Van Hazel et al (2004).(72) The 2010 report by the California Technology Assessment Forum assessed 25 studies, including the two RCTs, a retrospective comparative study (n=36), and 21 case series.(67) 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.(73) Townsend et al (2009) found insufficient evidence to demonstrate that RE improved survival or quality of life.(73) 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.(10)

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.(74) 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 hepatic PFS 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 or fewer 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 III RCT by van Hazel et al (2016) compared modified fluorouracil, leucovorin, and oxaliplatin (FOLFOX) chemotherapy and FOLFOX chemotherapy plus RE with SIR-Spheres in 530 patients with chemotherapy-naive liver-dominant metastatic disease.(75) The use of bevacizumab was allowed with FOLFOX chemotherapy, at the investigator's discretion. The

primary end point was overall (any site) PFS. Secondary end points included liver-specific outcomes such as PFS in the liver, tumor response rate, and liver resection rate. The primary end point of PFS at any site showed no difference between groups (10.6 months for RE vs 10.2 months for control; hazard ratio, 0.93; $p=0.43$). Secondary end points 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 two other studies of chemotherapy with and without RE in the first-line setting.(76) Overall, 549 patients were randomly assigned to FOLFOX alone and 554 patients were assigned FOLFOX plus SIRT. The overall survival was not significantly different between groups (HR, 1.04; 95% CI, 0.90 to 1.19). Wolstenholme et al (2020) published a follow-up analysis of health-related quality of life (HRQOL) measures as assessed by the three-level EQ-5D, European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30), and EORTC Colorectal Liver Metastases cancer module (EORTC QLQ-LMC21).(77) HRQOL was statistically significantly lower in RE + FOLFOX patients ≤ 3 months after administration according to all three 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.(69) Accrual was halted early, entering 74 patients rather than the planned 95 at the discretion of the investigator rather than by planned data monitoring board oversight. To monitor responses to therapy, investigators serially measured serum levels of carcinoembryonic antigen and estimated tumor cross-sectional area and volume from repeated computerized tomography scans read by physicians blinded to treatment assignment. For HAI plus RE vs HAI, they reported increased overall responses (complete remission plus partial response) measured by area (44% vs 18% $p=0.01$) 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 III-IV) included 23 events in each arm (primarily changes in liver function tests). While in this trial, response rate and time to progression after SIRT plus HAI appeared superior to the same outcomes after HAI alone, results for the SIRT plus HAI group are within the range reported by other randomized trials of HAI in comparable patients.(78,79)

A phase II 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.(72) Disease time to progression was greater in those receiving combination therapy (18.6 months vs 3.6 months, respectively; $p<0.001$).

A phase III 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.(70) 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 ten 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=.014), as was occurrence of ≥ 10 liver lesions (42.2% vs. 68.8%; p=.001). Toxicity was not significantly different between DEB-TACE and RE (27% vs. 9.1%, respectively; p=.057). Treatment with DEB-TACE was not a prognostic factor for survival (HR, 0.94; 95% CI, 0.54 to 1.65).

Seidensticker et al (2012) published a retrospective, matched-pair comparison of RE plus best supportive care versus 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; hazard ratio, 0.3; 95% CI, 0.16 to 0.55; p<.001). Adverse events were considered generally mild-to-moderate and manageable.

Section Summary: Unresectable Intrahepatic Metastatic Colorectal Cancer

The evidence for the use of RE to treat unresectable intrahepatic metastatic CRC includes systematic reviews, 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 individuals 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 following PICO was used to select literature to inform this review.

Populations

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

Interventions

The treatment being considered is RE. RE may also be referred to as selective internal radiation therapy (SIRT) or transarterial radioembolization (TARE).

Comparators

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

Outcomes

The general outcomes of interest are OS, functional outcomes, quality of life, and treatment-related morbidity (see Table 6).

Table 6. Outcomes of Interest for Individuals with Unresectable Intrahepatic Metastases from Other Cancers (eg, Breast, Melanoma, Pancreatic)

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

OS: overall survival; PFS: progression-free survival.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Studies with duplicative or overlapping populations were excluded.

Metastatic Intrahepatic Breast Cancer

Most studies on the use of RE for metastatic breast cancer evaluate the use of RE alone (ie, not in combination with chemotherapy) either during a hiatus between lines of chemotherapy or in individuals refractory to standard of care chemotherapy.(82)

Review of Evidence

Systematic Review

Liu et al (2022) published a systematic review and meta-analysis assessing the evidence for Y90 SIRT in liver metastatic breast cancer.(83) A total of 24 studies (N=412) were included, most of which were retrospective or non-comparative. Patient demographic information was not summarized in this publication. The median survival time after SIRT was 9.8 months (95% CI, 9 to 11.6 months). The cumulative OS rates at 6 months and 1, 2, and 3 years were 65.6% (95% CI, 60.8% to 70.0%), 39.0% (95% CI, 34.3% to 43.7%), 13.3% (95% CI, 10.3% to 16.8%), and 4.4% (95% CI, 2.7% to 6.6%), respectively. Patients who had a hepatic metastatic burden exceeding 25% experienced a median survival time of 6.8 months, while those with a burden less than 25% had a median survival time of 10.5 months ($p < .0001$).

Aarts et al (2021) published a systematic review and meta-analysis assessing the evidence for intra-arterial therapies in liver metastatic breast cancer.(84) 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. Patient demographic information was not summarized in this publication. 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. The 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.(85) 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. The age of included patients ranged from 52 to 61 years; other patient demographic information was not summarized. 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.(86) RE was performed with glass (66%) or resin (34%) microspheres based on operator preference. The mean age of included patients was 51 years; other patient demographic information was not summarized. Imaging response assessments were available for 60/64 patients, of which 46 (77%, 95% CI, 64% to 86%) achieved an objective response (OR), demonstrating a 30% or greater reduction in metabolic activity. Patients with OR had a high median dose deliver to the tumor (167 Gy) compared to patients not achieving an OR (54 Gy; p<.001). Eight patients developed grade III 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.(87) The median age of included patients was 57 years and the majority of patients were White (54.2%). Extrahepatic metastases were reported in 18 and 20 continued to receive concurrent chemotherapy and/or immunotherapy. Median OS was 35.4 months from first RE. Radioembolization within 6 months of hepatic metastasis diagnosis and estrogen receptor-positive status were identified as positive predictors of overall survival.

Metastatic Melanoma

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

Review of Evidence

Systematic Reviews

Alexander et al (2022) published a systematic review of RE for hepatic metastases of uveal melanoma.(88) 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, SIRT, and immunoembolization.(89) However, due to

heterogeneity in available data, meta-analysis was not performed. The authors descriptively reported that six non-comparative retrospective cohort studies (n=150; range, 8 to 71) evaluated the use of SIRT, 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.(90) 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 progression-free survival from liver metastasis was 8.1 months (95% CI, 6.4, 11.8), and median OS was 18.5 months (95% CI, 11.3 to 23.5). Among patients who progressed after immunoembolization, complete response, partial response, or stable disease was achieved in 14 of 24 patients (58.3%; 95% CI, 36.3% to 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 with unresectable melanoma (both uveal and cutaneous) liver metastases refractory to standard chemotherapy treated with Y90 RE (n=28) or best supportive care (n=30).(91) 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 tumor size at baseline than those treated with best supportive care (mean, 7.28 cm vs 4.19 cm; p=0.02). Median OS from diagnosis of melanoma liver metastases was longer in RE-treated subjects (19.9 mo vs 4.8 mo; p<0.000), as was the median OS from diagnosis of the primary melanoma (119.9 months vs 26.1 months; p<0.001). Pre- and post-treatment imaging studies were available for 24 of 28 (85.7%) of those treated with RE. Of those, no patients had a CR; 5 patients (17.9%) had PR, 9 patients (32.1%) had SD, and 10 patients (35.7%) had PD. Two patients receiving RE had major (grade V) 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.(92) The 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 patients (86%) had CT or magnetic resonance imaging evaluation of treatment response at three months post-RE. Of those, five patients (8%) had a PR, 32 patients (52%) had SD, and 24 patients (39%) had disease progression. Median OS was 12.3 months (range, 1.9 to 9.3 months).

Several smaller studies published from 2009 to 2020 reported on the use of RE in patients with hepatic metastases from melanoma.(93-96) Three included only patients with ocular melanoma,(93-95) and 2 included patients with ocular or cutaneous melanoma.(96,97) Sample sizes ranged between 11 patients and 32 patients. Four studies reported those with poor performance status. Median age was in the 50s for 3 studies and in the 60's for 2. 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.(97) 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.(93) In

the study of 13 patients by Klingenstein et al (2013), none had complete remission; 8 (62%) had partial response; 2 (15%) had stable disease; and 3 (23%) had progressive disease.(95) Nine of 11 patients in Kennedy et al (2009) provided response data: 1 had complete remission; 6 had partial response; 1 had stable disease; and 1 had progressive disease.(94) 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.(97) 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 III or IV liver toxicity. Klingenstein et al (2013) observed 1 patient with marked hepatomegaly. Kennedy et al (2009) described 1 patient with a grade III gastric ulcer. Piduru et al (2012; n=12) (96); 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.(98) A response was seen in 47% with median local PFS in the liver of 3.4 months (range, 0.9 to 45.0). Median OS was 9.0 months (range, 0.9 to 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.(99) All patients had received at least one course of chemotherapy before receiving resin-based (n=17) or glass-based (n=22) yttrium-90. Most toxicities observed (93%) were grade I or II, and objective response rate (complete and partial responses) was 36%. Six months after treatment, 30 patients showed stable disease or response, and the overall median survival 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 liver metastatic breast cancer consists of case series and systematic reviews. One meta-analysis demonstrated a pooled median survival of 9.2 months for RE and another meta-analysis reported a median survival of 9.8 months following SIRT, 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 for liver metastatic melanoma has demonstrates 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 for liver 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 nonrandomized 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 transarterial chemoembolization and transarterial chemoembolization with drug-eluting beads. 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 phase 2 studies and case series. Relevant outcomes are overall survival, 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 intrahepatic cholangiocarcinoma 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, accruing data illustrate ICC as a radiation-sensitive tumor. RE prolongs survival with minimal side effects, and can downstage select patients to curative resection, especially when used in combination with chemotherapy. Moreover, neoadjuvant radioembolization followed by resection for ICC demonstrates a survival advantage over upfront surgery. Taken together, RE has an evolving role as first line through salvage therapy for ICC.⁽¹⁰⁰⁾ 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 II study, retrospective reviews, and case series, some of which have compared RE with other transarterial liver-directed therapies. The relevant outcomes are overall survival, 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 liver tumor. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable intrahepatic metastases from colorectal cancer and prior treatment failure who receive RE, the evidence includes several small- to moderate-sized RCTs, prospective trials, and retrospective studies using a variety of comparators, as well as systematic reviews of these studies. Relevant outcomes are overall survival, functional outcomes, quality of life, and treatment-related morbidity. While studies of patients with prior chemotherapy failure have methodologic problems and 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 combined use of RE and chemotherapy. For example, the Efficacy Evaluation of TheraSphere Following Failed First Line Chemotherapy in Metastatic Colorectal Cancer (EPOCH) RCT found significantly prolonged primary endpoints of progression-free survival (PFS) (hazard ratio [HR], 0.69; 95% confidence interval [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 (eg, breast, melanoma, pancreatic) who receive RE, the evidence includes nonrandomized studies. Relevant outcomes are overall survival, functional outcomes, quality of life, and treatment-related morbidity. These studies have shown significant tumor response; however, improvement in survival has not been demonstrated in controlled comparative studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

CLINICAL INPUT RECEIVED THROUGH PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

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

2015 Input

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

2010 to 2011 Input

In response to requests, the Blue Cross Blue Shield Association received input from 2 physician specialty societies (with 5 individual responses) and 6 academic medical centers, for a total of 11 respondents, while this policy was under review for July 2010 and again for March 2011. For the 2011 review, input was received from two physician specialty societies and three academic medical centers; all but one academic medical center had provided input in 2010. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. There was strong support for the use of RE in patients with primary HCC, as a bridge to liver transplant in HCC, and in neuroendocrine tumors. There was also strong support for use of RE in patients with liver metastases from CRCs and support for its use in patients with liver metastases from other cancers but with less consensus than for colorectal metastases. Those providing input were split as to whether RE should be used as monotherapy or in combination with other agents.

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

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

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network

Primary Hepatobiliary Carcinoma

The National Comprehensive Cancer Network (v.2.2023) guidelines on the treatment of hepatobiliary cancers indicate that the use of arterially directed therapies, including transarterial bland embolization, transarterial chemoembolization (TACE), and drug-eluting beads TACE, 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.(29)

Metastatic Neuroendocrine Tumors

The NCCN guidelines (v.1.2023) on the treatment of neuroendocrine tumors recommend consideration of transarterial radioembolization (TARE) for lobar or segmental disease distribution and in patients with prior Whipple surgery or biliary tract instrumentation.(101) TARE is better tolerated than transarterial embolization/transarterial chemoembolization, but late radioembolization-induced chronic hepatotoxicity may occur in long-term survivors, and is particularly a concern among patients undergoing bilobar radioembolization.

Metastatic Colon Cancer

The NCCN guidelines (v.4.2023) on the treatment of colon cancer provides a consensus recommendation that: "...arterial-directed therapies, 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." (102)

Metastatic Uveal Melanoma

The NCCN guidelines (v.1.2023) on the treatment of uveal melanoma state the following regarding RE: "Further study is required to determine the appropriate patients for risks and benefits of this approach". (103)

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.(104) 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."(105)

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).(106) 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."(107)

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."(108)

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 9.

Table 7. Summary of Key Trials

| NCT No. | Name | Planned Enrollment | Completion Date |
|--|---|---------------------------|------------------------|
| <i>Hepatocellular Carcinoma Ongoing</i> | | | |
| 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 | Jun 2025 (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 Pick-the-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 Locally Advanced Hepatocellular Carcinoma (HCC) (STRATUM) | 176 | Nov 2025 (recruiting) |
| 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 (suspended) |
| <i>Unpublished</i> | | | |
| NCT04090645 | A Humanitarian Device Exemption Treatment Protocol of TheraSphere for Treatment of Unresectable Primary or Unresectable Secondary Liver Cancer | 187 | Apr 2021 (completed) |
| NCT01176604 | Protocol for Use of TheraSphere® for Treatment of Unresectable Hepatocellular Carcinoma | 305 | Apr 2021 (completed) |
| NCT01556490^a | A Phase III Clinical Trial of Intra-arterial TheraSphere® in the Treatment of Patients With Unresectable Hepatocellular Carcinoma (HCC) (STOP-HCC) | 526 | Apr 2022 (completed) |
| NCT02072356 | A Humanitarian Device Exemption Treatment Protocol of TheraSphere® For Treatment of Unresectable Hepatocellular Carcinoma | 800 | Jun 2021 (completed) |
| <i>Metastatic Colorectal Cancer</i> | | | |

| | | | |
|--|---|-----|--------------------------|
| NCT05195710^a | Preoperative Y-90 Radioembolization for Tumor Control and Future Liver Remnant Hypertrophy in Patients With Colorectal Liver Metastases | 50 | Mar 2024 (recruiting) |
| Intrahepatic Cholangiocarcinoma Unpublished | | | |
| 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 (completed) |
| 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) |

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

Government Regulations

National:

There is no National Coverage Determination on this topic.

Local:

There is no Local Coverage Determination on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Radiofrequency Ablation of Primary or Metastatic Liver Tumors
- Transcatheter Arterial Chemoembolization of Hepatic Tumors (TACE)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 12/12/23, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

| Policy Effective Date | BCBSM Signature Date | BCN Signature Date | Comments |
|-----------------------|----------------------|--------------------|---|
| 7/21/03 | 07/21/03 | 07/11/03 | Joint policy established |
| 1/12/04 | 1/12/04 | 1/12/04 | Policy updated S code obtained all inclusive |
| 01/10/06 | 01/10/06 | 01/20/06 | Routine maintenance |
| 05/01/08 | 2/19/08 | 05/01/08 | Routine maintenance, policy retired |
| 1/1/12 | 10/11/11 | 11/9/11 | Policy unretired; title changed from “Yttrium-90 Microsphere Therapy (Therasphere®; SIR-Spheres®)” to “Radioembolization for Primary and Metastatic Tumors of the Liver”; addition of new indications; medical policy statement revised. |
| 5/1/13 | 2/19/13 | 3/4/13 | Routine maintenance |
| 9/1/14 | 6/20/14 | 6/23/14 | Routine maintenance; added new code 37243, effective 1/1/14 |
| 11/1/15 | 8/18/15 | 9/16/15 | Routine maintenance; added new indications melanoma (ocular or cutaneous) and breast cancer as primary cancer sites in treating unresectable hepatic metastases. Added indication “primary intrahepatic cholangiocarcinoma in patients with unresectable tumors”; added Inclusion “Treatment of other radiosensitive tumors metastatic to the liver with liver-limited or liver-dominant disease for symptom palliation or prolongation of survival”; Added code 79445. |
| 11/1/16 | 9/23/16 | 8/26/16 | <ul style="list-style-type: none"> • Routine maintenance – updated references and rationale; • added previously untreated metastatic colorectal cancer to the exclusions. • Addition of “Relative Indication” with bullets pulled from contraindications under Exclusions |
| 11/1/17 | 8/15/17 | 8/15/17 | Routine maintenance |
| 11/1/18 | 8/21/18 | 8/21/18 | Routine maintenance |

| | | | |
|--------|----------|----------|---|
| 3/1/19 | 12/11/18 | 12/11/18 | Routine maintenance |
| 5/1/19 | 2/19/19 | | Routine maintenance |
| 5/1/20 | 2/18/20 | | Routine maintenance |
| 5/1/21 | 2/16/21 | | Routine maintenance |
| 5/1/22 | 2/15/22 | | Routine maintenance |
| 5/1/23 | 2/21/23 | | Routine maintenance Vendor: S2095 require authorization by eviCore. (ky) |
| 5/1/24 | 2/20/24 | | <p>Routine maintenance Vendor: S2095 require authorization by eviCore.</p> <p>Aligned JUMP policy Inclusions section with eviCore Radiation Oncology clinical guidelines V1.0.2024 DRAFT effective 4.1.2024 pg 290.</p> <p>Added the below bullet under the Inclusions section of Unresectable and/or medically inoperable primary or metastatic liver malignancies from ANY of the following:</p> <ul style="list-style-type: none"> ○ Treatment of other radiosensitive tumors metastatic to the liver with liver-limited or liver-dominant disease for symptom palliation or prolongation of survival <p>Deleted the section below under Exclusions: Yttrium-90 has relative contraindications for patients who have:</p> <ul style="list-style-type: none"> – Ascites or are in clinical liver failure – Markedly abnormal liver function tests (LFTs) <p>Added the below bold under Exclusions to align with vendor eviCore under: Yttrium-90 is contraindicated for patients who have:</p> <ul style="list-style-type: none"> • Treatment that would result in greater than 25 to 30 Gy dose to the lung in one session or 50 Gy |

| | | | |
|--|--|--|---|
| | | | <p>cumulative as assessed by Technetium MAA scan.</p> <ul style="list-style-type: none"> • Post JUMP: <p>The below updates are made on 3/8/24:</p> <ul style="list-style-type: none"> • Added code Q3001 as payable to the policy as payable in the office setting. • Code S2095 is also made payable in the office setting. • Code Q3001 is vendor managed by Carelon for PPO. • (ky) |
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Next Review Date: 1st Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE

POLICY: RADIOEMBOLIZATION FOR PRIMARY AND METASTATIC TUMORS OF THE LIVER

I. Coverage Determination:

| | |
|--|--|
| Commercial HMO (includes Self-Funded groups unless otherwise specified) | Covered, criteria apply. |
| BCNA (Medicare Advantage) | Refer to the Medicare information under the Government Regulations section of this policy. |
| BCN65 (Medicare Complementary) | Coinsurance covered if primary Medicare covers the service. |

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.