
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, two 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-fluorouridine 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 two 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).

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 have been established. It may be considered a useful therapeutic option when indicated.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:

- Primary hepatocellular carcinoma that is unresectable and limited to the liver
- Primary hepatocellular carcinoma as a bridge to liver transplantation
- Hepatic metastases from neuroendocrine tumors (carcinoid and noncarcinoid) with diffuse and symptomatic disease when systemic therapy has failed to control symptoms

- Unresectable hepatic metastases from colorectal carcinoma, melanoma (ocular or cutaneous), or breast cancer that are both progressive and diffuse, in patients with liver-dominant disease who are refractory to chemotherapy or are not candidates for chemotherapy or other systemic therapies
- Primary intrahepatic cholangiocarcinoma in patients with unresectable tumors.
- Treatment of other radiosensitive tumors metastatic to the liver with liver-limited or liver-dominant disease for symptom palliation or prolongation of survival

Criteria for unresectable hepatocellular carcinoma:

- Multiple liver metastases together with involvement of both lobes; or
- Tumor invasion where the three hepatic veins enter the inferior vena cava; or
- None of the hepatic veins could be preserved if the metastases were resected; or
- Tumor invasion of the porta hepatis such that neither the origin of the right or left portal veins could be preserved if resection were undertaken; or
- Widespread metastases such that resection would leave less liver than is compatible with survival

Exclusions:

- Used to treat, previously untreated, unresectable, hepatic metastases from colorectal carcinoma
- 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 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)

Yttrium-90 has **relative** contraindications for patients who have:

- Ascites or are in clinical liver failure
- Markedly abnormal liver function tests (LFTs)

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:

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 Test Purpose

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

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

The following PICOs were used to select literature to inform this review.

Patients

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, also referred to as selective internal radiotherapy, delivers small beads (microspheres) impregnated with yttrium-90 (Y90) intra-arterially via the hepatic artery. The microspheres, which become permanently embedded, are delivered to tumors preferentially because the hepatic circulation is uniquely organized, whereby tumors greater than 0.5 cm rely on the hepatic artery for blood supply while the normal liver is primarily perfused via the portal vein. RE has been proposed as a therapy for multiple types of primary and metastatic liver tumors.

RE or RE and liver transplant are performed by transplant surgeons, hepatologists, radiologists, oncologists, and primary care providers in an inpatient clinical setting.

Comparators

The following practice is currently being used to make decisions about 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)

Standard of care is performed by hepatologists, transplant surgeons, radiologists, oncologists, and primary care providers in an inpatient clinical setting.

Outcomes

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

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

Outcomes	Details
Treatment-related morbidity	Outcomes of interest include complete remission, partial response, PFS, and stable disease

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). Results of these meta-analyses are summarized below.

Abdel-Rahman et al (2020) conducted a meta-analysis of RCTs comparing RE alone or combined with other systemic or locoregional treatments to placebo, no treatment, or other similar interventions in patients with unresectable HCC.(4)

Six RCTs (total n=1340) were identified, all of which were assessed by authors as being at high risk of bias. The authors reported the certainty of evidence as low to very low. Meta-analysis was able to be performed using data from more than one RCT for few comparisons. Based on meta-analysis of two RCTs, disease control rate was not significantly different between RE and sorafenib (relative risk [RR], 0.94; 95% confidence interval [CI], 0.84 to 1.05), though RE was associated with less hand-foot skin reactions (RR, 0.02; 95% CI, 0.00 to 0.06), skin rash (RR, 0.11; 95% CI, 0.04 to 0.34), diarrhea (RR, 0.11, 95% CI, 0.04 to 0.34), and hypertension (RR, 0.10; 95% CI, 0.01 to 0.88). Based on meta-analysis of three RCTs, the risk of serious adverse events did not differ between RE and TACE (RR, 1.47; 95% CI, 0.66 to 3.25). Meta-analysis could not be performed for other comparisons; thus, results of other included trials are described individually in the section below on RCTs.(5,6)

Venerito et al (2020) performed a meta-analysis to assess the noninferiority of SIRT as monotherapy or followed by sorafenib versus sorafenib monotherapy on OS.(7) A noninferiority margin of 1.08 in terms of hazard ratio (HR) was prespecified. Three RCTs were included (n=1,243), and meta-analysis demonstrated SIRT with or without sorafenib was noninferior to sorafenib monotherapy in OS (median, 10.2 and 9.2 months; HR, 0.91; 95% CI, 0.78 to 1.05). Treatment-related severe adverse events were reported in 28.9% vs 43.3% of patients treated with SIRT and sorafenib monotherapy, respectively (p<0.01).

Yang et al (2020) conducted a meta-analysis of RCTs to compare effects of DEB-TACE, TACE, and RE on the primary outcome of overall survival.(8) Compared with TACE, RE was associated with similar one-year OS (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). 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 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.(9) Fourteen studies (total n=2065 patients) 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) included 5 retrospective observational studies (total n=533 patients).(10) Survival at one year did not differ statistically for RE vs TACE (42% vs 46%; relative risk [RR], 0.93; 95% CI, 0.81 to 1.08; p=0.33). At two years, survival was higher for RE (27 vs 18%; RR=1.36; 95% CI, 1.05 to 1.76; p=0.02), but there was no statistically significant difference in survival rates at three, four, or five years. Postprocedural complications were also similar in the two groups. Facciorusso et al (2016) included ten studies (total n=1557 patients), two of which were randomized controlled trials (RCTs).(11) The odds ratio for survival was not statistically significant at 1 year (OR=1.0; 95% CI, 0.8 to 1.3; p=0.93) but favored RE in years 2 (OR=1.4; 95% CI, 1.1 to 1.90; p=0.01) and 3 (OR=1.5; 1.0 to 2.1; p=0.04).

Vente et al (2009) conducted a meta-analysis evaluating tumor response and survival in patients who received yttrium-90 glass or resin microsphere radioembolization (RE) for the treatment of primary HCC or metastases from colorectal cancer (CRC).(12) (Refer to the Unresectable Metastatic CRC section for the data from the meta-analysis as pertains to that disease.) Selected studies were from 1986 through 2008 and presented tumor response (measured by computed tomography) and data on median survival times. To allow comparability of results for tumor response, the category of "any response" was introduced and included complete remission, partial response, and stable disease. Overall tumor response could only be assessed as any response because response categories were not uniformly defined in the analyzed studies. In 14 articles, clinical data were presented on tumor response and survival for 425 patients with HCC who had received 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

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

Pitton et al (2015) reported on results from a small RCT comparing RE with DEB-TACE for the treatment of unresectable HCC.(6) The trial included 24 patients, with 12 randomized to each group. No deaths occurred within 30 days of the procedure. There were no statistically significant differences between groups in terms of in PFS (180 days for RE vs 216 days for DEB-TACE, $p=0.619$) or OS (592 days for RE vs 788 days for DEB-TACE, $p=0.927$).

Nonrandomized Comparative Studies

Facciorusso et al (2020) performed a retrospective analysis that compared patients with HCC treated with RE plus sorafenib (n=45) with propensity score-matched patients treated with sorafenib alone (n=90).(13) 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.(14) Patients receiving chemoembolization had poorer ECOG Performance Status ratings and Child-Pugh class while those receiving RE had larger and more infiltrative tumors. Overall complete remission was 84% with RE and 58% with chemoembolization ($p=0.001$). Median PFS was 564 days and 271 days ($p=0.002$) and median OS was 1198 days and 1043 days ($p=0.35$), respectively, for the RE group and the chemotherapy group.

Soydal et al (2016) retrospectively assessed outcomes of patients receiving RE and TACE for HCC.(15) Each group included 40 patients. RE patients had a mean survival of 39 months versus 31 months for TACE ($p=0.014$). 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.(16) A total of 189 patients with unresectable HCC (77 receiving RE, 112 receiving EBRT) were treated between 2004 and 2011. Median OS for RE was 12 months and 14 months for EBRT. Median disease-specific survival was identical for both groups at 14 months. After adjustment for differences between patients, multivariable

survival analysis showed no association between treatment and OS or disease-specific survival.

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

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

Carr et al (2010) reported on a consecutive series of patients with HCC seen at a single medical center and who were not candidates for surgical resection.(19) Patients received conventional cisplatin-TACE between the years 1992 and 2000 (n=691), Y90 microspheres between 2000 and 2005 (n=99), or no treatment (n=142). Median OS for the Y90 group was 11.5 months (95% CI, 8 to 16 months) and 8.5 months (95% CI, 8 to 10 months) for the TACE group (p<0.05). Untreated patients had a median survival of 2 months. Although the authors detected a slight selection bias toward milder disease in the RE group, they concluded that Y90 and TACE appeared to be equivalent regional therapies for patients with unresectable, nonmetastatic HCC.

Section Summary: Radioembolization for Unresectable Hepatocellular Carcinoma

Systematic reviews, RCTs, and nonrandomized comparative studies have not demonstrated the superiority of RE over alternative active comparators. 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. Limitations of the existing evidence include lack of formal noninferiority analysis, which would be helpful to establish whether RE is as effective as alternatives, and the small size of the available RCTs, which limits conclusions about the relative efficacy of RE vs alternatives. Nonetheless, in all studies, 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).⁽²⁰⁾ Of the 18 comparative studies, two studies (n=257 patients) reported on the incidence of dropout from transplantation wait-lists, and patients receiving bridging therapy. This group had reduced risk of dropout due to disease progression, compared with those receiving transplantation alone (RR=0.32) (see Table 3). Between-group differences were not statistically significant for mortality (five comparative studies; n=531 patients) or recurrence rate (10 comparative studies; n=889 patients). Subgroup analysis was conducted for types of bridging therapy: for all-cause mortality after transplantation, the RR was 1.124 with transarterial embolization (TAE) compared with transplantation alone (1 cohort). For disease recurrence, the RR for this bridging therapy type was 2.374 compared with transplantation alone. No RCTs were identified, and most of the selected studies had a high risk of bias on patient selection, adequate follow-up, and funding source, when reported.

Table 2. Characteristics of Systematic Reviews

Study	Dates	Trials	Participants ^a	Design
Kulik et al (2018) ²⁰	1996-2016	49	Unresectable hepatocellular carcinoma	<ul style="list-style-type: none"> • 18 comparative • 31 noncomparative

^aPatients needed liver transplantation and received transplant alone or bridging therapy in addition to transplant.

Table 3. Results of Systematic Reviews

Study	Dropout From Wait-list	Mortality	Recurrence Rate	Subgroup Analysis by Therapy Type	Comments
Kulik et al (2018) ²⁰					
Comparative studies (n=18)	2 studies (n=257 patients)	5 studies (n=531 patients)	10 studies (n=889 patients)		
	Reduced risk of dropout in patients with bridging therapy vs transplant alone (RR=0.32; 95% CI, 0.06 to 1.85; $I^2=0\%$)	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, adequate follow-up, and funding source

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.⁽²¹⁾ 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, 3-17 months). In the Y90 group, there were 13 transplants at a median of 9 months (range, 4-15 months). Median time to progression exceeded 26 months in the Y90 group and 6.8 months in the TACE group (hazard ratio, 0.12; 95% CI, 0.03 to 0.56; p=0.007). Median survival was 19 months with Y90 and 18 months in TACE (p=0.99). Adverse events were similar between groups, with the exception of more

diarrhea (21% vs 0%) and hypoalbuminemia (58% vs 4%) in the conventional TACE group. A limitation of the OS analysis was the censoring of the survival outcome at liver transplantation given that transplantation is related to the treatment effect.

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

Nonrandomized Studies

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. 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. 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=0.052). However, microvascular invasion occurred in 3.6% versus 27% of patients treated with RE versus TACE (p=0.013).

In a retrospective review, 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: RE as a Bridge to Liver Transplantation for Unresectable HCC

Studies have shown that successful liver transplant can be achieved in some patients who are initially treated with RE. Only one retrospective cohort compared results between RE and other therapy, finding no significant differences in OS between RE and TACE at three years.

RE FOR UNRESECTABLE INTRAHEPATIC CHOLANGIOCARCINOMA

The evidence on the use of RE for intrahepatic cholangiocarcinoma (ICC) consists primarily of case series. The studies have demonstrated tumor response to RE. Tumor response may improve survival, but without direct comparison of survival with a control group this improvement cannot be ascertained from case series.

Clinical Context and Test Purpose

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

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

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

Patients

The relevant population of interest is individuals with unresectable ICC. Cholangiocarcinomas are tumors that arise from the epithelium of the bile duct and are separated into intrahepatic and extrahepatic types. ICC appear in the hepatic parenchyma and are also known as peripheral cholangiocarcinomas.

Interventions

The treatment being considered is RE.

Comparators

The following practice is currently being used to make decisions about unresectable ICC: standard of care, usually palliative. Resection is the only treatment with potentially curative effect, and five-year survival rates have ranged from 20% to 43%.(28) Patients with unresectable disease may select among fluoropyrimidine- or gemcitabine-based chemotherapy, fluoropyrimidine chemoradiation, or best supportive care.

Outcomes

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

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

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

PFS: progression-free survival.

Review of Evidence

Systematic Reviews

Al-Adra et al (2015) reported on outcomes in a systematic review of studies on RE for ICC.(29) The review included 12 publications, seven of which were published in abstract form only. Of the peer-reviewed articles, three were described as prospective cohort studies, which are detailed below (Mouli et al [2013] (30); Hoffmann et al [2012] (31); Saxena et al [2010] (32); of note, the Hoffmann study was reported as retrospective). The overall weighted median survival was 15.5 months (range, 7-22.2 months), based on 11 studies. A weighted mean partial response was seen in 28% of patients and stable disease was seen in 54% at 3 months post-treatment.

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.(33) 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.

Case Series

Chan et al (2017) retrospectively analyzed data from 10 patients from a prospectively collected database who were treated with resin- (n=6) or glass-based (n=4) RE for unresectable combined hepatocellular cholangiocarcinoma.(34) No toxicities of grade III or greater were reported. Seven patients had elevated α -fetoprotein and/or cancer antigen 19-9 levels before treatment: of these, four saw one or more of the biomarkers decrease by 50% or more, and two patients saw a decrease of 25% to 49%. According to RECIST version 1.1 criteria, all patients had stable disease; however, under the modified RECIST criteria, six patients had a partial response to RE. Median OS from the first RE was 10.2 months, and median progression-free survival from the same time point was 5.2 months. Macrovascular invasion was reported to be a significant prognostic factor of OS (p=0.005).

Table 5. Summary of Retrospective Case Series Characteristics

Study	Institution	Participants	Treatment Delivery
Chan et al (2017) ³⁴	Prospectively collected database	Unresectable combined HCC-CC	<ul style="list-style-type: none"> • 6 treated with resin-based RE • 4 treated with glass-based RE

HCC-CC: hepatocellular-cholangiocarcinoma; RE: radioembolization.

Table 6. Summary of Retrospective Case Series Results

Study	Median Survival, mo ^a	Toxicity	AFP and CA 19-9 Levels	Tumor Response (RECIST)
Chan et al (2017) ³⁴	<ul style="list-style-type: none"> • OS=10.2 • PFS=5.2 	<ul style="list-style-type: none"> • No toxicities grade \geq3 	<ul style="list-style-type: none"> • 4 had decrease in AFP and/or CA 19-9 of \geq50% • 2 had decrease of 25%-49% 	<ul style="list-style-type: none"> • RECIST v1.1: All patients had SD • mRECIST: 6 had PR

AFP: a-fetoprotein; CA 19-9: cancer antigen 19-9; OS: overall survival; PFS: progression-free survival; SD: stable disease; mRECIST: modified RECIST; PR: partial response

^a Measured from first radioembolization.

Jia et al (2017) retrospectively reviewed all 24 patients who underwent Y90 RE for unresectable and failed first-line chemotherapy for ICC at a single institution.(35) Mean follow-up was 11 months (range, 3-36 months). Median OS from time of diagnosis was 24 months (range, 18-30 months) and from the RE procedure was 9 months (range, 6-12 months). Survival at 6, 12, and 30 months was 70%, 33%, and 20%, respectively.

Mosconi et al (2016) retrospectively analyzed 23 consecutive patients with unresectable/recurrent ICC at a single institution.(36) Overall median survival was 18 months

(95% CI, 14 to 21 months). Survival was significantly longer in treatment-naive patients than in those who received other treatments before RE (52 months vs 16 months, $p=0.009$).

Rayar et al (2015) reported on successful down staging of unresectable ICCs after RE in eight patients with initial unresectability due to involvement of hepatic veins or portal veins of the future liver remnant.(37) After RE, all patients underwent successful resection.

Mouli et al (2013) reported on 46 patients treated with RE for ICC via a retrospective review of prospectively collected data from a single institution.(30) Survival varied by level of disease, multifocal, infiltrative and bilobar and ranged from 5.7 to 15.6 months. Five patients achieved a resectable status and underwent curative resection.

A retrospective study by Hoffman et al (2012) assessing RE with Y90 resin microspheres included 24 patients with nonresectable chemo-refractory ICC and no extrahepatic disease.(31) Mean age of the sample was 65.2 years. ECOG Performance Status score was 0 in 51.5%, 1 in 21.2%, and 2 in 27.3%. Previous therapy included chemotherapy in 78.8%, surgery in 36.4%, TACE in 9.1%, radiofrequency ablation in 5.1%, and EBRT in 3.0%. Tumor response was assessed by RECIST criteria. Complete remission was seen in 0%, partial response in 36.4%, stable disease in 51.5%, and progressive disease in 15.2%. Follow-up ranged from 3.1 to 44 months (median, 10 months). Median OS was 22 months and the median time to progression was 9.8 months. Favorable subgroups with respect to survival included those with ECOG Performance Status score of 0, tumor burden as a percentage of the liver volume of 25% or less, response by cancer antigen 19-9 criterion, and RECIST partial response. The same subgroups, except those with a cancer antigen 19-9 response, had favorable time to progression results. Data were collected retrospectively, and no toxicity results were reported.

A study by Haug et al (2011) evaluated prognostic factors of RE treatment in 26 consecutive patients with unresectable ICC who underwent RE with Y90 glass microspheres.(38) All patients had a Karnofsky Performance Status of 60% or more. Mean age was 64.3 years, 31% had extrahepatic disease. Prior treatments included chemotherapy in 65%, surgery in 28%, localized therapy in 20%, and none in 24%. Tumor response results according to RECIST criteria were: complete remission in 0%; partial response in 22%; stable disease in 65%; and progressive disease in 13%. Median OS was 51 weeks, and multivariate analysis found that a partial response from quantitative interpretation of positron emission tomography was a significant independent predictor of survival. The authors found no cases of grade III toxicity in transaminases or bilirubin.

Saxena et al (2010) prospectively evaluated 25 patients with unresectable ICC who received RE with Y90 resin microspheres.(32) Extrahepatic disease was present in 48% and the mean age was 57 years. Prior treatments included surgery in 40%, chemotherapy in 72%, radiofrequency ablation in 6.1%, and EBRT in 3.0%. By RECIST tumor response criteria, complete remission was seen in 0%, partial response in 24%, stable disease in 48%, and progressive disease in 20%. Follow-up was collected between 0.4 months and 55 months (median, 8.1 months). In the entire group, the median OS was 9.3 months. Among subgroups, longer survival duration was seen in patients with peripheral tumors and those with ECOG Performance Status score of 0. The proportion of patients with both grade 3 albumin toxicity and grade 3 bilirubin toxicity was 8%. Grade 3 alkaline phosphatase toxicity was observed in 4%. One (4%) patient experienced duodenal ulcer due to malperfusion of Y90 microspheres.

A study by Ibrahim et al (2008) reported results for RE with Y90 glass microspheres among 24 patients with unresectable ICC.(39) The group was 33% female and had a median age of 68 years. Extrahepatic disease was present in 33%. ECOG Performance Status was 0 in 42%, 1 in 50%, and 2 in 8%. Prior chemotherapy had been used in 29%. Using the WHO tumor response criteria, CR was observed in 0%; CR, 27%; SD, 68%; and PD, 5%. Follow-up was collected over a median of 17.7 months and median OS was 14.9 months. Subgroups that had favorable survival results included those with ECOG Performance Status of 0, no previous chemotherapy and peripheral tumor. Grade 3 albumin toxicity was found in 17%, grade III bilirubin toxicity in 4%, and 1 patient (4%) developed a duodenal ulcer.

Rayar et al (2015) reported on successful down staging of unresectable ICCs after RE in 8 patients with initial unresectability due to involvement of hepatic veins or portal veins of the future liver remnant.(37) After RE, all patients underwent successful resection.

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 24 months across studies. There is little, direct comparative data available to demonstrate effect on survival. Side effects are common but generally mild.

RADIOEMBOLIZATION FOR UNRESECTABLE NEUROENDOCRINE TUMORS

Clinical Context and Test Purpose

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

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

The following PICOs were used to select literature to inform this review.

Patients

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.

Interventions

The treatment being considered is RE.

Comparators

The following practice is currently being used to make decisions about 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.(40) Chemoembolization has shown response rates of nearly 80%, but the effect is of short duration, and a survival benefit has not been demonstrated.(40)

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 five years.

Review of Evidence

Systematic Reviews

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.(41) 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%).

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

Engelman et al (2014) retrospectively compared transarterial, liver-directed therapies, including RE, hepatic artery embolization (HAE), and hepatic artery chemoembolization (HACE), in 42 patients treated for metastatic neuroendocrine tumors.(43) 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 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.(44) 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 six 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.(45) 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.(40) 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, 32-79 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.(46) 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 good tumor response and improvement in clinical symptoms with RE.(47-51)

Section Summary: Unresectable Neuroendocrine Tumors

The evidence for the use of RE to treat unresectable neuroendocrine tumors primarily consists of retrospective case reviews. Objective response rates ranged from 12% to 80% and disease control rates ranged from 62% to 100% in a 2014 systematic review. In a small nonrandomized comparative study, RE, HAE, and HACE appeared similar in terms of radiographic response, time to progression, and OS, but inference is limited by study designs and small sample sizes.

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

Clinical Context and Test Purpose

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

The following PICOs were used to select literature to inform this review.

Patients

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.

Comparators

The following practice is currently being used to make decisions about 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.(52) Recent advances in chemotherapy, including oxaliplatin, irinotecan, and targeted antibodies like cetuximab, have doubled the median survival in this population from less than one year to

more than two years. Palliative chemotherapy using combined systemic and HAI may increase disease-free intervals for patients with unresectable hepatic metastases from CRC.

Outcomes

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

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

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

PFS: progression-free survival.

Review of Evidence

Systematic Reviews

In a systemic review, Saxena et al (2014) evaluated 20 experimental and observational studies on RE for chemoresistant, unresectable CRC liver metastasis (total n=979 patients).(53) They included two RCTs (Gray et al [2001],(54) Hendlisz et al [2010],(55) described below), 5 non-RCTs or well-designed cohort studies, and 13 observational studies. After RE, the average reported complete remissions and partial response rates from 16 studies were 0% (range, 0%-6%) and 31% (range, 0%-73%), respectively. Nine months was the median time to intrahepatic progression (range, 6-16 months). In 11 studies reporting on OS, the median survival time was 12 months (range, 8.3-3.6 months).

Rosenbaum et al (2013) evaluated 13 relevant articles on RE as monotherapy and 13 studies on RE combined with chemotherapy for chemoresistant, unresectable CRC liver metastasis.(56) 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.

A 2010 technology assessment from the California Technology Assessment Forum assessed 25 studies on the use of RE and inoperable metastatic CRC to the liver, including two RCTs (Gray et al [2001] (54) and Van Hazel et al [2004],(57) described below), a small retrospective study comparing selective internal radiotherapy (SIRT) with chemoembolization (n=36), and 21 case series.(52) The assessment concluded that, the three comparative studies used different control interventions and that the nonrandomized study did not show any convincing improvements over chemoembolization. The reviewer found it feasible to deliver radiotherapy to liver metastases and achieve at least partial response in a substantial portion of patients with relatively few serious adverse events. He also found that the results of the two randomized studies were encouraging but not definitive, because the trials were very small, response rates in the control groups were lower than expected, and control groups were not given what was then considered standard first-line chemotherapy for metastatic CRC. The assessment concluded that the use of SIRT for unresectable CRC did not meet any of the California Technology Assessment Forum criteria.

A Cochrane review by Townsend et al (2009) assessed the efficacy and toxicity of RE, alone or with systemic or regional hepatic artery chemotherapy, in the treatment of metastatic CRC liver metastases.(58) Two trials met reviewers' inclusion criteria were included, Gray et al

(2001) (54) and van Hazel et al (2004),(57). Reviewers concluded that there was a lack of evidence that SIRT improves survival or quality of life (QOL) in patients with metastatic CRC, whether it is given alone or with chemotherapy, and that there is a need for well-designed, adequately powered phase III trials assessing the effect of SIRT when used with modern combination chemotherapy regimens.

The meta-analysis by Vente et al (2009; previously described) included 19 studies (total n= 792 patients) assessing metastatic CRC patients treated with Y90 RE.(12) Included in the meta-analysis were two RCTs (Gray et al [54] and van Hazel et al [57]). Two covariates were included in the meta-regression model: (1) whether an older generation of cytostatic agents (5-FU/LV [leucovorin or floxuridine]) or a newer generation (5-FU/LV plus oxaliplatin [FOLFOX] or 5-FU/LV plus irinotecan) was used, and (2) whether Y90 RE was given as salvage therapy or as first-line treatment with adjuvant chemotherapy. The specific cytostatic agent(s) used did not affect response ($p=0.96$). Tumor response to Y90 RE was high, with any response rates of approximately 80% in a salvage setting, and more than 90% when used as first-line neoadjuvant treatment to chemotherapy, regardless of the chemotherapy regimen used. Median survival after Y90 RE, irrespective of differences in determinants (microspheres type, chemotherapy protocol, salvage or first line), varied from 6.7 to 17.0 months.

Randomized Controlled Trials

A Phase III RCT by van Hazel et al (2016) compared modified FOLFOX chemotherapy and FOLFOX chemotherapy plus SIRT in 530 patients with previously untreated liver-dominant metastatic disease.(59) Bevacizumab was permitted as additional treatment at the discretion of the treating physician. About 40% of patients had extrahepatic metastases at randomization and about 28% had metastases with more than 25% liver involvement. 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. Wasan et al (2017) analyzed OS from this study in combination with two other studies of chemotherapy with and without RE.(60) Overall, 549 patients were randomly assigned to FOLFOX alone and 554 patients were assigned FOLFOX plus SIRT. Overall survival was not significantly different between groups (HR, 1.04; 95% CI, 0.90 to 1.19).

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.(54) The investigators closed the trial after entering 74 patients (n=70 eligible for randomization). The original goal was 95 patients. The smaller study population was adequate to detect increases in response rate (from 20% to 55%) and median disease time to progression (by 32% from 4.5 months), with 80% power and 95% confidence, but lacked sufficient statistical power to detect changes in survival. 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. However, there were no statistically significant differences

between treatment arms in actuarial survival rates ($p=0.18$) or in 11 quality of life measures. Treatment-related complications (grades III-IV) included 23 events in each arm (primarily changes in liver function tests). Nevertheless, investigators concluded that a “single injection of SIR-Spheres plus HAI is substantially more effective” than the same HAI regimen delivered alone. Although the trial showed significantly longer time to progression with RE, several issues make the conclusion less certain. Accrual was halted early, leaving the study underpowered. Although the trial had an institutional review board oversight, the reporting suggested early closure was at the sole discretion of the principal investigator without independent review or prospectively designed data monitoring procedures and stopping rules. 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.(19,61) Results of this trial may reflect use of a shorter-than-standard duration of HAI therapy and could be confounded by administration of nonprotocol chemotherapy before and after SIRT. The reported increases in response rates and time to progression improved neither duration of survival nor quality of life.

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.(57) 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.(55) 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 F-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 ($n=155$). (62) Extra-hepatic metastasis was more frequent with DEB-TACE (68.1% vs. 47.7%; $p=0.014$), as was occurrence of ≥ 10 liver lesions (42.2% vs. 68.8%; $p=0.001$). Toxicity was not significantly different between DEB-TACE and RE (27% vs. 9.1%, respectively; $p=0.057$). Treatment with DEB-TACE was not a prognostic factor for survival (HR, 0.94; 95% CI, 0.54 to 1.65).

Seidensticker et al (2012) published a retrospective, matched-pair comparison of RE plus best supportive care versus best supportive care alone for patients with chemo-refractory, liver-dominant colorectal metastases ($n=29$ in each group).(63) 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; $p<0.001$). Adverse events were considered generally mild-to-moderate and manageable.

Section Summary: Unresectable Intrahepatic Metastatic Colorectal Cancer

The evidence for RE in unresectable intrahepatic metastatic CRC includes systematic reviews, RCTs and observational studies. RCTs report mixed results for RE compared with alternatives

with respect to time to progression or PFS, and OS was not significantly improved with RE plus chemotherapy versus chemotherapy alone. Radiofrequency ablation has been found inferior to resection in local recurrence rates and five-year OS rates; further, it is generally reserved for patients with disease that cannot be completely resected due to patient comorbidities, location of metastases (ie, adjacent to a major vessel), or an estimate of inadequate liver reserve following resection. Radiofrequency ablation is recommended for nonsurgical candidates with small metastases.(28) The role of local (liver-directed) therapy (including RE, chemoembolization, and conformal radiotherapy) in debulking unresectable metastatic disease remains controversial.(28)

RE FOR UNRESECTABLE INTRAHEPATIC METASTASES FROM OTHER CANCERS

Case reports have been published on the use of RE in many other types of cancer with hepatic metastases, including breast, melanoma, head and neck (including parotid gland), pancreaticobiliary, anal, thymic, thyroid, endometrial, lung, kidney, gastric, small bowel, esophageal, ovarian, cervical, prostatic, bladder, and for sarcoma and lymphoma.(64)

Clinical Context and Test Purpose

The purpose of RE in patients who have unresectable intrahepatic metastases from other cancers is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

The following PICOs were used to select literature to inform this review.

Patients

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

Interventions

The treatment being considered is RE.

Comparators

The following practice is currently being used to make decisions about other unresectable intrahepatic metastases: standard of care.

Outcomes

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

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

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

PFS: progression-free survival.

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 patients refractory to standard of care chemotherapy.(64)

Review of Evidence

Systematic Review

Feretis et al (2019) performed a systematic review of RE for treatment of metastatic intrahepatic breast cancer.(65) Twelve case series were included (total n=452; range, 7 to 81), with a duration of follow-up ranging from 6 to 15.7 months in studies reporting follow-up duration. Overall, 52.2% of patients had breast metastases not confined to the liver. Radioembolization provided disease control in 81% of patients, and OS ranged from 3.6 to 20.9 months, with an estimated mean survival of 11.3 months.

Case Series

Metastatic Melanoma

The evidence related to the use of RE for melanoma consists of relatively small observational studies, many of which focus on patients with uveal melanoma, for whom the liver is the most common site of metastatic disease.

Review of Evidence

Systematic Reviews

Rowcroft et al (2019) 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.(66) 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.(67) 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%, 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).(68) 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; five patients (17.9%) had PR, nine 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.(67) 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, 1.9-49.3 months).

Several smaller studies published from 2009 to 2013 reported on the use of RE in patients with hepatic metastases from melanoma.(70-73) Three included only patients with ocular melanoma,(70-72) and the fourth included patients with ocular or cutaneous melanoma.(73) Sample sizes ranged between 11 patients and 32 patients. Three studies excluded those with poor performance status. Median age was in the 50s for three studies and 61 in the fourth. One article did not describe any previous treatment, and another described it incompletely. Three 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.(70) 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.(72) 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.(71) Median survival in Gonsalves et al (2011), Klingenstein et al (2013), and Kennedy et al (2009) were 10.0 months, 19 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. The fourth study (Piduru et al [2012] (72); $n=12$) did not include any toxicity data.

Metastatic Pancreatic Cancer

Michl et al (2014) reported on a case series on RE for pancreatic cancer.(74) A response was seen in 47% with median local PFS in the liver of 3.4 months (range, 0.9-45.0). Median OS was 9.0 months (range, 0.9-53.0 months), and 1-year survival was 24%.

Hepatic Sarcoma

Miller et al (2018) retrospectively reviewed 39 patients with metastatic ($n=37$) or primary ($n=2$) liver sarcoma in a multicenter study.(75) All patients had received at least one course of chemotherapy before receiving resin-based ($n=17$) or glass-based ($n=22$) yttrium-90 (see Table 9). Most toxicities observed (93%) were grade I or II, and objective response rate (complete and partial responses) was 36% (see Table 8). Six months after treatment, 30 patients showed stable disease or response, and the overall median survival was 30 months (95% CI, 12 to 43 months). The study was limited by its retrospective nature and by

differences in patient selection and therapy techniques among the four centers represented. Also, the study might have been statistically underpowered.

Table 9. Summary of Case Series Characteristics

Study	Institution	Participants	Treatment Delivery	Follow-Up
Miller et al (2018) ⁷⁵	4 centers	39 patients with metastatic (n=37) or primary (n=2) liver sarcoma	Previous chemotherapy prior to resin-based (n=17) or glass-based (n=22) yttrium-90 RE	6 mo

RE: radioembolization.

Table 10. Summary of Case Series Results

Study	Median OS (95% CI), mo	Toxicity	ORR, %	Tumor Response at 6-Month Follow-Up
Miller et al (2018) ⁷⁵	30 (12 to 43)	93% of toxicities grade 1 or 2	36	30 patients had stable disease or response to treatment

CI: confidence interval; ORR: objective response rate; OS: overall survival.

Section Summary: Unresectable Intrahepatic Metastases From Other Cancers

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

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

SUMMARY OF EVIDENCE

For individuals who have unresectable hepatocellular carcinoma who receive RE or RE with a liver transplant, the evidence includes primarily retrospective and prospective observational studies, with limited evidence from randomized controlled trials (RCTs). The relevant outcomes are overall survival, functional outcomes, quality of life, and treatment-related morbidity. Observational studies have suggested that RE has high response rates compared with historical controls. Two small pilot RCTs have compared RE with alternative therapies for hepatocellular carcinoma, including transarterial chemoembolization and transarterial chemoembolization with drug-eluting beads. Both trials reported similar outcomes for RE compared with alternatives. Evidence from observational studies has demonstrated that RE can permit successful liver transplantation in certain patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have unresectable intrahepatic cholangiocarcinoma who receive RE, the evidence includes case series. The 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. RE may play a role for patients with unresectable tumors that are chemorefractory or who are unable to tolerate systemic chemotherapy. However, the evidence is not yet sufficiently robust

to draw definitive conclusions about treatment efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 a meaningful 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. RCTs of patients with prior treatment failure have methodologic problems, do not show definitive superiority of RE compared with alternatives, but tend to show greater tumor response with RE. The evidence is sufficient to determine that the technology results in a meaningful 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 observational 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 the effects of the technology on health outcomes.

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 three physician specialty societies (with five individual responses) one academic medical center (with four individual responses), for a total of nine 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.

2010-2011 Input

In response to requests, the Blue Cross Blue Shield Association received input from two physician specialty societies (with 5 individual responses) and six 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.2.2020) guidelines on the treatment of hepatobiliary carcinoma 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.(76)

Metastatic Neuroendocrine Tumors

The NCCN guidelines (v.1.2020) on the treatment of neuroendocrine tumors give a category 2B recommendation for hepatic regional therapy (arterial embolization, chemoembolization, RE) in the setting of advanced locoregional disease.(77)

Metastatic Colon Cancer

The NCCN guidelines (v.3.2019) 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.”(78)

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 11.

Table 11. Summary of Key Trials

NCT No.	Name	Planned Enrollment	Completion Date
Hepatocellular Carcinoma			
<i>Ongoing</i>			
NCT01135056	Phase III Multi-Centre Open-Label Randomized Controlled Trial of Selective Internal Radiation Therapy (SIRT) Versus Sorafenib in Locally Advanced Hepatocellular Carcinoma (SIRveNIB)	360	Jul 2018 (ongoing)
NCT01556490 ^a	A Phase III Clinical Trial of Intra-arterial TheraSphere® in the Treatment of Patients With Unresectable Hepatocellular Carcinoma (HCC)	526	Sept 2019
<i>Unpublished</i>			
NCT01482442	A Prospective Randomized Open-labeled Trial Comparing RADIOEMBOLIZATION With Yttrium 90 Microspheres and Sorafenib in Patients With Advanced Hepatocellular Carcinoma	496	Apr 2016 (completed)
NCT00846131	A Single-Center Proof of Concept Pilot Study to Evaluate the Safety, Efficacy, and Tolerability of Sorafenib Combined With TheraSphere in Subjects With Hepatocellular Carcinoma Awaiting Liver Transplantation	24	Sep 2016 (completed)
NCT01381211	Transarterial RAdioembolization Versus ChemoEmbolization for the Treatment of HCC: A Multicenter Randomized Controlled Trial (TRACE Trial)	140	Dec 2016 (unknown)
NCT01126645 ^a	Evaluation of Sorafenib in Combination With Local Micro-therapy Guided by Gd-EOB-DTPA Enhanced MRI in Patients With Inoperable Hepatocellular Carcinoma	529	Dec 2018 (Completed)
Metastatic colorectal cancer			
NCT01483027 ^a	A Phase III Clinical Trial Evaluating TheraSphere® in Patients With Metastatic Colorectal Carcinoma of the Liver Who Have Failed First Line Chemotherapy	420	August 2020
Cholangiocarcinoma			
<i>Ongoing</i>			
NCT02807181 ^a	SIRT Followed by CIS-GEM Chemotherapy Versus CIS-GEM Chemotherapy Alone as 1st Line Treatment of Patients With Unresectable Intrahepatic Cholangiocarcinoma (SIRCCA)	89	June 2021
<i>Unpublished</i>			
NCT01912053	An Open-label, Multicenter, Phase II Trial, to Evaluate the Efficacy of Intra-hepatic Administration of Yttrium 90-labeled Microspheres (Therasphere®, Nordion) in Association With Intravenous Chemotherapy With Gemcitabine and Cisplatin for the Treatment of Intra-hepatic Cholangiocarcinoma, First Line	41	Nov 2017 (completed)
Metastatic uveal melanoma			
NCT02936388	Transarterial Radioembolisation in Comparison to Transarterial Chemoembolisation in Uveal Melanoma Liver Metastasis (SirTac)	108	Jan 2021

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 a retired Local Coverage Determination (LCD) for Selective Internal Radiation Therapy (SIRT) for Primary and Secondary Hepatic Malignancy (90Y-Microsphere Hepatic Brachytherapy) (L30137). Revision Effective Date 10/01/14; retired 9/30/15:

Coverage Indications, Limitations, and/or Medical Necessity

Selective Internal Radiation Therapy (SIRT) is one of several treatment options for treatment of metastatic liver disease and hepatocellular carcinoma (HCC).

In patients with surgically unresectable liver disease with or without extrahepatic disease, systemic chemotherapy has become the standard for first and second-line treatment. Combination therapy with angiogenesis inhibitors and surgical resection has now become an integral part of first and second-line therapies. Patients with liver-dominant disease in which standard first- and second-line therapies have failed may be considered for treatment with 90Y. The liver is the most frequent site of metastases, primarily as a result of the spread of cancer cells through the portal circulation. In fact, approximately 60% of patients with colorectal carcinoma eventually have liver disease as the predominant site. Similarly to HCC, surgical resection of metastatic hepatic disease is the treatment of choice. However, surgical resection is feasible in fewer than 20% of patients. In HCC available treatment options depend on the size, number, and location of tumors; presence or absence of cirrhosis; operative risk based on extent of cirrhosis and comorbid diseases; overall performance status; patency of portal vein; and presence of metastatic disease. Before instituting definitive therapy, it is best to treat the complications of cirrhosis with diuretics, paracentesis for ascites, lactulose for encephalopathy, ursodiol for pruritus, sclerosis or banding for variceal bleeding, and antibiotics for spontaneous bacterial peritonitis. Since there is a paucity of liver allografts for transplantation, transplant is a limited option. Thus the main goal currently is disease control, Methods of disease control include:

- Surgical resection (partial hepatectomy which in the United States, is possible in only 5% of patients)
- Liver transplantation (Many patients are not candidates for partial hepatectomy due to extent of underlying liver disease. Some of these patients are good candidates for liver transplantation since it has the potential for eliminating the cancer as well as curing the underlying liver disease.) Partial hepatectomy and transplantation are the only chances of cure.
- Systemic chemotherapy (however HCC is a relatively chemotherapy resistant tumor) - Chemoimmunotherapy (a combination of chemotherapy and immunomodulatory agents)
- Chemoembolization - Hepatic Arterial Chemotherapy (HAC), Embolizing agents such as cellulose, microspheres, lipoidal, and gelatin foam particles are used to deliver intra-arterial chemotherapy (Other terms: Transarterial embolization and transarterial chemoembolization (TACE))
- Local tumor ablation (Intratumoral injections of ethanol or acetic acid, heat (via radiofrequency, microwave, or laser ablation), or cold (cryoablation with liquid nitrogen), laser photocoagulation)

- Radiation therapy (radiation therapy is limited by dose-related radiation hepatitis, which precludes the administration of external beam radiation in doses effective for tumor eradication. It is sometimes used for palliation)
- A new technology that uses a combination of robotics and image guidance to deliver concentrated and highly focused beams of radiation to the tumor while minimizing radiation exposure to the surrounding healthy liver tissue. (i.e. CyberKnife, SBRT)

Bridging therapy with local therapies, such as chemoembolization or radiofrequency ablation (RFA) is sometimes considered for patients on the transplant waiting list.

The main objectives for management of unresectable liver tumor are to control pain, to prolong survival and, if possible, to try to convert unresectable tumor to resectable tumor. Neoadjuvant therapy has been used clinically to downstage unresectable liver tumor, this can be achieved in 20 %- 66% of these patients depending on the study.

Indications:

1. Per the FDA approved package insert, SIR-Spheres™ is indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine). Patients are indicated for treatment with SIR-Spheres® when the metastatic colorectal cancer in the liver is considered non-resectable. In any of the following circumstances, patients would generally be considered nonresectable:
 - a. multiple liver metastases together with involvement of both lobes;
 - b. tumor invasion of the hepatic confluence where the three hepatic veins enter the IVC such that none of the hepatic veins could be preserved if the metastases were resected;
 - c. tumor invasion of the porta hepatis such that neither origin of the right or left portal veins could be preserved if resection were undertaken; and widespread metastases such that resection would require removal of more liver than is necessary to maintain life
2. It is also covered for patients with unresectable hepatocellular cancer (HCC) who can have appropriately positioned hepatic arterial catheters. (See below under TheraSphere for post treatment and complication information.)

Contraindications to SIR-spheres Yttrium microsphere therapy for metastatic colorectal cancer to the liver:

- a. previous external beam radiation to the liver
- b. ascites or liver failure
- c. markedly abnormal liver function tests; specifically, an increased total bilirubin indicates reduced hepatic reserve.
- d. greater than 20% shunting to the lungs on hepatic arterial administration of Tc-MAA scan
- e. assessment visceral arteriogram that demonstrates abnormal vascular anatomy that would result in increased chance of gastrointestinal complication
- f. widely disseminated extrahepatic disease
- g. has received capecitabine within the previous two months or who will be treated with capecitabine at any time following treatment with SIR-spheres microspheres.
- h. total portal thrombosis or circulatory reversal
- i. technical obstacle with securely placing catheter

Relative Contraindications

- a. Evidence of bone metastases which show no activity during systemic therapy
- b. Shunt Volume between liver and lung > 10% <20%; a reduced dose therapy is still possible.
- c. Partial thrombosis of the portal vein

TheraSphere

TheraSphere (glass microsphere; MDS Nordion, Kanata, ON, Canada) was approved in 1999 by the U. S. Food and Drug Administration (FDA) under a humanitarian device exemption for the treatment of unresectable hepatocellular carcinoma (HCC) in patients who can have appropriately positioned hepatic arterial catheters. It is subject to the FDA requirements for use under a humanitarian device exemption protocol.

Indications:

1. TheraSphere is indicated 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. The device is also indicated for HCC patients with partial or branch portal vein thrombosis (PVT)/occlusion when clinical evaluation warrants the treatment.
2. TheraSphere is indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine). Patients are indicated for treatment when the metastatic colorectal cancer in the liver is considered nonresectable. In any of the following circumstances, patients would generally be considered non-resectable:
 - a. multiple liver metastases together with involvement of both lobes;
 - b. tumor invasion of the hepatic confluence where the three hepatic veins enter the IVC such that none of the hepatic veins could be preserved if the metastases were resected;
 - c. tumor invasion of the porta hepatis such that neither origin of the right or left portal veins could be preserved if resection were undertaken; and
 - d. widespread metastases such that resection would require removal of more liver than is necessary to maintain life

Contraindications:

TheraSphere is contraindicated in patients with:

- a. Uncorrectable Yttrium 90 microsphere deposition to the gastrointestinal tract
- b. Shunting to the lungs, in a single treatment, exceeding 16.5 mCi (or 30 Gy) of Yttrium 90 microspheres to the lungs
- c. Contraindication to hepatic artery catheterization
- d. Severe liver dysfunction or pulmonary insufficiency
- e. Complete occlusion of the main portal vein

Non-covered Conditions

There is insufficient evidence in the peer-reviewed literature to support the safety and efficacy of 90Y microsphere radioembolization for liver metastases from any site other than colorectal or neuroendocrine including but not limited to breast cancer, cholangiocarcinoma, and pancreatic cancer.

(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 Unresectable Hepatic Tumors
 - Transcatheter Arterial Chemoembolization (TACE) of Hepatic Tumors
-

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 11/25/20, 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

Next Review Date: 1st Qtr, 2022

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.