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Populations	Interventions	Comparators	Outcomes
Individuals: • With unresectable hepatocellular cancer	Interventions of interest are: • Radioembolization • Radioembolization and liver transplant	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With unresectable intrahepatic cholangiocarcinoma	Interventions of interest are: • Radioembolization	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Functional outcomes • Quality of life • Treatment-related morbidity

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Populations	Interventions	Comparators	Outcomes
Individuals: • With unresectable neuroendocrine tumors	Interventions of interest are: • Radioembolization	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With unresectable intrahepatic metastases from colorectal cancer and prior treatment failure	Interventions of interest are: • Radioembolization	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With unresectable intrahepatic metastases from other cancers (eg, breast, melanoma, pancreatic)	Interventions of interest are: • Radioembolization	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Functional outcomes • Quality of life • Treatment-related morbidity

DESCRIPTION

Radioembolization (RE), also referred to as selective internal radiotherapy, is the intra-arterial delivery of small beads (microspheres) impregnated with yttrium-90 via the hepatic artery. The microspheres, which become permanently embedded, are delivered to tumor preferentially to normal liver, because the hepatic circulation is uniquely organized, whereby tumors greater than 0.5 cm rely on the hepatic artery for blood supply while 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.

Objective

The objective of this evidence review is to determine whether radioembolization improves the net health outcome in individuals with primary or metastatic liver tumors.

Background

RADIOEMBOLIZATION

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 normal liver to radiation compared with the higher doses of radiation needed to kill the tumor.

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

Radioembolization (referred to as selective internal radiation therapy in older literature) is the intra-arterial delivery of small beads (microspheres) impregnated with yttrium-90 via the hepatic artery. The microspheres, which become permanently embedded, are delivered to tumor preferentially to normal liver, 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-labelled albumin particles are delivered via the hepatic artery to simulate microspheres. Single-photon emission computed tomography imaging is used to detect possible shunting of the albumin particles into the gastrointestinal or pulmonary vasculature.

Currently, 2 commercial forms of yttrium-90 microspheres are available: a glass sphere (TheraSphere) and a resin sphere (SIR-Spheres). Noncommercial forms are mostly used outside the United States. While the commercial products use the same radioisotope (yttrium-90) and have the same target dose (100 Gray), they differ in microsphere size profile, base material (ie, resin vs glass), and size of commercially available doses. The physical characteristics of the active and inactive ingredients affect the flow of microspheres during injection, their retention at the tumor site, spread outside the therapeutic target region, and dosimetry calculations. The Food and Drug Administration (FDA) granted premarket approval of SIR-Spheres for use in combination with 5-floxuridine chemotherapy by hepatic arterial infusion to treat unresectable hepatic metastases from colorectal cancer (CRC). In contrast, TheraSphere was approved by humanitarian device exemption (HDE) for use as monotherapy to treat unresectable hepatocellular carcinoma (HCC). In 2007, this HDE was expanded to include patients with HCC who have partial or branch portal vein thrombosis. For these reasons, results obtained with one product do not necessarily apply to another commercial (or noncommercial) products (see Regulatory Status section).

CARCINOMAS TREATED WITH RADIOEMBOLIZATION

Unresectable Primary HCC
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. Results of two randomized controlled trials 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]

Unresectable Intrahepatic Cholangiocarcinoma
Cholangiocarcinomas are tumors that arise from the epithelium of the bile duct and are separated into intrahepatic and extrahepatic types. Intrahepatic cholangiocarcinomas appear in the hepatic parenchyma and are also known as peripheral

cholangiocarcinomas. Resection is the only treatment with the potential for cure, and 5-year survival rates have been in the range of 20% to 43%.[3] Patients with an unresectable disease may select among fluoropyrimidine-based or gemcitabine-based chemotherapy, fluoropyrimidine chemoradiation, or best supportive care.

Unresectable Metastatic Neuroendocrine Tumors
Neuroendocrine 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) or pancreatic islet cells. 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).

Although they are considered to be indolent tumors, at the time of diagnosis, up to 75% of patients have liver metastases, and with metastases to the liver, 5-year survival rates are less than 20%. Surgical resection of the metastases is considered the only curative option; however, less than 10% of patients are eligible for resection, as most patients have diffuse multiple lesions.

Conventional therapy is largely 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 analogs like octreotide), systemic chemotherapy, ablation (radiofrequency or cryotherapy), TAE or TACE, or radiation. 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 a few things: (1) that modest response rates are of limited duration, (2) that it is better for pancreatic neuroendocrine tumors than carcinoids, and (3) that it is frequently associated with significant toxicity.[4] Chemoembolization has shown response rates of nearly 80%, but the effect is of short duration, and a survival benefit has not been demonstrated.[4]

Unresectable Metastatic Colorectal Cancer
Fifty to sixty percent of patients with colorectal cancer (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 patients with metastatic disease limited to the liver, preoperative chemotherapy is sometimes used to downsize the metastases to convert the metastatic lesions to a resectable status (conversion chemotherapy).

In patients with unresectable disease, the primary treatment goal is palliative, with a survival benefit shown in both second- and third-line systemic chemotherapy.[5] 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 2 years.[5] Palliative chemotherapy using combined systemic and hepatic arterial infusion may increase disease-free intervals for patients with unresectable hepatic metastases from CRC.

Radiofrequency ablation (RFA) has been found inferior to resection in local recurrence rates and five-year overall survival rates; further it is generally reserved for patients with potentially resectable 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. RFA is recommended when the goal is complete resection with curative intent.[5] The role of local (liver-directed) therapy (including radioembolization, chemoembolization, and conformal radiotherapy) in debulking unresectable metastatic disease remains controversial.[6]

Miscellaneous Metastatic Tumors
Case reports have been published on the use of radioembolization 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.[7]

Regulatory Status
Currently 2 forms of yttrium-90 microspheres have been 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 radiotherapy or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (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 FDA through the premarket approval process for the treatment of inoperable colorectal cancer metastatic to the liver.
FDA product code: NAW.

POLICY

A.   Radioembolization may be considered **medically necessary:**
1.   to treat primary hepatocellular carcinoma that is unresectable and limited to the liver (see Policy Guidelines section).
2.   in primary hepatocellular carcinoma as a bridge to liver transplantation.
3.   to treat hepatic metastases from neuroendocrine tumors (carcinoid and noncarcinoid) with diffuse and symptomatic disease when systemic therapy has failed to control symptoms.
4.   to treat unresectable hepatic metastases from colorectal carcinoma, melanoma (ocular or cutaneous), or breast cancer that are both progressive and diffuse, in patients with liver-dominant disease who are refractory to chemotherapy or are not candidates for chemotherapy or other systemic therapies.
5.   to treat primary intrahepatic cholangiocarcinoma in patients with unresectable tumors

B.   Radioembolization is considered **experimental / investigational** for all other hepatic metastases except as noted above.

C.   Radioembolization is considered **experimental / investigational** for all other indications not described above.

Policy Guidelines
1.   In general, radioembolization is used for unresectable hepatocellular carcinoma that is greater than 3 cm.
2.   There is little information on the safety or efficacy of repeated radioembolization treatments or about the number of treatments that should be administered.
3.   Radioembolization should be reserved for patients with adequate functional status (Eastern Cooperative Oncology Group Performance Status 0-2), adequate liver function and reserve, Child-Pugh score A or B, and liver-dominant metastases.
4.   Symptomatic disease from metastatic neuroendocrine tumors refers to symptoms related to excess hormone production.

RATIONALE
This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through June 2, 2017. Randomized trials and high-quality comparative studies were sought. Representative case series studies are included if higher quality evidence is not available.

Hepatocellular Carcinoma

Unresectable Hepatocellular Carcinoma

Systematic Reviews
Tao et al (2017) reported on a network meta-analysis comparing nine minimally invasive surgeries for treatment of unresectable hepatocellular carcinoma (HCC).[8] The interventions included were transarterial chemoembolization (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 radioembolization (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 a meta-analysis of studies that indirectly 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 2 years, survival was 61% for DEB-TACE and 34% or RE (OR=0.65; 95% CI, 0.29 to 1.44; p=0.29) and at 3 years survival was 56% and 21% (OR=0.71; 95% CI, 0.21 to 2.55; p=0.62), respectively.

Two systematic reviews published in 2016 compared RE with TACE for the treatment of unresectable HCC. Lobo et al (2016) selected 5 retrospective observational studies (total N=533 patients).[10] Survival at 1 year did not differ statistically between RE (42%) and TACE (46%; relative risk [RR], 0.93; 95% CI, 0.81 to 1.08; p=0.33). At 2 years, the survival rate was higher for RE (27% vs 18%; RR=1.36; 95% CI, 1.05 to 1.76; p=0.02), but there was no statistically significant difference in survival rates at 3, 4, or 5 years. Postprocedural complications were also similar in the 2 groups. Facciorusso et al (2016) included 10 studies (total N=1557 patients), two of which were randomized controlled trials (RCTs).[11] The OR for survival was not statistically significant at 1 year (OR=1.0; 95% CI, 0.8 to 1.3; p=0.93) but favored RE in years 2 (OR=1.4; 95% CI, 1.1 to 1.90; p=0.01) and 3 (OR=1.5; 1.0 to 2.1; p=0.04).

Vente et al (2009) conducted a meta-analysis evaluating tumor response and survival in patients who received 90Y glass or resin microsphere RE for the treatment of primary HCC or metastases from colorectal cancer (CRC).[12] (Refer to the Unresectable Metastatic CRC section for the data from the meta-analysis as pertains to that disease.) Selected studies were from 1986 onward and presented tumor response (measured by computed tomography) and data on median survival times. To allow comparability of results regarding 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 7 studies, in which survival time was defined as survival from microsphere treatment or diagnosis or recurrence of HCC. Median survival from microsphere treatment varied between 7.1 months and 21.0 months, and median survival from diagnosis or recurrence ranged from 9.4 to 24.0 months.

Randomized Controlled Trials
In 2015, Kolligs et al reported results for a small pilot RCT (the SIR-TACE study) comparing RE with TACE for the treatment of unresectable HCC.[13] The trial included 28 subjects with unresectable HCC, preserved liver function, and an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 2 or less, with no vascular invasion or extrahepatic spread, who had 5 or fewer liver lesions or a single lesion of 10 cm or less. Patients were randomized to RE (n=13) or TACE (n=15). Over posttreatment follow-up, partial response rates were 13.3% for TACE and 30.8% for RE, with rates of disease control (complete remission, stable disease, and 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.

Also in 2015, Pitton et al reported results from a small RCT comparing RE with DEB-TACE for the treatment of unresectable HCC.[14] The study included 24 patients, with 12 randomized to each group. No deaths occurred within 30 days of the procedure for either group. There were no statistically significant differences between the groups in terms of in PFS (180 days for RE vs 216 days for DEB-TACE; p=0.619) or overall survival (OS; 592 days for RE vs 788 days for DEB-TACE; p=0.927).

These RCTs did not show the superiority of RE to an active comparator. Insights into the efficacy of RE may be inferred from the observed response rates and similarity to an effective comparator.

Nonrandomized Comparative Studies
Padia et al (2017) reported on a single-center, retrospective study (2010-2015) comparing segmental RE with segmental chemoembolization in 101 patients with localized, unresectable HCC not amenable to ablation.[15] 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.

In 2016, Soydal et al retrospectively assessed outcomes for patients receiving RE and TACE for HCC.[16] Each group included 40 patients. RE patients had a mean survival of 39 months vs 31 months for TACE patients (p=0.014). There were no significant differences in complication rates or disease recurrence rates.

In 2016, Oladeru reported on a retrospective analysis of SEER registry data comparing survival outcomes for patients with HCC receiving RE with EBRT.[17] 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.

In 2015, El Fouly et al reported on results of a nonrandomized study comparing RE with TACE for 86 patients with intermediate stage, nonresectable HCC.[18] 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.

In 2015, Gramenzi et al conducted a retrospective cohort study comparing RE with the kinase inhibitor sorafenib for intermediate- or advanced-stage HCC.[19] Patients with HCC refractory to other therapies and no metastases or systemic chemotherapy were included, 74 of whom were treated with sorafenib and 63 with RE. Median OS between groups was similar (14.4 months for sorafenib-treated patients vs 13.2 months for RE-treated patients). After propensity-score matching of 32 subjects in each group, there were no significant differences in median OS or 1-, 2-, and 3-year survival rates between groups.

Carr et al (2010) reported on a consecutive series of patients with HCC seen at a single medical center and not candidates for surgical resection.[20] 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 felt there was 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: 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.

RE as a Bridge to Liver Transplantation for Unresectable HCC
Salem et al (2016) reported on results of a phase 2 RCT comparing conventional TACE and TheraSphere radioembolization (Y90) for treatment of unresectable, unablatable HCC.[21] Twenty-four patients were assigned to Y90 and 21 patients to conventional TACE; the ultimate goal 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 conventional 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 conventional TACE group (hazard ratio, 0.12; 95% CI, 0.03 to 0.56; p=0.007). Median survival was 19 months in Y90 and 18 months in conventional 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.

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

In a 2013 retrospective review, Tohme et al reported on 20 consecutive HCC patients awaiting liver transplant who received RE as bridge therapy.[23] When RE began, Milan criteria were met by 14 patients and sustained until transplantation. Of the 6 patients who did not meet Milan criteria initially, RE was able to downstage 2 patients to meet Milan criteria. After onset of RE, median time to liver transplant was 3.5 months. Complete or partial radiologic response to RE, assessed using modified Response Evaluation Criteria In Solid Tumors (RECIST), occurred in 9 patients. Additionally, on pathologic examination, 5 patients had no evidence of viable tumor whose disease met the Milan criteria.

In 2014, Ramanathan et al reported on various therapies, including RE, for 715 HCC patients of whom 231 were intended for transplant.[24] In the intention-to-treat transplantation arm, 60.2% received a transplant. Survival rates posttransplant were 97.1% and 72.5% at 1 and 5 years, respectively. Tumor recurrence rates were 2.4%, 6.2%, and 11.6% at 1, 3, and 5 years, respectively.

Lewandowski et al (2009) compared the efficacy of RE with chemoembolization in downstaging 86 patients with HCC from stage T3 to T2 (potentially making patients liver transplant candidates).[25] Patients were treated with RE using Y90 microspheres (n=43) or TACE (n=43). Median tumor sizes were similar between treatment groups (5.7 cm for TACE vs 5.6 cm for RE). Partial response rates were 61% for RE and 37% for TACE, with downstaging from T3 to T2 in 58% of patients treated with RE vs 31% with TACE (p<0.05).

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. Studies did not demonstrate the comparative efficacy of RE to alternatives for this indication.

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.

Systematic Reviews
In 2015, Al-Adra et al reported outcomes in a systematic review of studies on RE for ICC.[26] Reviewers 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 we detail next (Mouli et al [2013],[27] Hoffmann et al [2012],[28] and Saxena et al [2010][29]; of note, the Hoffmann study was reported by authors as retrospective). The overall weighted median survival was 15.5 months (range, 7-22.2 months), based on 11 studies. A weighted mean partial response was seen in 28% of patients and stable disease was seen in 54% at 3 months posttreatment.

Also in 2015, Boehm et al conducted a systematic review comparing hepatic artery–based therapies, including hepatic arterial infusion (HAI), TACE, DEB-TACE, and Y90 RE, for unresectable ICC.[30] Of 20 studies that met inclusion criteria, 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. Complete remission or partial response occurred in 56.9% of patients treated with HAI compared with 27.4% of those treated with RE and 17.3% of those treated with TACE.

Case Series
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.[31] 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 rates at 6, 12, and 30 months was 70%, 33%, and 20%, respectively.

Mosconi et al (2016) retrospectively analyzed 23 consecutive patients with unresectable or recurrent ICC at a single institution.[32] Overall median survival was 18 months (95% CI, 14 to 21 months). Survival was significantly longer in treatment-naive patients (52 months) than in those who received other treatments before RE (16 months; p=0.009).

In 2013 Mouli et al reported on 46 patients treated with RE for ICC using a retrospective review of prospectively collected data from a single institution.[27] Survival varied by level of disease (multifocal, infiltrative, and bilobar), and ranged from 5.7 to 15.6 months. Five patients achieved resectable status and underwent curative resection.

A 2012 retrospective study by Hoffmann et al of RE with Y90 resin microspheres included 24 patients with nonresectable chemorefractory ICC and no extrahepatic disease.[28] Mean age of the sample was 65.2 years, and the sample was 45.5% female. 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 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 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 2011 study by Haug et al evaluated prognostic factors of RE treatment in 26 consecutive patients with unresectable ICC who underwent RE with Y90 glass microspheres.[33] All patients had a Karnofsky Performance Status of 60% or more. Mean age was 64.3 years, 31% had extrahepatic disease, and 42% were female. Prior Treatment included chemotherapy in 65%, surgery in 28%, local 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 3 toxicity in transaminases or bilirubin.

In 2010, Saxena et al prospectively evaluated 25 patients with unresectable ICC who received RE with Y90 resin microspheres.[29] Extrahepatic disease was present in 48%, mean age was 57 years, and 48% of patients were female. Prior treatment 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, 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 2008 study by Ibrahim et al reported on results for RE with Y90 glass microspheres among 24 patients with unresectable ICC.[34] The group was 33% female and had a median age of 68 years. Extrahepatic disease was present in 33%. ECOG Performance Status scores were 0 in 42%, 1 in 50%, and 2 in 8%. Prior chemotherapy had been used in 29% of patients. Using WHO tumor response criteria, complete remission was observed in 0%; partial response, 27%; stable disease, 68%; and progressive disease, 5%. Follow-up was collected over a median of 17.7 months and median OS was 14.9 months. Subgroups that had favorable survival results included those with ECOG Performance Status score of 0, no previous chemotherapy, and peripheral tumor. Grade 3 albumin toxicity was found in 17%, grade 3 bilirubin toxicity in 4%, and 1 (4%) patient developed a duodenal ulcer.

Rayar et al (2015) reported on successful downstaging 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.[35] After RE, all patients underwent successful resection.

Section Summary: Intrahepatic Cholangiocarcinoma

The evidence for RE in intrahepatic cholangiocarcinoma primarily consists of retrospective case reviews. Across studies, the median survival in patients treated with RE ranged from 7 to 24 months. There is little, direct comparative data available to demonstrate effect on survival. Side effects are common but generally mild.

Metastatic Liver Tumors

Unresectable Neuroendocrine Tumors

Systematic Reviews

In 2014, Devcic et al published the results of a meta-analysis of studies evaluating RE for liver-dominant metastatic neuroendocrine tumors.[36] The analysis included 12 studies that provided RECIST data for hepatic metastatic neuroendocrine tumors treated with RE. For Y90 RE with resin microspheres only, objective radiographic response rates (complete remission or partial response by RECIST) ranged from 12% to 80%, with a random-effects weighted average of 50% (95% CI, 38% to 62%). Disease control rates (complete remission, partial response, stable disease) ranged from 62% to 100%, with a random-effects weighted average of 86% (95% CI, 78% to 92%).

Nonrandomized Comparative Studies

In 2014, Engelman et al 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.[37] 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 postprocedure (p=0.134), time to progression (p=0.968), or OS (p=0.30).

Case Series

In 2008, Rhee et al reported the results of a multicenter, open-label, phase 2 study that assessed the safety and efficacy of RE, using glass or resin microspheres, in 42 patients with metastatic neuroendocrine liver disease who had failed prior treatment(s), including medical (eg, octreotide), surgical resection, bland or chemoembolization, and radiofrequency ablation or cryoablation.[38] RECIST criteria were used to assess tumor response, which showed 92% of glass patients and 94% of resin patients had partial response or had stable disease at 6 months after treatment. Median survival was 22 months for glass and 28 months for resin.

In 2010, Cao et al reported on outcomes for 58 patients with unresectable neuroendocrine liver metastases from 2 hospitals who were treated with RE from 2003 to 2008.[39] Response was assessed with radiographic evidence before and after RE and measured using RECIST guidelines. Systemic chemotherapy was routinely given at a single institution. Mean patient age at the time of RE was 61 years (range, 29-84 years), and 67% of patients were men. Primary tumor site varied and included small bowel, pancreas, colon, thyroid, lung, and unknown. Thirty-one

patients underwent surgical resection of their primary tumor, which was classified as low grade in 15, intermediate grade in 7, and high grade in 7. Forty-three percent of patients had extrahepatic metastatic disease at study entry. Median follow-up was 21 months (range, 1-61 months). Fifty-one patients were evaluable, and 6 achieved complete remission, 14 had a partial response, 14 had stable disease, and 17 experienced disease progression. OS rates at 1, 2, and 3 years were 86%, 58%, and 47%, respectively. Median survival was 36 months (range, 1-61 months). Prognostic factors for survival included extent of tumor involvement of the liver, radiographic response to treatment, presence of extrahepatic disease at the time of RE, histologic grade of tumor, and whether patients responded to RE.

In 2008, King et al reported on outcomes for patients treated in a single-institution prospective study.[4] Thirty-four patients with unresectable neuroendocrine liver metastases were given radioactive microspheres (SIR-Spheres) and concomitant 7-day systemic infusion of fluorouracil (5-FU), between 2003 and 2005. Mean patient age was 61 years (range, 32-79 years), and 65% were men. Mean follow-up was 35.2 months. Primary tumor sites varied and included bronchus (n=1), thyroid (n=2), gastrointestinal (n=15), pancreas (n=8), and unknown (n=8). Subjective changes from baseline hormone symptoms were reported every 3 months. Twenty-four (71%) patients had, at baseline assessment, symptoms of carcinoid syndrome, including diarrhea, flushing, or rash. At 3 months, 18 (55%) of 33 patients reported improvement of symptoms, as did 16 (50%) of 32 at 6 months. Radiologic tumor response was observed in 50% of patients and included 6 (18%) complete remission and 11 (32%) partial response. Mean OS was 29.4 months.

In 2008, Kennedy et al retrospectively reviewed 148 patients from 10 institutions with unresectable hepatic metastases from neuroendocrine tumors.[40] All patients had completed treatment of the primary tumor and metastatic disease and were not excluded based on prior therapy. 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.[41-45]

Section Summary: Unresectable Neuroendocrine Tumors
The evidence for RE in 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 small nonrandomized comparative study, RE, HAE, and HACE appeared similar with respect to radiographic response, time to progression, and OS but inference is limited by study designs and small sample sizes.

Unresectable Intrahepatic Metastatic CRC
The evidence related to the use of RE for metastatic CRC consists of several small- to moderate-sized RCTs, prospective trials, and retrospective studies using a variety of comparators, along with systematic reviews of these studies.

Systematic Reviews

In a 2014 systematic review, Saxena et al evaluated 20 experimental and observational studies on RE for chemoresistant, unresectable CRC liver metastasis (total N=979 patients).[46] The review included 2 RCTs (Gray et al [2001],[47] Hendlisz et al [2010],[48] described next), 5 non-RCTs or well-designed cohort studies, and 13 observational studies. After RE, the average reported complete remissions and partial responses from 16 studies was 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, median survival time was 12 months (range, 8.3-3.6 months).

In a 2013 systematic review, Rosenbaum et al evaluated 13 relevant studies on RE as monotherapy and 13 studies on RE combined with chemotherapy for chemoresistant, unresectable CRC liver metastasis.[49] Complete remission, partial response, and stable disease rates ranged from 29% to 90% with RE only and from 59% to 100% for RE plus chemotherapy. At 12 months, survival rates ranged from 37% to 59% with RE only and from 43% to 74% for RE plus chemotherapy.

A 2010 technology assessment from the California Technology Assessment Forum assessed 25 studies on the use for RE and inoperable metastatic CRC to the liver, including 2 RCTs (Gray et al [2001],[47] Van Hazel et al [2004],[50] described next), a small retrospective study comparing selective internal radiotherapy (SIRT) with chemoembolization (N=36), and 21 case series.[5] The assessment concluded that the 3 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 2 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 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, with the exception that the technology had final approval from the appropriate government regulatory bodies.

A 2009 Cochrane review assessed the efficacy and toxicity of RE, alone or with systemic or regional hepatic artery chemotherapy, in the treatment of metastatic CRC liver metastases [51] Two articles met reviewers' inclusion criteria: Gray et al[47] and van Hazel et al.[50] Reviewers concluded that there was a lack of evidence that SIRT improves survival or quality of life (QOL) in patients with metastatic CRC, whether given alone or with chemotherapy, and that there was a need for well-designed, adequately powered phase 3 trials assessing the effect of SIRT when used with modern combination chemotherapy regimens.

The 2009 meta-analysis by Vente et al (previously described) included 19 studies (total N=792 patients) assessing metastatic CRC patients treated with Y90 RE.[12] Included in the meta-analysis were 2 RCTs (Gray et al,[47] van Hazel et al[50]). 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 [FOLFIRI]) 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
The 2001 RCT by Gray et al 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.[47] 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. They reported for HAI plus RE vs HAI 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 3-4) 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 study 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.[20,52] 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 2004 phase 2 RCT 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.[50] Disease time to progression was greater in those receiving combination therapy (18.6 months vs 3.6 months, respectively; p<0.001).

A 2010 phase 3 RCT of 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.[48] The time to liver progression (the primary outcome) was significantly improved 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).

A 2016 phase 3 RCT by van Hazel et al compared modified FOLFOX chemotherapy and FOLFOX chemotherapy plus SIRT in 530 patients with previously untreated liver-dominant metastatic disease.[53] 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. OS outcomes were not available at the time of publication. The investigators plan to analyze OS in combination with 2 other studies of chemotherapy with and without RE that have also not been completed. This combined preplanned analysis should provide important data on the efficacy of RE (in combination with current chemotherapy regimens) in first-line treatment of unresectable metastatic CRC.

Nonrandomized Comparative Studies
In 2012, Seidensticker et al published a retrospective, matched-pair comparison of RE plus best supportive care with best supportive care alone for patients with chemorefractory, liver-dominant colorectal metastases (n=29 in each group).[54] 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 CRC
The evidence for RE in unresectable intrahepatic metastatic CRC includes systematic reviews, RCTs and observational studies. RCTs reported mixed results for RE compared with alternatives with respect to time to progression or PFS; data are generally not available for OS.

Other Unresectable Intrahepatic Metastases

Metastatic Intrahepatic Breast Cancer
Most studies on the use of RE for metastatic breast cancer have evaluated 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.[7]

Case Series
In 2013, Smits et al reviewed 6 studies on RE for metastatic breast cancer (total N=198 participants) (see Table 1).[55] Complete remission, partial response, and stable disease control rates at 2 to 4 months posttreatment varied from 78% to 96%. In 4 studies, the median survival ranged from 10.8 to 20.9 months. Ten patients had gastric ulceration, and 3 patients died due to treatment.

Table 1. Retrospective Case Series of Radioembolization for Liver Metastases in Breast Cancer

Study (Year)	Populations	Outcomes
Pieper et al (2016)[56]	44 women with unresectable liver-dominant breast metastases who had failed 2+ lines of chemotherapy who underwent yttrium-90 RE at a single center from 2006-2015	ORR: 29% Disease control rate: 71% Median TTP: 101 d Median survival: 184 d Grade 2 toxicity: 1 (cholecystitis) Grade 3 toxicity: 1 (duodenal ulceration)
Gordon et al (2014)[57]	75 women with stable extrahepatic disease who had hepatic tumor progression after systemic chemotherapy treated with yttrium-90 RE at a single center	30-day mortality: 4% Median OS: 6.6 mo (95% CI, 5.0 to 9.2 mo) Median hepatic TTP: 3.2 mo (95% CI, 1.2 to 8.5 mo) Median distant TTP: 4.1 mo (95% CI, 2.7 to 7.0 mo)

Saxena et al (2014)[58]	40 women with unresectable, chemo-resistant breast cancer–related liver metastases treated from 2006-2012 at a single institution who had received at least 1 line of systemic chemotherapy	Grade 1 or 2 clinical toxicity: 40%
		Of 38 women with ≥1 mo follow-up:
		  CR: 5%
		  PR: 26%
		  SD: 39%
		  PD: 29%
		Median survival: 13.6 mo

Cianni et al (2013)[59]	52 women with chemotherapy-refractory breast cancer and inoperable liver metastases; chemotherapy administered previously to all patients, surgery in 17.3%, TACE in 3.8%, and RFA in 3.8%	CR: 0% PR: 56% SD: 35% PD: 10% Median OS: 11.5 mo
Haug et al (2012)[60]	58 women with chemotherapy-refractory breast cancer and unresectable hepatic metastases	Mean follow-up: 27.5 wk CR: 0% PR: 25.6% SD: 62.8% PD: 11.6% Median OS: 47 wk

Jakobs et al (2008)[61]	30 (29 women, 1 man) patients who underwent RE with resin microspheres in a single-session, whole-liver treatment for breast cancer metastases and had failed prior polychemotherapy regimens	For 23 patients with follow-up data, after median follow-up of 4 mo:
		  PR: 61%
		  SD: 35%
		  PD: 4%
		One death due to treatment-related hepatic toxicity
		after median follow-up of 14.2 mo
		Median OS: 11.7 mo

Bangash et al (2007)[62]	27 women with progressive liver metastases from breast cancer while on polychemotherapy	After 90-d follow-up
		  CR: 39%
		  PR: 39%
		  SD: 52%
		  PD: 9%
		Median survival
		ECOG Performance Status 0: 6.8 mo
		ECOG Performance Status 1-3: 2.6 mo

Study (Year)	Populations	Outcomes
Coldwell et al (2007)[63]	44 patients with hepatic metastases at 3 hospitals who failed 1st-, 2nd-, or 3rd-line treatment for primary breast tumor and were not candidates for RFA, TACE, resection, IMRT, or SRT	After 12-wk follow-up PR: 47% No radiation-related liver failures were observed Median survival: >14 mo

CI: confidence interval; CR: complete response; ECOG: Eastern Cooperative Oncology Group; IMRT: intensity-modulated radiotherapy; ORR: response rate; OS: overall survival; PD: progressive disease; PR: partial response; RE: radioembolization; RFA: radiofrequency ablation; SD: stable disease; SRT: stereotactic radiotherapy ;TACE: transarterial chemoembolization; TTP: time to progression.

Section Summary: Metastatic Intrahepatic Breast Cancer
The evidence for RE for metastatic breast cancer consists of case series including 27 to 75 patients, primarily patients who progressed while on chemotherapy. Median survival ranged from 3 to 13 months and partial response ranged from 25% to 60%.

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.

Nonrandomized Comparative Studies
In 2017, Xing et al conducted a retrospective observational study to compare 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).[64] The groups were similar at baseline in terms of Child-Pugh class, ECOG Performance Status scores, age, sex, and race. Patients treated with RE had larger tumors at baseline (mean, 7.28 cm) than those treated with best supportive care (mean, 4.19 cm; p=0.02). Median OS from diagnosis of melanoma liver metastases was longer in RE-treated subjects (19.9 months vs 4.8 months; p<0.000), as was median OS from diagnosis of the primary melanoma (119.9 months vs 26.1 months; p<0.001), respectively. Pre- and posttreatment imaging studies were available for 24 (85.7%) of 28 of those treated with RE. Of those, no patients had complete remission, 5 (17.9%) patients had partial response, 9 (32.1%) patients had stable disease, and 10 (35.7%) patients had progressive disease. Two patients receiving RE had major (grade 5) clinical toxicities (ascites and hepatic encephalopathy and eventual mortality).

Case Series
In 2016, Eldredge-Hindy et al retrospectively evaluated outcomes for the use of Y90 RE in 71 patients with biopsy-confirmed uveal melanoma liver metastases.[65] Median time from the diagnosis of liver metastases to RE was 9.8 months (95% CI, 7.4 to 12.2 months), and 82% of patients had received prior liver-directed therapies. Sixty-one (86%) patients had computed tomography or magnetic resonance imaging evaluation of treatment response at 3 months post-RE. Of those, 5 (8%) patients had a partial response, 32 (52%) patients had stable disease, and 24 (39%) patients had disease progression. Median OS was 12.3 months (range, 1.9-49.3 months).

Several smaller studies published from 2009 to 2013 have reported on the use of RE in patients with hepatic metastases from melanoma.[66-69] Three studies included only patients with ocular

melanoma,[66-68] and the fourth included patients with ocular or cutaneous melanoma.[69] Sample sizes ranged between 11 patients and 32 patients. Three studies excluded those with poor performance status. Median age was in the 50s for 3 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.[66] 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.[68] 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.[67] Median survival in Gonsalves, Klingenstein, and Kennedy were 10.0 months, 19 months, and not yet reached, respectively. Gonsalves reported 4 (12.5%) patients with grade 3 or 4 liver toxicity. Klingenstein observed 1 patient with marked hepatomegaly. Kennedy described 1 patient with a grade 3 gastric ulcer. The fourth study (Piduru et al [2012][69]; N=12) did not include any toxicity data.

Metastatic Pancreatic Cancer
Michl et al reported a case series on RE for pancreatic cancer in 2014.[70] Response was seen in 47% with median local PFS in the liver of 3.4 months (range, 0.9-45.0 months). Median OS was 9.0 months (range, 0.9-53.0 months) and 1-year survival was 24%.

Summary of Evidence
For individuals who have hepatocellular carcinoma who receive radioembolization (RE) or RE with a liver transplant, the evidence includes primarily retrospective and prospective observational studies, with limited evidence from randomized controlled trials (RCTs). Relevant outcomes are overall survival, 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 revealed similar outcomes for RE compared with alternatives. Evidence from observational studies has demonstrated that RE can allow 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. 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. 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 2 study, retrospective reviews, and case series, some of which have compared RE with other transarterial liver-directed therapies. Relevant outcomes are overall survival, functional outcomes, quality of life, and treatment-related morbidity. This evidence has suggested that RE has 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, along with 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.

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

2015 Input
In response to requests, input was received from 3 physician specialty societies (with 5 individual responses) and 1 academic medical center (with 4 individual responses), for a total of 9 respondents, while this policy was under review in 2015 to address the use of radioembolization (RE) for liver metastases from tumors other than colorectal cancer and neuroendocrine tumors and for primary hepatic cholangiocarcinoma. 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 on the use of RE for hepatic metastases from other specific tumor types, including pancreatic cancer. However, many reviewers supported the use of RE for treatment of other radiosensitive tumors metastatic to the liver with liver-limited or liver-dominant disease for symptom palliation or prolongation of survival.

2010-2011 Input
In response to requests, input was received from 2 physician specialty societies (with 5 individual responses) and 6 academic medical centers, for a total of 11 respondents, while this policy was under review in 2010 and again in 2011 to readdress specifically metastases from colorectal cancer and other metastatic tumors besides neuroendocrine tumors. For the 2011 review, input was received from 2 physician specialty societies and 3 academic medical centers; all but 1 academic medical center had provided input in 2010. There was strong support for the use of RE in patients with primary 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

colorectal cancers and support for its use in patients with liver metastases from other cancers but with less consensus than for colorectal metastases. Those providing input were split as to whether RE should be used as monotherapy or in combination with other agents.

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

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

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Primary Hepatocellular Carcinoma
National Comprehensive Cancer Network (NCCN) guidelines (v.2.2017) for the treatment of primary hepatocellular carcinoma mention the use of arterially directed therapies, including transarterial bland embolization, transarterial chemoembolization (TACE), and drug-eluting beads TACE, and radioembolization (RE) with yttrium-90 microspheres for specific categories of patients.[3] The guidelines do not distinguish between the different arterially directed therapies, and all statements carry category 2A recommendations.

Primary Cholangiocarcinoma
NCCN guidelines for the treatment of primary intrahepatic cholangiocarcinoma list locoregional therapy as an option for unresectable or metastatic disease, or for residual local disease after resection (category 2B recommendation), although primary treatment is fluoropyrimidine-based or gemcitabine-based chemotherapy (category 1 recommendation). The guidelines note that no RCTs of radiofrequency ablation, TACE, or RE exist.[3]

Metastatic Neuroendocrine Tumors
NCCN guidelines (v.2.2017) for the treatment of metastatic neuroendocrine tumors give a category 2B recommendation for hepatic regional therapy (arterial embolization, chemoembolization, RE) in certain clinical situations.[71]

Metastatic Colon Cancer
NCCN guidelines (v.2.2017) for the treatment of colon cancer state: "...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."[72]

Metastatic Breast Cancer
NCCN guidelines (v.2.2017) for the treatment of breast cancer do not address the use of RE in the treatment of metastatic breast cancer.[73]

Metastatic Melanoma

NCCN guidelines (v.1.2017) for the treatment of melanoma do not address the use of RE in the treatment of metastatic melanoma.[74]

RE Brachytherapy Oncology Consortium

In 2007, the Radioembolization Brachytherapy Oncology Consortium made 14 recommendations with level 2A evidence (panel consensus with low-level evidence).[75] Some of the Consortium's recommendations about specific indications for RE therapy were as follows:

- There is sufficient evidence to support the safety and effectiveness of yttrium-90 (Y90) microsphere therapy in selected patients.
- Candidates for radioembolization are patients with unresectable primary or metastatic hepatic disease with liver-dominant tumor burden and a life expectancy greater than 3 months.
- Absolute contraindications to Y90 microsphere treatment include pretreatment 99mTc macroaggregated albumin scan demonstrating the potential of 30 Gy radiation exposure to the lung or flow to the gastrointestinal tract that cannot be corrected by catheter techniques.
- Relative contraindications to Y90 microsphere treatment include limited hepatic reserve, irreversibly elevated bilirubin levels, compromised portal vein (unless selective or superselective radioembolization can be performed), and prior radiotherapy involving the liver.

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 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Hepatocellular carcinoma			
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	Apr 2017 (ongoing)
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	Mar 2018
NCT01556490[a]	A Phase III Clinical Trial of Intra-arterial TheraSphere® in the Treatment of Patients With Unresectable Hepatocellular Carcinoma (HCC)	390	Oct 2019
Unpublished			
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	24	Sep 2016 (completed)

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Hepatocellular Carcinoma Awaiting Liver Transplantation		
NCT01381211	Transarterial RAdioembolization Versus ChemoEmbolization for the Treatment of HCC: A Multicenter Randomized Controlled Trial (TRACE Trial)	140	Dec 2016 (unknown)
Metastatic colorectal cancer			
ISRCTN83867919	FOXFIRE: An open-label randomised phase III trial of 5-Fluorouracil, OXaliplatin and Folinic acid +/- Interventional Radio-Embolisation as first line treatment for patients with unresectable liver-only or liver-predominant metastatic colorectal cancer	490	Oct 2016
NCT00724503[a]	Randomised Comparative Study of Folfox6m Plus Sir-Spheres® Microspheres Versus Folfox6m Alone as First Line Treatment in Patients With Nonresectable Liver Metastases From Primary Colorectal Carcinoma (SIRFLOX)	532	Nov 2016
NCT01483027[a]	A Phase III Clinical Trial Evaluating TheraSphere® in Patients With Metastatic Colorectal Carcinoma of the Liver Who Have Failed First Line Chemotherapy	340	Feb 2019
NCT01721954[a]	Assessment of Overall Survival of FOLFOX6m Plus SIR-Spheres Microspheres Versus FOLFOX6m Alone as First-line Treatment in Patients With Non-resectable Liver Metastases From Primary Colorectal Carcinoma in a Randomised Clinical Study	200	Dec 2019
Cholangiocarcinoma			
NCT01912053	An Open-label, Multicenter, Phase II Trial, to Evaluate the Efficacy of Intra-hepatic Administration of Yttrium 90-labelled Microspheres (Therasphere®, Nordion) in Association With Intravenous Chemotherapy With Gemcitabine and Cisplatin for the Treatment of Intra-hepatic Cholangiocarcinoma, First Line	41	Apr 2018

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction
75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
77399	Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services

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77778	Interstitial radiation source application, complex, includes supervision, handling, loading of radiation source, when performed
79445	Radiopharmaceutical therapy, by intra-arterial particulate administration
C2616	Brachytherapy source, nonstranded, Yttrium-90, per source
S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using Yttrium-90 microspheres

- The coding for radioembolization may depend on the medical specialty that is actually providing the therapy. The following CPT codes might possibly be used: 79445, 77778, 75894.
- The following code is available for the embolization procedure: 37243.
- Because this therapy involves radiotherapy, a variety of radiotherapy planning codes may be a component of the overall procedure. For example, CPT code 77399 may be used.
- The following HCPCS code is also available for radioembolization: S2095.

ICD-9 Diagnoses

| 155.0 | Malignant neoplasm of liver, primary |
| 209.72 | Secondary neuroendocrine tumor of liver |

ICD-10 Diagnoses (Effective October 1, 2015)

C22.0	Liver cell carcinoma
C22.2	Hepatoblastoma
C22.3	Angiosarcoma of liver
C22.4	Other sarcomas of liver
C22.7	Other specified carcinomas of liver
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C7B.02	Secondary carcinoid tumors of liver

REVISIONS	
05-10-2012	Policy added to the bcbsks.com web site.
12-12-2013	Updated Description section.
	In Policy section: ▪ In Item E, added "experimental/" to read "Radioembolization is considered experimental / investigational..." ▪ Added Item F, "Radioembolization is considered experimental / investigational to treat primary intrahepatic cholangiocarcinoma."
	Updated Rationale section.
	In Coding section: ▪ CPT code 37204 will be a deleted code *(Effective December 31, 2013)* ▪ Added CPT code 37243 *(Effective January 1, 2014)* ▪ Added ICD-10 Diagnosis codes *(Effective October 1, 2014)*
	Updated Reference section.
03-10-2016	Published 02-09-2016. Effective 03-10-2016.
	Description section updated
	In Policy section: ▪ In Item A added "that is unresectable and" and "(see Policy Guidelines section)" to read "Radioembolization may be considered medically necessary to treat primary hepatocellular carcinoma that is unresectable and limited to the liver (see Policy Guidelines section)."

REVISIONS	
	▪ In Item C added "(carcinoid and noncarcinoid) with diffuse" and "when systemic therapy has failed to control symptoms" to read "Radioembolization may be considered medically necessary to treat hepatic metastases from neuroendocrine tumors (carcinoid and noncarcinoid) with diffuse and symptomatic disease when systemic therapy has failed to control symptoms" ▪ In Item D added "melanoma (ocular or cutaneous), or breast cancer that are both progressive and diffuse," to read "Radioembolization may be considered medically necessary to treat unresectable hepatic metastases from colorectal carcinoma melanoma (ocular or cutaneous), or breast cancer that are both progressive and diffuse, in patients with liver-dominant disease who are refractory to chemotherapy or are not candidates for chemotherapy or other systemic therapies." ▪ In Item E removed "is considered experimental / investigational" and added "may be considered medically necessary" and "inpatient with unresectable tumors" to read "Radioembolization may be considered medically necessary to treat primary intrahepatic cholangiocarcinoma in patients with unresectable tumors" ▪ In Item F removed "for metastatic neuroendocrine tumors and metastases from colorectal cancer" to read "Radioembolization is considered experimental / investigational for all other hepatic metastases except as noted above." ▪ Added Item G "Radioembolization is considered experimental / investigational for all other indications not described above." ▪ Added the Policy Guidelines section with the following guidelines: "1. In general, radioembolization is used for unresectable HCC that is greater than 3 cm. 2. There is little information about the safety or efficacy of repeated RE treatments or about the number of treatments that should be administered. 3. Radioembolization should be reserved for patients with adequate functional status (Eastern Cooperative Oncology Group [ECOG] Performance Status 0-2), adequate liver function and reserve, Child-Pugh score A or B, and liver-dominant metastases. 4. Symptomatic disease from metastatic neuroendocrine tumors refers to symptoms related to excess hormone production."
	Rationale section updated
	In Coding section: ▪ Removed CPT Code: 37204 ▪ Revised nomenclature of CPT Code: 77778 (Effective 01-01-2016) ▪ Corrected location of HCPCS codes C2616 and S2095 from the Diagnosis section to the CPT/HCPCS section. ▪ Added ICD-10 Code: C78.7. ▪ Updated Coding notations.
	References updated
01-18-2017	Description section updated
	Rationale section updated
	In Coding section: ▪ Coding notations updated
	References updated
08-15-2017	Description section updated
	Rationale section updated
	References updated

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