Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110
Original Effective Date: 02/23/2004
Current Effective Date: 11/16/2016

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider the use of radioembolization (RE) to treat primary hepatocellular carcinoma (HCC) that is unresectable and limited to the liver to be eligible for coverage.

Based on review of available data, the Company may consider the use of radioembolization (RE) in primary hepatocellular carcinoma (HCC) as a bridge to liver transplantation to be eligible for coverage.

Based on review of available data, the Company may consider the use of radioembolization (RE) to treat hepatic metastases from neuroendocrine tumors (carcinoid and noncarcinoid) with diffuse and symptomatic disease when systemic therapy has failed to control symptoms to be eligible for coverage.

Based on review of available data, the Company may consider the use of radioembolization (RE) to treat unresectable hepatic metastases from colorectal carcinoma (CRC), 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 to be eligible for coverage.

Based on review of available data, the Company may consider radioembolization (RE) to treat primary intrahepatic cholangiocarcinoma (ICC) in patients with unresectable tumors to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers radioembolization (RE) for all other hepatic metastases except as noted above to be investigational.*

Based on review of available data, the Company considers radioembolization (RE) for all other indications not described as above to be investigational.*
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Background/Overview
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 diffuse, multiple 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 [RFA]), particle and wave physics (microwave or laser ablation), or arterial embolization therapy including chemoembolization, bland embolization, or radioembolization.

Radioembolization (referred to as selective internal radiotherapy 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 tumors 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. Yttrium-90 is a pure beta-emitter with a relatively limited effective range and 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 is 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 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 granted premarket approval of SIR-Spheres for use in combination with 5-flourouracil chemotherapy by hepatic arterial infusion to treat unresectable hepatic metastases from CRC. In contrast, TheraSphere was approved by humanitarian device exemption (HDE) for use as monotherapy to treat unresectable HCC. In January 2007, this HDE was expanded to include patients with HCC who have partial or branch portal vein thrombosis. For these reasons, results obtained with 1 product do not necessarily apply to other commercial (or noncommercial) products.

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 2 randomized controlled trials have shown a survival benefit for transarterial chemoembolization (TACE) therapy compared to supportive care in patients with unresectable HCC. In 1 study, patients were randomly assigned 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
Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110
Original Effective Date: 02/23/2004
Current Effective Date: 11/16/2016

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.

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%. Patients with unresectable disease may select among fluoropyrimidine-based or gemcitabine-based chemotherapy, fluoropyrimidine chemoradiation, or best supportive care.

Unresectable Metastatic Colorectal Cancer
Fifty to sixty 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 tumor with negative surgical margins. Most patients diagnosed with metastatic colorectal disease are initially classified as having unresectable disease. In 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 survival benefit shown with both second- and third-line systemic chemotherapy. Recent advances in chemotherapy, including oxaliplatin, irinotecan, and targeted antibodies like cetuximab, have doubled the median survival in this population from less than 1 year to more than 2 years. Palliative chemotherapy using combined systemic and hepatic arterial infusion may increase disease-free intervals for patients with unresectable hepatic metastases from CRC.

RFA has been found inferior to resection in local recurrence rates and 5-year OS and 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 generally recommended when the goal of complete resection with curative. The role of local (liver-directed) therapy (including radioembolization, chemoembolization, and conformal radiotherapy) in debulking unresectable metastatic disease remains controversial.

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).
Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110  
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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, because 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 analogues 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 shown modest response rates of limited duration, is better for pancreatic neuroendocrine tumors than carcinoids, and is frequently associated with significant toxicity.\(^6\) Chemoembolization has shown response rates of nearly 80%, but the effect is of short duration and a survival benefit has not been demonstrated.

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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Currently 2 forms of yttrium-90 microspheres have been approved by the U.S. 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 hepatocellular carcinoma who can have placement of appropriately positioned hepatic arterial catheters (H980006).

In 2002, SIR-Spheres\(^{\ddagger}\) (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.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.
Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110
Original Effective Date: 02/23/2004
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Rationale/Source
Unresectable Hepatocellular Carcinoma
Systematic Reviews
Vente et al (2009) conducted a meta-analysis evaluating tumor response and survival in patients who received yttrium-90 glass or resin microsphere RE for the treatment of primary HCC or metastases from CRC. (Refer to Unresectable Metastatic CRC section for the data from the meta-analysis as pertains to that disease.) Included studies were from 1986 onward and presented tumor response measured by computed tomography (CT) scans and data on median survival times. To allow comparability of results with regard to tumor response, the category of “any response” was introduced and included complete response (CR), partial response (PR), and stable disease (SD). 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 yttrium-90 radioembolization. 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 from 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 was 9.4 to 24.0 months.

In a 2002 review of the use of yttrium-90 RE for unresectable liver cancer, Salem et al described a previously unpublished series of approximately 300 patients with liver carcinoma with selective internal radiotherapy (SIRT) under a humanitarian device exemption at 8 unnamed institutions. The report provided no additional details on baseline patient characteristics and did not specify inclusion or exclusion criteria for treatment. Investigators only reported outcomes for a cohort of 54 HCC patients with Okuda stage I and II (median survival, 23 and 11 months, respectively; overall survival [OS] at 1 year, 68% and 37%, respectively).

Randomized Controlled Trials
In 2015, Kolligs et al reported results of a small pilot randomized controlled trial (RCT) comparing RE with TACE for the treatment of unresectable HCC, the SIR-TACE study. The trial included 28 subjects with unresectable HCC, preserved liver function, and an Eastern Cooperative Oncology Group [ECOG] Performance Status 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, PR rates were 13.3% for TACE and 30.8% for RE, with rates of disease control (CR, SD, PR) 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 to TACE with drug-eluting beads TACE (DEB-TACE) for the treatment of unresectable HCC. The study included 24 patients, 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 TACE; p=0.619) and OS (592 days for RE vs 788 days for TACE; p=0.927).
Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110
Original Effective Date: 02/23/2004
Current Effective Date: 11/16/2016

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

Nonrandomized Comparative Studies
In 2016, Soydal et al reported a retrospective study comparing outcomes of patients receiving RE and TACE for HCC. Each group included 40 patients. RE patients had a mean survival of 39 months versus 31 months for TACE patients (p=0.014). There were no significant differences in complications or recurrence of disease.

In 2016, Oladeru reported a retrospective study based on SEER registry data comparing survival outcomes of patients receiving RE and external-beam radiotherapy (EBRT) of HCC. A total of 189 patients with unresectable HCC (77 receiving RE, 112 EBRT) receiving treatment between 2004 and 2011 were evaluated. Median OS for RE was 12 months versus 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 of treatment and OS or disease-specific survival.

In 2015, El Fouly et al reported results of a nonrandomized study comparing RE with TACE for 86 patients with intermediate stage, nonresectable HCC. Sixty-three patients at 1 institution were treated with TACE, while 53 patients at a second institution were treated with RE. Median OS in for TACE (18 months) and RE (16.4 months) did not differ significantly between groups; similarly median time to progression (TTP) 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 sorafenib for intermediate- or advanced-stage HCC. Patients with HCC refractory to other therapies and no metastases or systemic chemotherapy were included, 74 of whom were treated with sorafenib and 63 treated 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. Patients either received conventional cisplatin-TACE between the years 1992 and 2000 (n=691), yttrium-90 microspheres between 2000 and 2005 (n=99), or no treatment (n=142). Median OS for the yttrium-90 group was 11.5 months (95% confidence interval [CI], 8 to 16 months) versus 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 yttrium-90 and TACE appeared to be equivalent regional therapies for patients with unresectable, nonmetastatic HCC.

Case Series
A comparison of tumor response and survival among subgroups of patients with and without portal vein thrombosis (PVT) was reported by Kulik et al in 2008. Thirty-four percent of this phase 2 open-label cohort of 108 unresectable HCC patients treated with TheraSphere had had either branch or main PVT. At 6
Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110
Original Effective Date: 02/23/2004
Current Effective Date: 11/16/2016

months, World Health Organization (WHO) criteria for PR were observed in 42.2% of the overall cohort and in 34% and 66% of those with and without PVT, respectively. Kaplan-Meier survival was statistically longer in the PVT-free group (467 days) than in the branch (304 days) or main PVT (133.5 days) groups. At baseline, the PVT groups had higher tumor burden, Okuda stage, pretreatment bilirubin concentrations, and proportion of patients with portal hypertension than the non-PVT groups. Adverse events for the PVT groups were presented among those with and without baseline cirrhosis. Cirrhotic patients with main PVT were more likely than those without PVT to experience worsening of baseline ascites (55% and 15%, respectively) with yttrium-90 microsphere treatment; no difference was seen among those without cirrhosis, although the numbers were small.

In 2010, Salem et al reported the results of a single-center, prospective, longitudinal cohort study of 291 patients with HCC treated between January 2004 and December 2008. The patient population was heterogeneous and included patients with PVT (43%), advanced disease, and extrahepatic metastases (16%), which are usually exclusionary criteria for studies using locoregional therapy. Data were collected prospectively and included toxicity, imaging, and survival outcomes. Patients were staged by Child-Pugh class. Eighty-seven percent of patients had received no prior therapy. A total of 526 treatments were administered (mean, 1.8; range, 1-5). Scans were performed 4 to 6 weeks after each treatment and then at 2 to 3 month intervals once all disease was treated. Median follow-up time was 30.9 months. Imaging follow-up was available in 273 patients, with an average of 4.3 scans per patient. By WHO criteria, response rates were 42%; by European Association for the Study of the Liver (EASL) criteria, 57%, with 23% CR and 34% PR. Response rates were better in patients with Child-Pugh A disease (WHO=49%, EASL=66%) than those with Child-Pugh class B disease (WHO=36%, EASL=51%), and WHO response rates varied by baseline largest tumor size: smaller than 5 cm, 44%; 5 to 10 cm, 42%; and larger than 10 cm, 33%. Survival for patients with Child-Pugh classes A and B disease was 17.2 months and 7.7 months, respectively (p=0.002). The authors concluded that patients with Child-Pugh class A disease, with or without PVT, benefitted most from the treatment but that the role of yttrium-90 in certain patients with HCC requires further exploration, including controlled studies comparing yttrium-90 with alternative locoregional therapies (radiofrequency ablation [RFA], TACE) and yttrium-90 in various combinations with systemic targeted therapies in advanced disease.

Additional case series have described outcomes for RE for HCC, with similar outcomes, including Kwok et al (N=46) and Saxena et al (N=45).

Section Summary: Unresectable Hepatocellular Carcinoma

RCTs and nonrandomized comparative studies do not demonstrate superiority of RE compared to alternative active comparators. If the active comparators are effective treatments for HCC, these results are consistent with some efficacy of RE for treatment of HCC, although without a formal noninferiority analysis it cannot be determined whether RE is as effective as alternatives. The RCTs are too small to make firm conclusions about the relative efficacy of RE versus alternatives. In all studies, tumor response is observed, which may improve survival.
Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110
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Current Effective Date: 11/16/2016

RE as a Bridge to Liver Transplantation for Primary HCC
In 2014, Kulik et al reported results of a pilot RCT of yttrium-90 RE with or without sorafenib for patients with HCC awaiting liver transplantation. The study 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 (ITT) 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 on liver transplant waiting lists who received RE as bridge therapy. 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 on 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. In the ITT transplantation arm, 60.2% were able to receive 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 RE with chemoembolization in the efficacy of downstaging 86 patients with HCC from stage T3 to T2 (potentially making patients liver transplant candidates). Patients were treated with either RE using yttrium-90 microspheres (n=43) or TACE (n=43). Median tumor size was similar between the 2 treatment groups (5.7 cm for TACE and 5.6 cm for RE). PR rates were 61% for RE versus 37% for TACE, with downstaging from T3 to T2 in 58% of patients treated with RE versus 31% with TACE (p<0.05).

Section Summary: RE as a Bridge to Liver Transplantation for Primary 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 related to the use of RE for intrahepatic cholangiocarcinoma (ICC) consists primarily of case series. The studies demonstrate tumor response to RE. Tumor response may improve survival, but 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. The review included 12 publications, 7 of which were published in abstract form only. Of the peer-reviewed articles, 3 were described as prospective cohort studies, which we describe in detail next (Mouli et al, Hoffmann et al,
and Saxena et al; of note, Hoffman et al is reported by the authors as a retrospective study). The overall weighted median survival was 15.5 months (range, 7-22.2 months), based on 11 included studies. A weighted mean PR was seen in 28% of patients and SD was seen in 54% at 3 months posttreatment.

Also in 2015, Boehm et al conducted a systematic review to compare hepatic artery–based therapies, including hepatic arterial infusion (HAI), TACE, DEB-TACE, and yttrium-90 RE, for unresectable ICC. Of 20 studies that met inclusion criteria, 5 evaluated yttrium-90 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**

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. Survival varied depending on 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 retrospective study by Hoffmann et al of RE with yttrium-90 resin microspheres included 24 patients with nonresectable chemorefractory ICC and no extrahepatic disease. 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%, RFA in 5.1%, and EBRT in 3.0%. Tumor response was assessed by RECIST criteria. A CR was seen in 0%, PR in 36.4%, SD in 51.5%, and progressive disease (PD) in 15.2%. Follow-up ranged from 3.1 to 44 months (median, 10 months). Median OS was 22 months and median TTP was 9.8 months. Favorable subgroups with respect to survival included those with ECOG Performance Status score of 0, tumor burden as percentage of liver volume of 25% or less, response by CA-19-9 criterion and RECIST PR. The same subgroups, except those with a cancer antigen 19-9 response, had favorable TTP 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 yttrium-90 glass microspheres. 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. Treatment given previously included chemotherapy in 65%, surgery in 28%, local therapy in 20%, and none in 24%. Tumor response results according to RECIST criteria were: CR in 0%; PR in 22%; SD in 65%; and PD in 13%. Median OS was 51 weeks, and multivariate analysis found that a PR 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 yttrium-90 resin microspheres. 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%, RFA in 6.1%, and EBRT in 3.0%. By RECIST tumor response criteria, CR was seen in 0%, PR in 24%, SD in 48%, and PD in 20%. Follow-up was collected between 0.4 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 yttrium-90 microspheres.

A 2008 study by Ibrahim et al reported results on RE with yttrium-90 glass microspheres among 24 patients with unresectable ICC. 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, 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 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 patient (4%) developed a duodenal ulcer.

Rayar et al reported 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. After RE, all patients underwent successful resection.

Metastatic Liver Tumors
Unresectable Neuroendocrine Tumors

Systematic Reviews
In 2014, Devcic et al published results of a meta-analysis of studies evaluating RE for liver-dominant metastatic neuroendocrine tumors. The analysis included 12 studies that provided RECIST data for hepatic metastatic neuroendocrine tumors treated with RE. For yttrium-90 RE with resin microspheres only, objective radiographic response rates (CR or PR by RECIST) ranged from 12% to 80%, with a random-effects weighted average of 50% (95% CI, 38% to 62%). Disease control rates (CR, PR, SD) ranged from 62% to 100%, with a random-effects weighted average of 86% (95% CI, 78% to 92%).

Nonrandomized Comparative Study
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. 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 from 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), TTP (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 to assess 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. RECIST criteria were used to assess tumor response, which showed 92% of glass patients and 94% of resin patients had PR or had SD at 6 months after treatment. Median survival was 22 months for glass and 28 months for resin.

In 2010, Cao et al reported outcomes for 58 patients with unresectable neuroendocrine liver metastases from 2 different hospitals treated with RE from 2003 to 2008. Response was assessed with radiographic evidence before and after RE and measured using RECIST guidelines. Systemic chemotherapy was routinely given at 1 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 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, histologic grade of tumor, and whether patients responded to RE.

In 2008, King et al reported outcomes in patients treated in a single-institution prospective study. 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%) CR and 11 (32%) PR. 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. 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 with 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 SD in 22.7%; PR, 60.5%; CR, 2.7%; and PD, 4.9%. Hepatic and extrahepatic metastases contributed to death in most patients, with 7% lost to follow-up. Median survival was 70 months.
Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110
Original Effective Date: 02/23/2004
Current Effective Date: 11/16/2016

Additional case series in patients with treatment-refractory, unresectable neuroendocrine hepatic metastases have shown good tumor response and improvement in clinical symptoms with RE.

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). The review included 2 RCTs (Gray et al [2001], Hendliz et al [2010], described next), 5 studies classified as non-RCTs or well-designed cohort studies, and 13 observational studies. After RE, the average reported CRs and PRs 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 OS rates, median survival time was 12 months (range, 8.3-3.6 months).

In another 2013 systematic review, Rosenbaum et al evaluated 13 relevant articles on RE as monotherapy and 13 studies on RE combined with chemotherapy for chemoresistant, unresectable CRC liver metastasis. CR, PR, and SD rates ranged from 29% to 90% with RE only and from 59% to 100% for RE plus chemotherapy. At 12 months, survival 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 (CTAF) assessed 25 studies on the use for RE and inoperable metastatic CRC to the liver, including 2 RCTs (Gray et al [2001], van Hazel et al [2004], described next), 1 small retrospective study comparing SIRT with chemoembolization (N=36), and 21 case series. 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 author stated that the assessment showed it is feasible to deliver radiotherapy to liver metastases and achieve at least PR in a substantial portion of patients with relatively few serious adverse events and 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 what is currently 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 CTAF criteria, with the exception of criterion number 1 (ie, the technology has 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. Two articles met authors’ inclusion criteria: Gray et al and van Hazel et al. Cochrane authors 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 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 yttrium-90 RE. Included in the meta-analysis were 2 RCTs (Gray et al, van Hazel et al). 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 [FOLFIRI] or 5-FU/LV plus irinotecan [FOLFOX]) was used, and (2) whether yttrium-90 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 yttrium-90 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 yttrium-90 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 yttrium-90 microspheres. The investigators closed the study 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 TTP (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 (CEA) and estimated tumor cross-sectional area and volume from repeated CT scans read by physicians blinded to treatment assignment. They reported for HAI plus RE versus HAI increased overall responses (CR plus PR) measured by area (44% vs 18% p=0.01) and volume (50% vs 24%, p=0.03), or by serum CEA levels (72% vs 47%, p=0.004), respectively. They also reported increased TTP detected by increased area (9.7 months vs 15.9 months, respectively; p=0.01) or volume (7.6 months vs 12.0 months, respectively; p=0.04). However, there were no significant differences between treatment arms in actuarial survival rates (p=0.18) or in 11 QOL 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 TTP with RE, several issues make the conclusion less certain. Accrual was halted early, leaving the study underpowered. Although the study had an institutional review board oversight, the report 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 study, response rate and TTP 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. Results of this study may reflect use of a shorter-than-standard duration of HAI therapy and are confounded by administration of nonprotocol chemotherapy before and after SIRT. The reported increases in response rates and TTP improved neither duration of survival nor QOL.

A 2004 phase 2 RCTG by the same research group involved 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. Disease TTP was greater in those receiving combination therapy (18.6 months vs 3.6 months, respectively; p<0.001).
Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110
Original Effective Date: 02/23/2004
Current Effective Date: 11/16/2016

A phase 3 RCT of 46 patients, compared intravenous 5-FU plus RE (SIR-Spheres) to intravenous 5-FU alone in CRC metastatic to the liver and refractory to standard chemotherapy. 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 10 patients 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 phase 3 RCT by van Hazel et al of 530 patients compared modified FOLFOX chemotherapy and FOLFOX chemotherapy plus SIRT in patients with previously untreated liver-dominant metastatic disease. Bevacizumab was allowed 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 (10.2 months for control vs 10.6 months for RE; hazard ratio [HR], 0.93; p=0.43). Secondary end points of median PFS in the liver and objective response rate for controls versus RE in the liver were improved in the RE group (liver PFS, 12.6 months vs 20.5 months; liver response rate, 68.8% vs 78.7%), 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 yet been completed. This combined preplanned analysis should determine 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 versus best supportive care alone for patients with chemorefractory, liver-dominant colorectal metastases (n=29 in each group). Patients were matched on tumor burden, prior treatments, and additional clinical criteria. Results showed prolongation of survival in patients who received RE (median survival, 8.3 months vs. 3.5 months ; p<0.001; HR=0.3; 95% CI, 0.16 to 0.55; p<0.001). Adverse events were considered generally mild-to-moderate and manageable.

Case Series
In 2015, Hickey reported results from a case series from 8 institutions with 531 patients receiving RE. Median OS from the first RE treatment was 10.6 months (95% CI, 8.8 to 12.4 months). Performance status, low tumor burden, absence of extrahepatic disease, and less chemotherapy exposure were associated with better outcomes.

A single-arm, open-label study was reported by Mulcahy et al (2009) and involved 72 patients with unresectable hepatic colorectal metastases. To determine response, 128 lesions were used. A PR rate using WHO criteria were noted in 29 (40.3%) of 72 patients, and, at the lesional level, the response rate was 40.6% (PR=37.5%; CR=3.1%). SD was observed in 44.5% of patients and disease progression in 14.8% of patients. Median follow-up was 26.2 months. Median OS was 40.3 months (95% CI, 29.0 to 51.6 months) for all patients from the time of cancer diagnosis, 34.6 months (95% CI, 24.4 to 41.8 months) from the time liver metastases were diagnosed, and 14.5 months (95% CI, 9.6 to 21.9 months) from the time of
Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110
Original Effective Date: 02/23/2004
Current Effective Date: 11/16/2016

yttrium-90 therapy. Favorable prognostic factors associated with benefit from RE included an ECOG Performance Status score of 0, a liver tumor burden of 25% or less, and the absence of extrahepatic disease. For the patients with an ECOG Performance Status score of 0 at the time of RE, the median OS from the onset of liver metastases was 42.8 months (5-year survival rate, 25.9%).

A 2015 study by Saxena retrospectively reviewed outcomes for 302 patients with unresectable, chemotherapy-resistant CRC liver metastases treated with yttrium-90 RE at a single institution from 2006 to 2012. One hundred fifteen (38%) subjects developed clinical toxicity after treatment, most of which (5%) was considered minor and self-resolved. Five (2%) patients died within 30 days of treatment, 2 from suspected pulmonary embolus, 2 from clinical disease progression, and 1 from radiation hepatitis. Two hundred ninety-three (97%) patients had follow-up beyond 2 months post-RE therapy with CT imaging. Of these, 2 (1%) patients had CR, 111 (37%) had PR, 96 (32%) had SD, and 84 (28%) had PD. Median OS after RE treatment was 10.5 months.

In another large prospective series, Lewandowski et al reported outcomes from a single-center review of 214 patients treated with RE for CRC liver metastases from 2001 to 2013. Median OS was 43 months from the time of primary cancer diagnosis, 34.6 months from the time of hepatic metastases diagnosis, and 10.6 months from the time of yttrium-90 initiation. Grade 3 absolute lymphocyte, bilirubin, albumin, alkaline phosphatase, and aspartate aminotransferase toxicities were observed in 39%, 11%, 10%, 8%, and 4% of patients, respectively; while grade 4 absolute lymphocyte and alkaline phosphatase toxicities were observed in 5% and 3% of patients, respectively. In multivariable models, a number of factors were independently associated with OS, including receiving fewer than 3 cytotoxic drugs before RE (OS, 15.2 vs 7.5 months; HR=0.67; 95% CI, 0.46 to 0.98; p=0.042), receiving no biologic agents before RE (OS, 18.6 months vs 9.4 months; HR=0.56; 95% CI, 0.36 to 0.88; p=0.012), and having no extrahepatic disease (HR=0.58; 95% CI, 0.41 to 0.83; p=0.002).

In another relatively large review, Kennedy et al reported results of 208 patients with liver metastases from CRC who had failed or were not candidates for standard chemotherapy. There were no CRs but were 35% PRs by CT, as determined by a 50% decrease in 1 tumor measure at 12 weeks. Median survival was 10.5 months for responders but 4.5 months for nonresponders. The authors noted that most patients died with persistent liver disease and had uncontrolled systemic metastases.

Kalva et al reported results of a retrospective study of 45 patients with CRC liver metastases who failed systemic chemotherapy and were treated with RE at a single center from 2005 to 2011. Twenty-three (51%) patients had no toxicities and 6 (13%) patients had grade 3 toxicities. One (2%) patient had a PR, 34 (71%) had SD, and 6 (13%) had PD. Median survival was 186 days (95% CI, 149 to 277 days).

Jakobs et al retrospectively reviewed patients with CRC liver metastases who failed chemotherapy and received a single-session, whole-liver treatment with yttrium-90 RE (N=41). Response was partial in 7 (17%) patients. Twenty-five (61%) patients had SD, and 4 (10%) had PD. Median OS was 10.5 months. Median survival rates for patients with PR, SD, and PD were 29.3 months, 10.9 months, and 4.3 months, respectively. No severe toxicities were observed.
Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110
Original Effective Date: 02/23/2004
Current Effective Date: 11/16/2016

Metastatic Intrahepatic Breast Cancer
Most studies on the use of RE for metastatic breast cancer 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.

Case Series
In 2013, Smits et al reviewed 6 studies on RE for metastatic breast cancer (total N=198 participants). CR, PR, and SD 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.

In 2014, Gordon et al retrospectively reviewed prospectively collected data for 75 patients with breast cancer–related liver metastases and stable extrahepatic disease treated with yttrium-90 RE at a single center. Included patients had hepatic tumor progression after cytotoxic systemic chemotherapy. For the 48 patients for whom data were available who had systemic chemotherapy with RE, 32 (66.7%) received additional systemic chemotherapy. The 30-day mortality rate after RE was 4% (n=3, including 1 case of sepsis and 2 cases of hepatic decompensation). Clinical grade 3 toxicity occurred in 5 (7.6%) patients and biochemical grade 3 toxicity occurred in 37 (54.4%) patients. Median OS was 6.6 months (95% CI, 5.0 to 9.2 months). Post-RE imaging was available for 68 (93.2%) of 73 living patients. Median time to hepatic progression was 3.2 months (95% CI, 1.2 to 8.5 months), while median distant TTP was 4.1 months (95% CI, 2.7 to 7.0 months).

In 2014, Saxena et al reported results of a retrospective analysis of 40 subjects who underwent RE treatment for unresectable, chemoresistant breast cancer–related liver metastases treated from 2006 to 2012 at a single institution. At study entry, all patients had received at least 1 line of systemic chemotherapy. Twenty-four (60%) patients had evidence of limited extrahepatic disease; for the 16 with liver-exclusive disease, 14 patients underwent RE for progression of disease, while 2 patients underwent RE for increasing symptoms. For patients with extrahepatic disease, the indication for RE was discordant liver progression in 20 patients and symptoms in the remaining 4 patients. Sixteen (40%) patients had clinical toxicity after treatment, all of which were grades 1 and 2. Thirty-eight (95%) patients had follow-up beyond 1 month post-RE with CT imaging. Overall, 2 (5%) of 38 patients had a CR, 10 (26%) of 38 patients had PR, 15 (39%) of 38 patients had SD, and 11 (29%) of 38 patients had PD. Median survival after the first RE treatment was 13.6 months.

A 2013 study by Cianni et al included 52 women with chemotherapy-refractory breast cancer and inoperable liver metastases. Median age was 57.5 years. ECOG Performance Status scores were 0 in 55.7%, 1 in 26.9%, and 2 in 17.3%. Extrahepatic disease was present in 46.1%. Chemotherapy had been administered previously in all patients, surgery in 17.3%, TACE in 3.8%, and RFA in 3.8%. Tumor response results by RECIST criteria were: CR in 0%; PR in 56%; SD in 35%; and PD in 10%. Median OS was 11.5 months. Patients were retrospectively divided into 2 risk groups based on ECOG Performance Status score, degree of liver tumor burden, and whether extrahepatic disease was present. Median survival in the low-risk group was 14.3 months, significantly better than in the high-risk group (8.2 months). Grade 3 gastritis was seen in 2 (4%) patients.

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Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110
Original Effective Date: 02/23/2004
Current Effective Date: 11/16/2016

Haug et al published a case series of 58 women with chemotherapy-refractory breast cancer and unresectable hepatic metastases. Mean age was 58 years, and all patients had a Karnofsky Performance Status of 60% or higher. Extrahepatic disease was present in 66%. Prior treatments were not mentioned. By RECIST criteria, a CR was seen in 0%; PR in 25.6%; SD in 62.8%; PD in 11.6%. Mean follow-up covered 27.5 weeks. Median OS for the sample was 47 weeks. Two indices derived from quantitative interpretation of positron emission tomography were significant predictors of survival. Bilirubin toxicity was grade 3 in 3% and grade 4 in 2%. Transaminase toxicity was grade 3 in 5% and grade 4 in 2%.

Jakobs et al reported on the safety and survival of 30 (29 women, 1 man) patients who underwent RE with resin microspheres in a single-session, whole-liver treatment for breast cancer metastases. All patients had failed prior polychemotherapy regimens. Twenty-three patients had follow-up data. At a median follow-up of 4.2 months, PR, SD, and PD were observed in 61%, 35%, and 4% of patients, respectively. Clinically significant toxicities were observed in 8 of 30 patients and included increasing liver enzymes and bilirubin levels, nausea and vomiting, gastric ulcers and ascites; 1 death was due to treatment-related hepatic toxicity. Median follow-up was 14.2 months, with a median OS of 11.7 months. Median survival for responders was 23.6 months and 1.7 months for nonresponders. Median survival of patients with and without extrahepatic disease was 9.6 months versus 16 months, respectively.

Bangash et al reported on the safety and efficacy of the use of RE with glass microspheres in 27 female patients with progressing liver metastases from breast cancer while on polychemotherapy. Seventeen patients received 20 left lobe of liver treatments, and 20 received 22 right lobe of liver treatments. At the 90-day follow-up CT, CR and PR were observed in 9 (39%) patients; SD in 12 (52%); and PD in 2 (9%). Median survival by an ECOG Performance Status score of 0 versus 1, 2, and 3 was 6.8 months versus 2.6 months, respectively, and for patients with tumor burden less than 25% versus greater than 25%, 9.4 months and 2.0 months, respectively.

Hepatic metastases from breast cancer in 44 patients at 3 hospitals were retrospectively reviewed by Coldwell et al. Patients had failed first-, second-, or third-line treatment for their primary tumor and were not candidates for RFA, TACE, resection, intensity-modulated radiotherapy, or stereotactic radiotherapy. At 12 weeks, a PR (using WHO criteria, at least 50% reduction in the cross-product of the tumor dimensions) to SIR-Spheres was observed by CT in 47% of patients with recorded follow-up (82% of the total). Symptoms were reported to improve, although no specifics were provided. No radiation-related liver failures were observed, and, at a median follow-up of 14 months, the cohort had not yet reached its expected median survival of 14 months.

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, in whom the liver is the most common site of metastatic disease.

Nonrandomized Comparative Studies
In 2014, 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.
Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110
Original Effective Date: 02/23/2004
Current Effective Date: 11/16/2016

treated with yttrium-90 RE (n=28) or best supportive care (n=30). 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 sizes 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 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). Pre- and posttreatment imaging studies were available for 24 (85.7%) of 28 of those treated with RE. Of those, no patients had a CR; 5 (17.9%) patients had PR, 9 (32.1%) patients had SD, and 10 (35.7%) patients had PD. 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 yttrium-90 RE in 71 patients with biopsy-confirmed uveal melanoma liver metastases. 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 CT or magnetic resonance imaging evaluation of treatment response at 3 months post-RE. Of those, 5 (8%) patients had a PR, 32 (52%) patients had SD, and 24 (39%) patients had disease progression. Median OS RE 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. Three studies included only patients with ocular melanoma, and the fourth included patients with ocular or cutaneous melanoma. 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 one 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 a CR; 1 had a PR; 18 (56%) had SD; and 12 (38%) had PD. In the study of 13 patients by Klingenstein et al (2013), none had a CR; 8 (62%), PR; 2 (15%), SD; and 3 (23%), PD. Nine of 11 patients in Kennedy et al (2009) provided response data: 1 had CR; 6, PR; 1, SD; and 1, PD. 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 patients with a grade 3 gastric ulcer. The fourth study (Piduru et al [2012]; 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. 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%.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Summary of Key Trials</th>
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<td>NCT No.</td>
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Page 18 of 26
## Radioembolization for Primary and Metastatic Tumors of the Liver

**Policy # 00110**  
Original Effective Date: 02/23/2004  
Current Effective Date: 11/16/2016

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<tr>
<th>Trial ID</th>
<th>Study Title</th>
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<td>NCT01482442</td>
<td>Selective Internal Radiation Therapy (SIRT) Versus Sorafenib in Locally Advanced Hepatocellular Carcinoma (SIRveNIB)</td>
<td>(ongoing)</td>
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<td>NCT01556490</td>
<td>A Prospective Randomized Open-labeled Trial Comparing RADIOEMBOLIZATION With Yttrium 90 Microspheres and Sorafenib in Patients With Advanced Hepatocellular Carcinoma</td>
<td>496 Apr 2016 (ongoing)</td>
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<td>NCT01381211</td>
<td>A Phase III Clinical Trial of Intra-arterial TheraSphere® in the Treatment of Patients With Unresectable Hepatocellular Carcinoma (HCC)</td>
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<td>NCT01126645</td>
<td>Transarterial RAdioembolization Versus ChemoEmbolization for the Treatment of HCC: A Multicenter Randomized Controlled Trial (TRACE Trial)</td>
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<td>NCT00846131</td>
<td>Evaluation of Sorafenib in Combination With Local Micro-therapy Guided by Gd-EOB-DTPA Enhanced MRI in Patients With Inoperable Hepatocellular Carcinoma</td>
<td>665 Mar 2017</td>
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<tr>
<td>NCT02004210</td>
<td>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</td>
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<td>NCT00956930</td>
<td>A Randomized, Multi-center, Open Label, Phase 3 Trial Comparing Conventional TACE and Transarterial Radioembolization in Patients With Unilobar Advanced Hepatocellular Carcinoma</td>
<td>102 Apr 2018</td>
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<td>NCT01483027</td>
<td>Metastatic colorectal cancer</td>
<td>360 Sep 2016</td>
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<td>ISRCTN83867919</td>
<td>Randomised Comparative Study of FOLFOX6m Plus Sir-Spheres® Microspheres Versus FOLFOX6m Alone as First Line Treatment in Patients With Non-resectable Liver Metastases From Primary Colorectal Carcinoma</td>
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<td>NCT01721954</td>
<td>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</td>
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<td>NCT01912053</td>
<td>Cholangiocarcinoma</td>
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NCT: national clinical trial.
Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110
Original Effective Date: 02/23/2004
Current Effective Date: 11/16/2016

* Denotes industry-sponsored or cosponsored trial.

Summary of Evidence

For individuals who have HCC who receive RE or RE with liver transplant, the evidence includes primarily retrospective and prospective observational studies, with limited evidence from 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 HCC, including TACE and TACE with drug-eluting beads. Both trials demonstrated 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 qualitatively that the technology results in a meaningful improvement in 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 1 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 shown that RE has similar outcomes to standard therapies and historical controls for patients with neuroendocrine tumor-related symptoms or progression of liver tumor. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in net health outcome.

For individuals who have unresectable intrahepatic metastases from CRC and prior treatment failure who receive RE, the evidence includes several small- to moderate-sized RCTs, prospective trials, and retrospective studies using a variety of comparators, 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 to alternatives, but tend to show greater tumor response with RE. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in net health outcome.

For individuals who have unresectable intrahepatic metastases from miscellaneous cancers (eg, breast cancer, melanoma) who receive RE, the evidence includes observational studies. Relevant outcomes are overall survival, functional outcomes, quality of life, and treatment-related morbidity. These studies generally have shown significant tumor response. The evidence is insufficient to determine the effects of the technology on health outcomes.
Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110
Original Effective Date: 02/23/2004
Current Effective Date: 11/16/2016

References

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01/31/2004 Medical Director review.
02/17/2004 Medical Policy Committee review.
02/23/2004 Managed Care Advisory Council approval.
02/01/2006 Medical Director review
02/15/2006 Medical Policy Committee review. Format revisions, Rationale/Source.
02/23/2006 Quality Care Advisory Council approval.
07/07/2006 Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
03/14/2007 Medical Director review.
03/21/2007 Medical Policy Committee approval. Coverage eligibility unchanged.
04/02/2009 Medical Director review.
04/15/2009 Medical Policy Committee approval. Added “(SIRT)” to title. Revised investigational statement from “Based on review of available data, the Company considers the use of internal radiation therapy for all indications including, but not limited to, the treatment of primary or metastatic tumors of the liver, to be investigational” to “Based on review of available data, the Company considers selective internal radiation therapy using intra-arterial injection of radiolabeled microspheres to treat primary or metastatic liver tumors to be investigational.” Coverage eligibility unchanged.
09/09/2010 Medical Policy Committee review.
09/15/2010 Medical Policy Implementation Committee approval. policy statement and title (“selective internal radiation therapy” changed to “radioembolization”). Policy statements changed to indicate that selective cases of hepatocellular carcinoma and metastatic neuroendocrine tumors may be considered medically necessary. Title changed to reflect current procedure name.
04/07/2011 Medical Policy Committee review.
04/13/2011 Medical Policy Implementation Committee approval. Added that “radioembolization to treat unresectable hepatic metastases from colorectal cancer that are both progressive and diffuse, in patients with liver-dominant disease who are refractory to chemotherapy or are not candidates for chemotherapy is eligible for coverage.
04/05/2012 Medical Policy Committee review.
04/18/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/11/2012 Medical Policy Committee review.
10/31/2012 Medical Policy Implementation Committee approval. Investigational statement for unresectable hepatic metastases from colorectal carcinoma removed, since it is eligible for coverage.
10/03/2013 Medical Policy Committee review

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10/16/2013 Medical Policy Implementation Committee approval. New investigational statement on intrahepatic cholangiocarcinoma added.
03/25/2014 Coding update due to codes added and deleted from policy
11/06/2014 Medical Policy Committee review
11/21/2014 Medical Policy Implementation Committee approval. Added “Based on review of available data, the Company considers radioembolization for all other indications not described as above to be investigational.”
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015 Medical Policy Committee review
11/16/2015 Medical Policy Implementation Committee approval. Melanoma (ocular or cutaneous), or breast cancer added to eligibility statement for unresectable hepatic metastases.
11/03/2016 Medical Policy Committee review
11/16/2016 Medical Policy Implementation Committee approval. Medically necessary statements added for unresectable metastatic breast cancer and melanoma with liver-dominant disease and unresectable intrahepatic cholangiocarcinoma.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
03/15/2017 Coding update

Next Scheduled Review Date: 11/2017

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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<th>Code Type</th>
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<tr>
<td>CPT</td>
<td>37243, 75894, 77399, 77778, 79445</td>
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<td>ICD-10 Diagnosis</td>
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</tbody>
</table>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient’s illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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