Medical Policy

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Title: Radioembolization for Primary and Metastatic Tumors of the Liver

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DESCRIPTION

Hepatic tumors can arise either as primary liver cancer or by metastasis to the liver from other organs. Local therapy by surgical resection with tumor-free margins or liver transplantation is the only potentially curative treatment. Unfortunately, most hepatic tumors are unresectable at diagnosis, due either to their anatomic location, size, and number of lesions, concurrent nonmalignant liver disease, or insufficient hepatic reserve.

The use of external beam radiotherapy (EBRT) and the application of more advanced radiotherapy approaches (e.g., intensity-modulated radiotherapy [IMRT]) may be of limited use in patients with diffuse, multiple lesions due to the low tolerance of normal liver to radiation compared to 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, particle and wave physics (microwave or laser ablation), or arterial embolization therapy including chemoembolization, bland embolization, or radioembolization.

Radioembolization (RE), referred to as selective internal radiation therapy or "SIRT" 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, as 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 RE are initially examined by hepatic angiogram to identify and map the hepatic arterial system, and at that time, a mixture of albumin particles is delivered via the hepatic artery to simulate microspheres. After, single-photon emission computed tomography (CT) gamma imaging is used to detect possible shunting of the albumin particles into gastrointestinal or pulmonary vasculature.

Currently, two commercial forms of yttrium-90 microspheres are available: a glass sphere, TheraSphere® (MDS Nordion, Inc., Ontario, Canada) and a resin sphere, SIR-Spheres® (Sirtex Medical Limited; Lake Forest, IL). Noncommercial forms are mostly used outside the U.S. While the commercial products use the same radioisotope (yttrium-90) and have the same target dose (100 Gy), they differ in microsphere size profile, base material (i.e., resin vs. glass), and size of commercially available doses. The physical characteristics of the active and inactive ingredients affect the flow of microspheres during injection, their retention at the tumor site, spread outside the therapeutic target region, and dosimetry calculations. Note also that the U.S. Food and Drug Administration (FDA) granted premarket approval of SIR-Spheres® for use in combination with 5-floxuridine (5-FUDR) chemotherapy by hepatic arterial infusion (HAI) to treat unresectable hepatic metastases from colorectal cancer. In contrast, TheraSphere® was approved by humanitarian device exemption (HDE) for use as monotherapy to treat unresectable hepatocellular carcinoma (HCC). In January 2007, this HDE was expanded to include patients with hepatocellular carcinoma who have partial or branch portal vein thrombosis. For these reasons, results obtained with one product do not necessarily apply to other commercial (or noncommercial) products.

Unresectable primary hepatocellular carcinoma

The majority of 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 (RCTs) have shown a survival benefit using transarterial chemoembolization (TACE) therapy versus supportive care in patients with unresectable HCC. (1, 2) In one 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, and 2-year survival rates were 63%, 50%, and 27%, respectively. A recent multicenter, randomized, double-blind placebo controlled Phase III trial that enrolled 602 patients with advanced HCC randomly assigned patients to receive sorafenib versus placebo. (3) Overall survival (OS) was significantly longer in the sorafenib group compared with placebo (10.7 vs. 7.9 months, respectively; hazard ratio [HR] for sorafenib: 0.69; $p<0.001$).

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%.(4) Patients with unresectable disease may select among fluoropyrimidine-based or gemcitabine-based chemotherapy, fluoropyridimine chemoradiation or best supportive care.
Unresectable metastatic colorectal carcinoma

Unresectable metastatic colorectal carcinoma
Fifty to sixty percent of patients with colorectal cancer 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%. Emphasis on treating these patients with potentially curable disease is on complete removal of all tumor with negative surgical margins. The majority of 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 in an attempt to downsize the metastases in order to convert the metastatic lesions to a resectable statue (conversion chemotherapy).

In patients with unresectable disease that cannot be converted to resectable disease, the primary treatment goal is palliative, with survival benefit shown with 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 1 year to more than 2 years. (5) Palliative chemotherapy by combined systemic and HAI may increase disease-free (DF) intervals for patients with unresectable hepatic metastases from colorectal cancer.

Radiofrequency ablation (RFA) has been shown to be 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 (i.e., adjacent to a major vessel), or an estimate of inadequate liver reserve following resection. RFA is generally recommended to be used with the goal of complete resection with curative intent. (6) The role of local (liver-directed) therapy (including RE, chemoembolization, and conformal radiation therapy) in debulking unresectable metastatic disease remains controversial. (6)

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, and 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), transcatheter arterial embolization (TAE) or chemoembolization (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 compared to carcinoids, and is frequently associated with significant toxicity. (7) Chemoembolization has shown response rates of nearly 80%, but the effect is of short duration and a survival benefit has not been demonstrated. (7)

Miscellaneous metastatic tumors
Small case reports have been published on the use of RE in many other types of cancer with hepatic metastases, including breast, melanoma, head, and neck (including parotid gland), pancreaticobiliary, anal, thymic, thyroid, endometrial, lung, kidney, gastric, small bowel, esophageal, ovarian, cervical, prostatic, bladder, and for sarcoma and lymphoma. (8)

POLICY

A. Radioembolization may be considered **medically necessary** to treat primary hepatocellular carcinoma limited to the liver.

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

C. Radioembolization may be considered **medically necessary** to treat hepatic metastases from neuroendocrine tumors and symptomatic disease.

D. Radioembolization may be considered **medically necessary** to treat unresectable hepatic metastases from colorectal carcinoma in patients with liver-dominant disease.

E. Radioembolization is considered **experimental / investigational** for all other hepatic metastases except for metastatic neuroendocrine tumors and metastases from colorectal cancer as noted above.

F. Radioembolization is considered **experimental / investigational** to treat primary intrahepatic cholangiocarcinoma.

RATIONALE

Unresectable Primary Hepatocellular Carcinoma (HCC)

Salem and colleagues (2010) reported the results of a single-center, prospective, longitudinal cohort study of 291 patients with HCC treated between January 2004 and December 2008. (9) The patient population was heterogeneous and included patients with portal vein thromboses (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 scores. 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 4-6 weeks after each treatment and then at 2-3 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 World Health Organization (WHO) criteria, response rates were 42%; by European Association for the Study of the Liver (EASL) criteria, 57%, with 23% complete response (CR) and 34% partial response (PR). Response rates were better in patients with Child Pugh A disease (WHO, 49%; EASL 66%) than those with Child Pugh B disease (WHO, 36%; EASL 51%), and WHO response rates varied by baseline largest tumor size: smaller than 5 cm, 44%; 5-10 cm, 42%; and larger than 10 cm, 33%. Survival for patients with Child Pugh disease A and B was 17.2 months and 7.7 months, respectively ($p=0.002$). The authors concluded that patients with Child Pugh A disease, with or without portal vein thrombosis, 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] and transarterial chemoembolization [TACE]) and yttrium-90 in various combinations with systemic targeted therapies in advanced disease.

Carr and colleagues (2010) reported on a consecutive series of patients with HCC who were seen at a single medical center and who were not candidates for surgical resection. (10) 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 overall survival (OS) for the yttrium-90 group versus the TACE group was 11.5 months [95% confidence interval [CI]: 8-16 months] versus 8.5 months [95% CI: 8-10 months], respectively ($p<0.05$). Untreated patients had a median survival of 2 months. Although the authors felt there was a slight selection bias toward milder disease in the yttrium-90 group, they concluded that yttrium-90 and TACE appear to be equivalent regional therapies for patients with unresectable, nonmetastatic HCC.

Vente and colleagues (2009) conducted a meta-analysis on tumor response and survival in patients who received yttrium-90 glass or resin microsphere radioembolization (RE) for the treatment of primary liver cancer (HCC) or metastases from colorectal cancer. (11) (See below under unresectable metastatic [colorectal carcinoma] CRC section for the data from the meta-analysis as pertains to that disease.) Included studies were from 1986 onward. Articles written in a language other than English or German were excluded, as were articles that did not present tumor response measured by computed tomography (CT) scans or that did not present data on median survival times. To allow comparability of results with regard to tumor response, the category of “any response” was introduced, and included CR, PR, 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 yttrium-90 RE. Treatment with resin microspheres was associated with a significantly higher proportion of any response than glass microsphere treatment (0.89 vs. 0.78, respectively; 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 and 21.0 months, and median survival from diagnosis or recurrence was 9.4–24.0 months.

The authors of the meta-analysis concluded that yttrium-90 RE is associated with high response rates, both in salvage and first-line settings, but that the true impact on survival will only become known after publication of several ongoing and/or to-be-initiated Phase III studies, as well as the results of trials in which yttrium-90 RE and modern chemotherapy agents are combined with novel biologic agents.

Lewandowski and colleagues (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). (12) 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 and 5.6 cm, for TACE vs.RE, respectively.) Partial response rates were 61% versus 37% for RE vs. TACE, respectively, with downstaging from T3 to T2 in 58% of patients treated with RE versus 31% with TACE ($p<0.05$).

A comparison of tumor response and survival among subgroups of patients with and without portal vein thrombosis (PVT) was reported by Kulik and colleagues in 2008. (13) Thirty-four percent of this Phase II open-label cohort of 108 unresectable HCC patients treated with TheraSphere® had had either branch or main PVT. At 6 months, WHO criteria PR was 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 the branch (304 days) and 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 have 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.

A large single series was reported by Salem and colleagues in 2002 that described treating approximately 300 patients with liver carcinoma with selective internal radiation therapy (SIRT) under a humanitarian device exemption (HDE) at 8 unnamed institutions. (14) The report provided no additional details on baseline characteristics of the patients 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).

Intrahepatic Cholangiocarcinoma (ICC)

Cholangiocarcinomas originate in the epithelium of the bile duct. Four case series on use of RE in ICC are summarized here.

A study by Hoffman et al. of RE with yttrium-90 resin microspheres included 24 patients with nonresectable chemorefractory intrahepatic ICC and no extrahepatic disease (15). The mean age of the sample was 65.2 years and the sample was 45.5% female. ECOG performance status 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%, stable disease (SD) in 51.5% and progressive disease in 15.2%. Follow-up ranged between 3.1 and 44 months (median: 10 months). Median overall survival was 22 months and median time to progression was 9.8 months. Favorable subgroups with respect to survival included those with ECOG performance status 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 CA-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. addressed 26 consecutive patients with unresectable ICC who underwent RE with yttrium-90 glass microspheres (16). 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 overall survival was 51 weeks and multivariate analysis of found that a partial response from quantitative interpretation of positron emission tomography was a significant independent predictor of survival. Authors found no cases of grade 3 toxicity in transaminases or bilirubin.

In 2010, Saxena et al. published results for 25 patients with unresectable ICC who received RE with yttrium-90 resin microspheres. (17) 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 overall survival was 9.3 months. Among subgroups, longer survival duration was seen in patients with peripheral tumors and those with ECOG performance status 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 patient (4%) experienced duodenal ulcer due to malperfusion of yttrium-90 microspheres.

A study by Ibrahim and colleagues from 2008 reported results on RE with yttrium-90 glass microspheres among 24 patients with unresectable ICC (18). The group was 33% female and had a median age of 68 years. Extrahepatic disease was present in 33%. ECOG performance status was 0 in 42%, 1 in 50% and 2 in 8%. Prior chemotherapy had been used in 29%. Using the WHO tumor response criteria, CR was observed in 0%, CR in 27%, SD in 68% and PD in 5%. Follow-up was collected over a median of 17.7 months and median overall survival was 14.9 months. Subgroups that had favorable survival results included those with ECOG performance status of 0, no previous chemotherapy and peripheral tumor. Grade 3 albumin

toxicity was found in 17%, grade 3 bilirubin toxicity in 4% and 1 patient (4%) developed a duodenal ulcer.

Unresectable Metastatic Colorectal Carcinoma

The literature for unresectable metastatic colorectal cancer to the liver and radioembolization consists of 3 small randomized studies, a technology assessment, Cochrane review, meta-analysis, a retrospective matched-pair comparison, and case series.

The first randomized study was published by Gray and colleagues in 2001, and randomly assigned 74 patients with bilobar unresectable liver metastases to monthly hepatic arterial infusion (HAI) with 5-fluorodeoxyuridine (5-FUDR) alone or with the same chemotherapy plus a single infusion of yttrium-90 microspheres. (19) The investigators closed the study after entering 74 patients (n=70 eligible for randomization). The original goal was 95 patients. Reasons cited for the early closure included: 1) increasing patient and physician reluctance to participate; 2) decision by the FDA to accept intermediate endpoints to support applications for premarket application approval; and 3) lack of funding to complete the study. The smaller study population was adequate to detect increases in response rate (from 20% to 55%) and median time to disease 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 (CEA) and estimated tumor cross-sectional area and volume from repeated computerized tomographic scans read by physicians blinded to treatment assignment. They reported increased overall responses (complete plus partial) measured by area (44% vs. 18%, p=0.01; HAI plus SIRT vs. HAI, respectively) and volume (50% vs. 24%, respectively; p=0.03), or by serum CEA levels (72% vs. 47%, respectively; p=0.004). They also reported increased time to disease progression detected by increased area (9.7 vs. 15.9 months, respectively; p=0.001) or volume (7.6 vs. 12.0 months, respectively; p=0.04). However, there were no significant differences between treatment arms in actuarial survival rates (p=0.18 by log rank test) 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.

Despite the investigators’ assertions, these results are inadequate to support their conclusions for the following reasons: 1) Accrual was halted early, leaving the study underpowered. 2) Although the study involved oversight by an institutional review board, the report suggests early closure was at the sole discretion of the principal investigator without independent review or prospectively designed data monitoring procedures and stopping rules. 3) While in this study, 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. (9, 10) 4) 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. 5) The reported increases in response rates and time to progression improved neither duration of survival nor quality of life.

The second randomized trial was a Phase II study published in 2004 by the same research group as the Phase III trial. (20) The study involved 21 patients with advanced colorectal liver metastases; a total of 11 patients received SIR-Spheres plus systemic chemotherapy (fluorouracil and leucovorin), and 10 received the same systemic chemotherapy alone. While the time to progressive disease was greater in those receiving combination therapy (18.6 versus 3.6 months, respectively; $p<0.0005$), the small size of the study limits any conclusions.

The third trial, a Phase III study, involved 46 patients and compared intravenous 5-fluorouracil (5-FU) to hepatic intra-arterial injection of yttrium-90 microspheres (SIR-Spheres) with intravenous 5-FU in colorectal cancer metastatic only to the liver and refractory to standard chemotherapy. (21) The time to liver progression, the primary outcome, was significantly improved in the group receiving SIR-Spheres, 2.1 versus 5.5 months, respectively ($p=0.003$). However, there was no difference in the more important outcome of median survival; this was 7.3 and 10.0 months, respectively ($p=0.80$).

A draft technology assessment (2010) from the California Technology Assessment Forum (CTAF) assessed 25 studies on the use of RE and inoperable metastatic colorectal cancer to the liver, including the 2 previously described randomized studies, 1 small retrospective study comparing SIRT to chemoembolization (n=36), and 21 case series. (5) The assessment concluded that the 3 comparative studies all 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 radiation therapy 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, as the trials were very small, the response rates in the control groups were lower than expected, and the control groups were not given what is currently considered standard first-line chemotherapy for metastatic colorectal cancer. The assessment concluded that the use of SIRT for unresectable colorectal cancer did not meet any of the CTAF technology assessment criteria, with the exception of criterion number 1 (i.e., the technology has final approval from the appropriate government regulatory bodies).

A 2009 Cochrane review assessed the above-outlined randomized controlled trials (RCTs). (22) The authors concluded that there was a lack of evidence that SIRT improves survival or quality of life in patients with metastatic colorectal cancer, whether it is given alone or with chemotherapy, and that there is a need for well-designed, adequately powered Phase III trials assessing the effect of SIRT when used with modern combination chemotherapy regimens.

In the aforementioned 2009 meta-analysis by Vente et al., in a total of 19 eligible studies, 792 patients with metastatic colorectal cancer had undergone yttrium-90 RE. (11) Included in the meta-analysis were the 2 randomized trials previously addressed in this section of the policy. Two covariates were included in the meta-regression model: 1) whether an older generation of cytostatic agents (5-FU/LV or floxuridine) or a newer generation (5-FU/LV [leucovorin] plus oxaliplatin [FOLFOX] or 5-FU/LV plus irinotecan [FOLFIRI]) 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) that were 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 treatment as neoadjuvant to chemotherapy, regardless of the chemotherapy regimen used. Median survival after yttrium-90 RE, irrespective

of differences in determinants (microspheres type, chemotherapy protocol, and salvage or first-line) varied from 6.7 to 17.0 months.

A single arm, open-label study was reported by Mulcahy and colleagues (2009) and involved 72 patients with unresectable hepatic colorectal metastases treated with yttrium-90 microspheres (TheraSphere®). (23) To determine response, 128 lesions were used. A PR rate using WHO criteria was noted in 29 of 72 patients (40.3%), and at the lesional level, the response rate was 40.6% (PR rate 37.5%; CR rate 3.1%).

Stable disease was observed in 44.5% of patients, and disease progression was found in 14.8% of patients. Median follow-up was 26.2 months. Median OS was 40.3 months (95% CI: 29.0–51.6 months) for all patients from the time of cancer diagnosis, 34.6 months (95% CI: 24.4–41.8 months) from the time liver metastases were diagnosed, and 14.5 months (95% CI: 9.6–21.9) from the time of yttrium-90 therapy. A substratification analysis was performed, and favorable prognostic factors that indicated a benefit from yttrium-90 therapy included an Eastern Cooperative Oncology Group (ECOG) performance status of 0, a liver tumor burden of 25% or less, and the absence of extrahepatic disease. For the patients with an ECOG performance status of 0 at the time of yttrium-90 treatment, the overall median survival from the onset of liver metastases was 42.8 months, or a 5-year survival rate of 25.9%, which are comparable outcomes to survival data for patients treated with primary resection, chemotherapy followed by resection, or RFA.

Jakobs and colleagues retrospectively reviewed case files of patients with colorectal cancer liver metastases in whom chemotherapy had failed and who therefore received a single-session, whole-liver treatment with yttrium-90 radioembolization (n=41). (24) Response was partial in 7 patients, 25 patients had stable disease, and 4 had progressive disease. Median OS was 10.5 months. Median survivals for patients with PR, stable disease, and progressive disease were 29.3 months, 10.9 months, and 4.3 months, respectively. No severe toxicities were observed. Kennedy and colleagues reported results for use of resin microspheres in 208 patients with liver metastases from colorectal cancer who had failed or were not candidates for standard chemotherapy. (25) There were no CRs but 35% PRs by computed tomography (CT; as determined by a 50% decrease in one tumor measure at 12 weeks). Median survival was 10.5 months for responders but 4.5 months for nonresponders. The authors noted that the majority of patients died with persistent liver disease and had uncontrolled systemic metastases. No quality of life or functional status measures were reported. In addition, the authors noted that their report was a retrospective review with associated problems of a mixture of patients and a lack of a controlled treatment protocol.

A retrospective, matched-pair comparison of radioembolization and best-supportive care (n=29) versus best-supportive care alone (n>500) for chemo-refractory, liver-dominant colorectal metastases showed prolongation of survival in the group of patients who received radioembolization. (26)

Unresectable Metastatic Neuroendocrine Tumors

The data on the use of radioembolization for unresectable liver metastases from neuroendocrine tumors include one open-label phase 2 study, retrospective reviews and case series.

In 2010, Cao and colleagues reported the outcomes of 58 patients with unresectable neuroendocrine liver metastases from 2 different hospitals treated with yttrium-90 microspheres (SIR-Spheres) from 2003 to 2008. Data were examined retrospectively from a database. (27) Response was assessed with radiographic evidence before and after radioembolization and measured by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Patients typically had a CT scan within 3 months of treatment and every 3 to 6 months until disease progression or death. Systemic chemotherapy was routinely given at 1 institution but not the other. Mean patient age at the time of RE was 61 (range: 29-84 years), and 67% of patients were men. Primary tumor site was variable and included small bowel, pancreas, colon, thyroid, lung, and unknown. Thirty-one patients underwent surgical resection of their primary tumor, which was classified as low-grade in 15, intermediate-grade in 7, and high-grade in 7. Forty-three percent of patients had extrahepatic metastatic disease at study entry. Prior therapies before RE included liver resection in 19 patients, transarterial embolization (TAE) or TACE in 6, ablation or percutaneous ethanol injection in 10, previous chemotherapy in 20, concurrent chemotherapy in 34, and post-RE chemotherapy in 5 patients. 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 stable disease, and 17 had disease progression. Overall survival 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, histological grade of tumor, and whether patients were responders (vs. nonresponders) to RE. Factors that were not significant prognostic features included age, sex, ECOG status, and previous therapy.

King and colleagues reported outcomes in patients treated in a single-institution prospective study. (7) Thirty-four patients with unresectable neuroendocrine liver metastases were given radioactive microspheres [SIR-Spheres] and concomitant 7-day systemic infusion of 5-FU, between 2003 and 2005. Mean patient age was 61 years (range: 32-79 years), and 65% were men. Mean follow-up was 35.2 +/- 3.2 months. The mean interval from diagnosis of hepatic metastases and treatment with SIR therapy was 36.6 +/- 6.7 months. Primary tumor sites were variable and included bronchus (n=1), thyroid (n=2), gastrointestinal (n=15), pancreas (n=8), and unknown (n=8). Subjective changes from baseline hormone symptoms were reported every 3 months. Twenty-four patients (71%) had, at baseline assessment, symptoms of carcinoid syndrome, including diarrhea, flushing, or rash. At 3 months, 18 of 33 patients (55%) reported improvement of symptoms, as did 16 of 32 (50%) at 6 months. Radiologic tumor response was observed in 50% of patients and included 6 CR (18%), and 11 PR (32%). Mean OS was 29.4 +/- 3.4 months.

Kennedy and colleagues conducted a retrospective review of 148 patients from 10 institutions with unresectable hepatic metastases from neuroendocrine tumors who received resin microspheres. (28) 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, and 2.7%, 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 censured

if a different type of therapy was given after the microspheres. The male to female ratio was 49% to 51%, respectively, and median age was 58 years (range: 26-95 years). Median follow-up was 42 months. By imaging, response rates were stable disease 22.7%, PR 60.5%, CR 2.7%, and progressive disease 4.9%. Hepatic and extrahepatic metastases contributed to death in the majority of patients, with 7% lost to follow-up. Median survival was 70 months. The authors conclude that RE can deliver high doses of radiation preferentially to hepatic metastases from neuroendocrine tumors with encouraging response rates by imaging and symptomatic improvement (although there were no data presented in the study regarding symptoms).

Rhee and colleagues reported the results of a multicenter, open label Phase II 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 (e.g., octreotide), surgical resection, bland or chemoembolization, and RFA or cryoablation. (29) Mean patient age was 58 +/- 12 years for glass and 61 +/- 11 years for resin microspheres. RECIST criteria were used to assess tumor response, which showed 92% of glass patients and 94% of resin patients were partial responders or had stable disease at 6 months after treatment. Median survival was 22 and 28 months for glass and resin, respectively.

Additional case series in patients with treatment-refractory, unresectable neuroendocrine hepatic metastases have shown good tumor response and improvement in clinical symptoms with radioembolization. (30, 31)

Miscellaneous Tumors

Data on the use of RE in metastatic breast cancer is limited to the use of RE alone (i.e., not in combination with chemotherapy), and studies have been conducted either during a hiatus between lines of chemotherapy or in patients refractory to standard of care chemotherapy. (8) Five studies have been published and consist of small numbers of heterogeneous patients.

A 2013 study by Cianni and colleagues included 52 women with chemotherapy-refractory breast cancer and inoperable liver metastases. (32) RE treatment entailed yttrium-90 resin microspheres. The median age was reported as 57.5 years. ECOG performance status was 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 overall survival was 11.5 months. Patients were retrospectively divided into two risk groups based on ECOG performance status, 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 two patients (4%).

Haug et al. published a case series of 58 women with chemotherapy-refractory breast cancer and unresectable hepatic metastases. (33) They received RE with yttrium-90 resin microspheres. The 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% and PD in 11.6%. Mean follow-up covered 27.5 weeks. The median overall survival for the sample was 47 weeks. Two indices derived from quantitative interpretation of positron emission tomography

were significant predictors of survival. Bilirubin toxicity was at grade 3 in 3% and grade 4 in 2%. Transaminase toxicity was grade 3 in 5% and grade 4 in 2%.

Jakobs and colleagues reported on the safety and survival of 30 patients (29 women and 1 man) who underwent RE with resin microspheres in a single-session, whole-liver treatment for breast cancer metastases. (34) All patients had failed prior polychemotherapy regimens (including at least anthracyclines and taxanes, hormonal therapy, and trastuzumab, when applicable). Twenty-three patients had follow-up data. At median follow-up of 4.2 months, PR, stable disease, and progressive disease was 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 of responders versus nonresponders was 23.6 and 5.7 months, respectively. Median survival of patients with and without extrahepatic disease was 9.6 versus 16 months, respectively.

Bangash and colleagues 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. (35) 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 was observed in 9 patients (39%), stable disease in 12 (52%), and progressive disease in 2 (9%). Median survival for ECOG 0 versus 1-3 was 6.8 versus 2.6 months, respectively, and for patients with tumor burden less than 25% versus greater than 25% was 9.4 and 2.0 months, respectively.

Hepatic metastases from breast cancer in 44 patients at 3 hospitals were retrospectively reviewed by Coldwell and colleagues. (36) Patients had failed first-, second-, or third-line treatment for their primary tumor and were not candidates for RFA, TACE, resection, IMRT, 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. There were no radiation-related liver failures observed, and, at a median follow-up of 14 months, the cohort had not yet reached its expected median survival of 14 months.

Four studies have reported on use of RE in patients with hepatic metastases from melanoma (37-40). Three studies included only patients with ocular melanoma (37-39) and the fourth included patients with either ocular or cutaneous melanoma. (40) Sample sizes ranged between 11 and 32 patients. Three studies excluded those with poor performance status. Median age was in the 50s for three studies and 61 in the fourth. One article did not describe any previous treatment and one described it incompletely. Three studies reported tumor response data, by RECIST criteria. Among 32 patients in the study by Gonsalves et al. (2011) one patient had a CR (3%), one had a PR, 18 patients had SD (56%) and 12 patients had PD (38%) (37). In the study of 13 patients published by Klingenstein et al. (2013), none had a CR, 8 had a PR (62%), 2 had SD (15%) and three had PD (23%) (39). Nine of 11 patients in the article by Kennedy et al. (2009) provided response data: one had CR, 6 had PR, 1 had SD and 1 had PD. (38) Median survival in Gonsalves, Klingenstein, and Kennedy were 10.0 months, 19 months and not yet reached, respectively. Gonsalves reported 4 patients (12.5%) with grade 3-4 liver toxicity.

Klingenstein observed one patient with marked hepatomegaly. Kennedy described one grade 3 gastric ulcer. The fourth study (Piduru et al., 2012, n=12) did not include any toxicity data.

Data on the use of RE in other tumors metastatic to the liver are limited and are composed of patient numbers too small to draw meaningful conclusions.

National Comprehensive Cancer Network (NCCN) Guidelines

Primary hepatocellular carcinoma
Guidelines recommend that patients with unresectable/inoperable disease who are eligible to undergo embolization therapy and have tumor lesions larger than 5 cm should be treated using arterial embolic approaches (chemoembolization, bland embolization, or radioembolization) or systemic therapy, whereas patients with lesions 3-5 cm can be considered for combination therapy with ablation and arterial embolization, and tumors of or less than 3 cm should be treated with ablation (all category 2A) but that randomized, controlled studies on the use of radioembolization therapy in the treatment of patients with HCC are needed. (4)

Primary Cholangiocarcinoma
Recommendations for unresectable ICC include chemotherapy, chemoradiation and supportive care. (4) The use of radioembolization is addressed only for resectable disease.
Metastatic colorectal cancer
Use of arterial-directed therapies such as radioembolization in highly select patients remains a category 3 recommendation based on the relatively limited amount of evidence and different institutional practices. (6)

Metastatic neuroendocrine tumors
For unresectable liver metastases (carcinoid or islet cell), recommendations include hepatic regional therapy with radioembolization (category 2B). (41)

Metastatic breast cancer
Current recommendations do not address the use of radioembolization in the treatment of metastatic breast cancer. (42)

Metastatic melanoma
Current recommendations do not address the use of radioembolization in the treatment of metastatic melanoma. (43)

Radioembolization Brachytherapy Oncology Consortium

Members met as an independent group of experts in interventional radiology, radiation oncology, nuclear medicine, medical oncology, and surgical oncology. Using level 2A evidence (panel consensus with low-level evidence), 14 recommendations were made. Conclusions included that there was sufficient evidence to support the safety and efficacy of yttrium-90 microsphere therapy and that its use requires multidisciplinary management, adequate patient selection, and meticulous angiographic technique. They also stated that the initiation of clinical trials was necessary to further define the role of yttrium-90 microsphere therapy in relation to other currently available therapies. (44)

National Cancer Institute (NCI) Clinical Trial Database (PDQ®) and ClinicalTrials.gov Registry

The following is a list of ongoing or unpublished comparative studies using radioembolization for primary or metastatic liver tumors.

Unresectable HCC

Four RCTs comparing yttrium-90 RE with TACE have either not been published or have not yet been completed. NCT00109954 enrolled a target of 120 patients with advanced unresectable HCC. The study start date was February 2005 and the current trial status is unknown. NCT00867750 began in March 2006, enrolling 28 patients with unresectable HCC and was completed in June 2011. The start date of NCT00956930 was August 2009 with an expected completion date of August 2016. NCT01381211 began in September 2011, enrolling a target of 140 patients with intermediate HCC.

Two RCTs compare sorafenib with yttrium-90 RE. NCT01135056 had a start date of July 2010. It aims to enroll 360 patients with locally advanced HCC and close in July 2015. NCT01482442 started in December 2011 and is scheduled to finish March 2015. The target sample size of 400 will include patients with advanced HCC not eligible for resection, transplantation and RFA.

In two RCTs, sorafenib is included in both treatment arms. NCT01556490 began in March 2012, comparing sorafenib alone with sorafenib plus RE in patients with unresectable HCC. It aims to enroll 400 patients and mark completion by October 2016. NCT01126645 compares RFA plus sorafenib with RE plus sorafenib among patients with inoperable HCC. It began in December 2010 and is expected to finish in February 2014.

NCT00846131 uses RE in both arms and one arm combines it with sorafenib. Included patients have pre-transplant HCC with the intention of downstaging/bridging. With a target enrollment of 40, the trial started in February 2009 and is scheduled for completion in February 2014.

Metastatic colorectal cancer

Four RCTs that have not been published or completed compare anticancer agents to those same agents plus RE. NCT00724503 assesses the effect of adding SIRT, using SIR-Spheres microspheres, to a standard chemotherapy regimen of FOLFOX as first-line therapy in patients with nonresectable liver metastases from primary colorectal adenocarcinoma (SIRFLOX). The primary outcome measure is progression-free survival. Trial status is active, with estimated enrollment of 450 and estimated study completion date of December 2012.

NCT01483027 began in January 2012 as a comparison between standard of care second-line chemotherapy versus that chemotherapy plus TheraSphere RE. Target enrollment is 360 patients with liver metastases from CRC that progressed after first-line therapy. Completion is expected in September 2016.

NCT01721954 is a comparison of the FOLFOX6m chemotherapy regimen +/- bevacizumab versus FOLFOX6m chemotherapy regimen +/- bevacizumab plus SirSphere RE. A target sample of 200 patients have liver metastases from CRC not treatable by surgery or local ablation. The start date is February 2013 and completion is expected in January 2014.

ISRCTN83867919 is an open-label randomized Phase III trial of 5-fluorouracil, oxaliplatin, and folinic acid +/- interventional radioembolization as first-line treatment for patients with unresectable liver only or liver-predominant metastatic colorectal cancer (FOXFIRE). The primary outcome measure is overall survival. Target number of participants is 490 with an anticipated end date of January 2014.

One RCT completed in 2010 but not yet published compared 5FU chemotherapy with SIR-Sphere RE. The patient population consists of patients who had liver metastases and were refractory to standard chemotherapy.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

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 for July 2010 and again for March 2011 to specifically readdress metastases from colorectal cancer and other metastatic tumors besides neuroendocrine tumors. For the March 2011 review, input was received from 2 physician specialty societies and 3 academic medical centers; all but one academic medical center had provided input in 2010. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. There was strong support for the use of radioembolization in patients with primary hepatocellular carcinoma (HCC), as a bridge to liver transplant in HCC and in neuroendocrine tumors. There was also strong support for use of radioembolization 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 radioembolization should be used as monotherapy or in combination with other agents.

The support for the use of radioembolization 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 radioembolization in this setting was for the palliation of symptoms from tumor growth and tumor bulk.

Support for the use of radioembolization 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.

Summary

- Hepatocellular carcinoma (HCC): Studies have demonstrated that radioembolization is comparable to TACE (which is considered to be therapy of choice) for patients with unresectable HCC in terms of tumor response and OS. Disadvantages of TACE include the necessity of multiple treatment sessions and hospitalization, its contraindication in patients with portal vein thrombosis, and its poorer tolerance by patients.
- Intrahepatic cholangiocarcinoma (ICC): To date, studies on use of radioembolization in patients with intrahepatic cholangiocarcinoma consist of small case series. No studies have been published comparing radioembolization to other treatments such as

chemotherapy or chemoradiation. Available studies varied with respect to patient characteristics, particularly presence of extrahepatic disease, previous therapy and performance status.

- Metastatic colorectal cancer: A major cause of morbidity and mortality in patients with colorectal disease metastatic to the liver is liver failure, as this disease tends to progress to diffuse, liver-dominant involvement. Therefore, the use of radioembolization to decrease tumor bulk and/or halt the time to tumor progression and liver failure, may lead to prolonged progression free and overall survival in patients with no other treatment options (i.e., those with chemotherapy refractory liver-dominant disease). Other uses include palliation of symptoms from tumor bulk.
- Two Phase III trials are currently underway that compare first-line chemotherapy with and without radioembolization in patients with metastatic colorectal cancer.
- Metastatic neuroendocrine tumors: Studies have included heterogeneous patient populations, and interpretation of survival data using radioembolization is difficult. Few studies report relief of symptoms from carcinoid syndrome in a proportion of patients. Surgical debulking of liver metastases has shown palliation of hormonal symptoms; debulking by radioembolization may lead to symptom relief in some patients.
- Miscellaneous: A few studies on the use of radioembolization in metastatic breast cancer and melanoma to the liver have shown promising initial results; however, the data are limited and the studies have been small and composed of heterogeneous patients. The use of radioembolization in other tumors metastatic to the liver is too limited to draw meaningful conclusions; this use is considered investigational.

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

37204	Transcatheter occlusion or embolization (e.g., for tumor destruction, to achieve hemostasis, to occlude a vascular malformation), percutaneous, any method, non-central nervous system, non-head or neck (*Deleted code, effective December 31, 2013*)
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 *(New code, effective January 1, 2014)*
75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
77399	Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services
77778	Interstitial radiation source application; complex
79445	Radiopharmaceutical therapy, by intra-arterial particulate administration

The coding for radioembolization may depend on the medical specialty that is actually providing the therapy. The following CPT codes might possibly be used:

1. 79445: Radiopharmaceutical therapy, by intra-arterial particulate administration
2. 77778: Interstitial radiation source application; complex
3. 37204: Transcatheter occlusion or embolization (e.g., for tumor destruction, to achieve hemostasis, to occlude a vascular malformation), percutaneous, any method, non-central nervous system, non-head or neck;
4. 75894: Transcatheter therapy, embolization, any method, radiological supervision and interpretation

Since this therapy involves radiation therapy, a variety of radiation therapy planning codes may be a component of the overall procedure. For example, CPT code 77399 (unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services) may be used.

S2095: Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres.

DIAGNOSIS

155.0	Malignant neoplasm of liver, primary
209.72	Secondary neuroendocrine tumor of liver
C2616	Brachytherapy source, nonstranded, Yttrium-90, per source
S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using Yttrium-90 microspheres

ICD-10 Diagnosis *(Effective October 1, 2014)*

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
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.

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