IMPLANTABLE BETA-EMITTING MICROSPHERES FOR TREATMENT OF MALIGNANT TUMORS

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INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this medical policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COVERAGE RATIONALE

Yttrium-90 (⁹⁰Y) microsphere radioembolization (SIR-Spheres® or TheraSphere®) is proven for the following indications:

- unresectable metastatic liver tumors from primary colorectal cancer (CRC)
- unresectable metastatic liver tumors from neuroendocrine tumors
- unresectable primary hepatocellular carcinoma (HCC)

Yttrium-90 (⁹⁰Y) microsphere radioembolization (SIR-Spheres® or TheraSphere®) is unproven for all other indications.

Limited evidence suggests that treatment with intrahepatic microsphere radiation (IMR) might shrink tumors and relieve symptoms in some patients, sometimes enough to render some inoperable tumors operable. However, limited available evidence has not shown improved
survival. In addition, the treatment's potential impact on quality of life has not been studied. No studies have yet compared the effects of IMR therapy with alternative treatments, such as chemoembolization. Randomized controlled trials are needed to determine the clinical utility of this treatment.

**Information Pertaining to Medical Necessity Review (When Applicable)**
The above indications apply to medical necessity review.

**BENEFIT CONSIDERATIONS**

When deciding coverage for use of implantable beta-emitting microspheres for a person who has a life threatening illness, refer to the enrollee-specific benefit document language for further information. In some benefit documents, coverage exists for unproven services for persons with life-threatening illnesses under certain circumstances.

Services requiring Institutional Review Board oversight are considered to be investigational in the 2001 Certificate of Coverage (COC).

Services requiring Institutional Review Board oversight are NOT considered to be investigational in the 2007 COC.

The enrollee-specific document must be used to determine coverage.

**BACKGROUND**

The preferred treatment for liver tumors is surgical excision. However, many liver tumors are inoperable because they are located too close to blood vessels or other critical structures or are too advanced, thus making surgery potentially unsafe and inadvisable. For inoperable liver tumors, physicians may recommend palliative treatments to reduce pain and improve quality of life.

Intrahepatic microsphere radiation (IMR) therapy or selective internal radiation (SIR) therapy is a palliative treatment for inoperable liver tumors designed to inhibit tumor growth and preserve remaining liver function by delivering radiation locally. During IMR therapy, a physician threads a catheter inserted at the femoral artery into the hepatic artery and injects millions of microscopic beads that contain the radioactive element yttrium-90 ($^{90}$Y). The microspheres become lodged in the liver's capillaries. The beta radiation, which penetrates about half an inch, is delivered directly to tumors and is less toxic to adjacent, healthy tissue than radiation delivered by other means.

After about two weeks, the radiation dissipates, but the beads remain in the liver permanently. According to manufacturers, the beads are so small and so widely diffused within the liver that they do not impede liver function. Initially, physicians treated the entire liver in one procedure. However, researchers subsequently discovered that patients tolerated the procedure better in two courses: the right lobe first and then the left lobe two to four weeks later. Physicians monitor patients' liver function during follow-up examinations.

IMR has been used to treat primary liver cancer (i.e., hepatocellular carcinoma) and metastatic liver tumors. The majority of liver tumors have metastasized from another organ, most often the colon. In some cases, IMR therapy has been reported to shrink tumors enough to allow patients to become good candidates for tumor excision surgery or liver transplantation (ECRI, 2010).
Liver Metastases from Colorectal Cancer and Hepatocellular Carcinoma (HCC)

There is evidence that yttrium-90 (\(^{90}\text{Y}\)) microsphere therapy may offer a safe palliative treatment for unresectable primary liver cancer and for unresectable metastatic liver tumors from primary colorectal cancer.

The National Comprehensive Cancer Network (NCCN) clinical practice guideline for hepatobiliary cancers states that all hepatocellular carcinomas, irrespective of their location in the liver, may be amenable to embolization (chemoembolization, bland embolization, radioembolization) provided that the arterial blood supply to the tumor may be isolated. General patient selection criteria for embolization procedures include unresectable/inoperable disease with tumors not amenable to ablation therapy only, and the absence of large-volume extrahepatic disease. Patients with unresectable/inoperable disease, who are eligible to undergo embolization therapy and have tumor lesions > 5 centimeters (cm), should be considered for treatment using arterial embolic approaches. Those patients with lesions 3–5 cm can be considered for combination therapy with ablation and arterial embolization (NCCN 2013a).

The NCCN clinical practice guidelines for colon and rectal cancers state that the role of liver-directed therapies, such as arterial radioembolization with yttrium-90 microspheres, in the treatment of colorectal metastases is controversial. Some institutions use arterially directed radioembolization in select patients with chemotherapy-resistant/refractory disease, without obvious systemic disease, and with predominant hepatic metastases. The use of arterial-directed therapies in selected patients remains a category 3 recommendation based on the relatively limited amount of evidence and different institutional practice patterns. A category 3 recommendation indicates that there is major disagreement among NCCN panel members that the intervention is appropriate (NCCN, 2013c; NCCN 2013d).

In a retrospective case-control study, Moreno-Luna et al. (2012) compared the outcomes and safety of transarterial radioembolization (TARE) versus transarterial chemoembolization (TACE) in patients with unresectable hepatocellular carcinoma (HCC). Sixty-one patients treated with TARE were retrospectively matched by age, sex and liver dysfunction with 55 TACE-treated patients. Complete tumor response was more common after TARE (12%) than after TACE (4%). When complete response was combined with partial response and stable disease, there was no difference between TARE and TACE. Median survival did not differ between the two groups (15.0 months for TARE and 14.4 months for TACE). Two-year survival rates were 30% for TARE and 24% for TACE. TARE patients reported more fatigue but had less fever than TACE patients. Treatment with TARE required less hospitalization than treatment with TACE.

Xie et al. (2012) performed a meta-analysis comparing the efficacy of transcatheter arterial chemoembolization (TACE) and microsphere embolization for treating unresectable hepatocellular carcinoma (HCC). Thirteen studies were included in the evaluation. A total of 597 patients were treated with microsphere embolization and 1,233 patients with chemoembolization. The data showed that microsphere embolization therapy was significantly better for longer overall survival, 1-year survival, longer time to progression and complete or partial response rate than that of chemoembolization treatment.

Sangro et al. (2011) conducted a multicenter analysis to evaluate the main prognostic factors driving survival after radioembolization using yttrium-90-labeled (\(^{90}\text{Y}\)) resin microspheres in patients with hepatocellular carcinoma. In total, 325 patients were treated, predominantly as whole-liver (45.2%) or right-lobe (38.5%) infusions. The median overall survival was 12.8 months (10.9-15.7), which varied significantly by disease stage, Eastern Cooperative Oncology Group (ECOG) performance status, hepatic function, tumor burden and presence of extrahepatic disease. The most significant independent prognostic factors for survival were ECOG status, tumor burden (nodules >5), international normalized ratio >1.2, and extrahepatic disease. Common adverse events were: fatigue, nausea/vomiting, and abdominal pain. Grade 3 or higher
Increases in bilirubin were reported in 5.8% of patients. All-cause mortality was 0.6% and 6.8% at 30 and 90 days, respectively. The authors concluded that this analysis provides robust evidence of the survival achieved with radioembolization, including those with advanced disease and few treatment options.

Lau et al. (2011) reviewed the role of selective internal irradiation (SIR) with yttrium-90 \(^{90}\text{Y}\) microspheres for hepatocellular carcinoma (HCC). The evidence was limited to cohort studies and comparative studies with historical controls. The authors concluded that \(^{90}\text{Y}\) microspheres are recommended as an option of palliative therapy for large or multifocal HCC without major portal vein invasion or extrahepatic spread. They can also be used for recurrent unresectable HCC, as a bridging therapy before liver transplantation, as a tumor downstaging treatment and as a curative treatment for patients with associated comorbidities who have otherwise excisable tumors but are not candidates for surgery.

Salem et al. (2011) performed a comparative effectiveness analysis of chemoembolization \((n=122)\) and radioembolization with yttrium-90 microspheres \((n=123)\) in patients with hepatocellular carcinoma (HCC). Patients were followed for signs of toxicity. All patients underwent imaging analysis at baseline and follow-up time points. Overall survival was the primary outcome measure. Secondary outcomes included safety, response rate, and time-to-progression. Abdominal pain and increased transaminase activity were more frequent following chemoembolization. Patients treated with radioembolization had a higher response rate than with chemoembolization (49% vs 36%, respectively). Although time-to-progression was longer following radioembolization than chemoembolization (13.3 months vs 8.4 months, respectively), median survival times were not statistically different (20.5 months vs 17.4 months, respectively). Among patients with intermediate-stage disease, survival was similar between groups that received chemoembolization (17.5 months) and radioembolization (17.2 months).

In a single-center, prospective, longitudinal cohort study, Salem et al. (2010) assessed the long-term clinical outcomes of 291 patients treated with yttrium-90 microspheres \((^{90}\text{Y})\). Toxicities included fatigue (57%), pain (23%) and nausea/vomiting (20%). Nineteen percent exhibited toxicity due to hyperbilirubinemia. The 30-day mortality rate was 3%. The overall time-to-progression was 7.9 months. Survival times differed between patients with Child-Pugh A and B disease (A, 17.2 months; B, 7.7 months). The authors concluded that patients with Child-Pugh A disease, with or without portal vein thrombosis (PVT), benefited most from treatment. Patients with Child-Pugh B disease who had PVT had poor outcomes. Time-to-progression and overall survival varied by patient stage at baseline.

Hepatic intra-arterial injection of the beta-emitting isotope yttrium-90 \((^{90}\text{Y})\) bound to resin microspheres (radioembolization) delivers therapeutic radiation doses to liver metastases with minimal damage to adjacent tissues. Hendlisz et al. (2010) conducted a prospective, multicenter, randomized phase III trial in patients with unresectable, chemotherapy-refractory liver-limited metastatic colorectal cancer (mCRC) comparing arm A (fluorouracil [FU] protracted intravenous infusion 300 mg/m(2) days 1 through 14 every 3 weeks) and arm B (radioembolization plus intravenous FU 225 mg/m(2) days 1 through 14 then 300 mg/m(2) days 1 through 14 every 3 weeks) until hepatic progression. The primary end point was time to liver progression (TTLP).
Cross-over to radioembolization was permitted after progression in arm A. Forty-six patients were randomly assigned and 44 were eligible for analysis (arm A, n = 23; arm B, n = 21). Median follow-up was 24.8 months. Median TTLP was 2.1 and 5.5 months in arms A and B, respectively. Median time to tumor progression (TTP) was 2.1 and 4.5 months, respectively. Grade 3 or 4 toxicities were recorded in six patients after FU monotherapy and in one patient after radioembolization plus FU treatment. Twenty-five of 44 patients received further treatment after progression, including 10 patients in arm A who received radioembolization. Median overall survival was 7.3 and 10.0 months in arms A and B, respectively. The authors concluded that radioembolization with $^{90}$Y-resin microspheres plus FU is well tolerated and significantly improves TTLP and TTP compared with FU alone. They further concluded that this procedure is a valid therapeutic option for chemotherapy-refractory liver-limited mCRC.

Cosimelli et al. (2010) conducted a prospective multicenter phase II study evaluating radioembolization using yttrium-90 resin microspheres in patients with unresectable, chemotherapy refractory colorectal liver metastases (mCRC). Of 50 eligible patients, 38 (76%) had received ≥ 4 lines of chemotherapy. Early and intermediate adverse events (mostly fever and pain) were observed in 16 and 22% of patients respectively. Two died due to renal failure or liver failure. One patient (2%) had a complete response, 11 (22%) partial response, 12 (24%) stable disease and 22 (44%) progressive disease. Four (8%) were non-evaluable. Median overall survival was 12.6 months. Two-year survival was 19.6%.

Schwarz et al. (2010) published the statements of the Consensus Conference on Multidisciplinary Treatment of Hepatocellular Carcinoma sponsored by the American Hepato-Pancreato-Biliary Association and co-sponsored by the Society of Surgical Oncology and the Society for Surgery of the Alimentary Tract. The consensus document reviewed the four most widely used modalities for treating advanced disease: transarterial chemoembolization (TACE), sorafenib, external beam radiation therapy and microsphere radioembolization. The consensus on yttrium-90 microspheres includes the following:

- $^{90}$Y is a safe microembolization treatment and can be administered in the outpatient setting.
- $^{90}$Y could be considered for treating hepatocellular carcinoma in the following scenarios:
  - downstaging/bridging to transplantation or resection
  - portal vein thrombosis
  - advanced disease
- There are no level 1 data for $^{90}$Y compared to other regional therapies. Considerations of efficacy and safety (given cirrhosis) have to be made on an individual basis.

The National Institute for Health and Care Excellence (NICE) states that selective internal radiation therapy (SIRT) is a potentially beneficial treatment for patients with non-resectable colorectal metastases in the liver, but more research and data collection are required to demonstrate its efficacy. The evidence on its efficacy in chemotherapy-naive patients is inadequate in quantity. Clinicians should offer eligible patients who have not been previously treated by chemotherapy entry into well-designed research studies. For patients who are not eligible or who prefer not to enter a research trial, the procedure should be used with special arrangements for clinical governance, consent and audit. For patients who have previously been treated with chemotherapy, comparative trials are needed to determine whether SIRT prolongs survival compared with best standard treatment, and to determine its effect on quality of life. There is also a need to identify which subgroups of patients are likely to derive clinical benefit from SIRT (NICE, 2011).

The National Institute for Health and Care Excellence (NICE) states that current evidence on the efficacy and safety of selective internal radiation therapy (SIRT) for primary hepatocellular carcinoma is adequate for use with normal arrangements for clinical governance, consent and audit (NICE 2013b).
Liver Metastases from Neuroendocrine Tumors

The NCCN clinical practice guideline for neuroendocrine tumors lists hepatic regional therapy, such as radioembolization, as an option for treating unresectable liver metastases. The 2B recommendation is based on lower-level evidence, although there is consensus among NCCN panel members that the intervention is appropriate (NCCN, 2013b).

Yang et al. (2012) systematically reviewed the clinical efficacy and safety of the use of hepatic arterial chemoembolization, bland embolization and radioembolization in the treatment of unresectable neuroendocrine tumor liver metastases (NETLM). Response to treatment, survival outcome and toxicity were examined in 37 studies that included 1575 patients. The authors concluded that these therapies are safe and effective in the treatment of NETLM. According to the authors, prospective clinical trials are needed to compare the relative efficacy and toxicity of these treatments.

Memon et al. (2012) retrospectively reviewed long-term outcomes on the safety and efficacy of yttrium-90 ($^{90}$Y) radioembolization in the treatment of unresectable hepatic neuroendocrine metastases refractory to standard-of-care therapy. Forty patients with hepatic neuroendocrine metastases were treated with $^{90}$Y radioembolization at a single center. Clinical toxicities included fatigue (63%), nausea/vomiting (40%), abdominal pain (18%), fever (8%), diarrhea and weight loss (5%). Grade 3 and 4 bilirubin toxicities were experienced by 2 patients and 1 patient, respectively. Response to therapy was assessed by World Health Organization (WHO) guidelines for size and European Association for the Study of the Liver disease (EASL) guidelines for necrosis. Different responses were noted by WHO (complete response, 1.2%; partial response, 62.7%) and EASL (complete response, 20.5%; partial response, 43.4%). Median time to response was 4 and 4.9 months by lesion and patient, respectively. The 1-, 2-, and 3-year overall survival rates were 72.5%, 62.5%, and 45%, respectively. The authors concluded that $^{90}$Y therapy for hepatic neuroendocrine metastases leads to satisfactory tumor response and patient survival with low toxicity.

Paprottka et al. (2012) evaluated the safety, efficacy and symptom-control of radioembolization in patients with unresectable liver metastases from neuroendocrine tumors (NETLMs). Forty-two patients with treatment-refractory NETLMs underwent radioembolization using yttrium-90 ($^{90}$Y) resin microspheres. Imaging follow-up at 3-months demonstrated partial response, stable disease and progressive disease in 22.5, 75.0 and 2.5% of patients, respectively. In 97.5% of patients, the liver lesions appeared hypovascular or partially necrotic. The median decrease in tumor-marker levels at 3 months was 54.8% (chromogranin A) and 37.3% (serotonin), respectively. Improvement of clinical symptoms 3 months after treatment was observed in 36 of 38 symptomatic patients. The mean follow-up was 16.2 months with 40 patients (95.2%) remaining alive. The authors concluded that further investigation is warranted to define the role of radioembolization in the treatment paradigm for NETLMs.

Cao et al. (2010) assessed the efficacy of $^{90}$Y microsphere therapy for patients with unresectable neuroendocrine tumor liver metastases (NETLMs). Fifty-eight patients were included in a retrospective analysis, of which 51 were evaluable at follow-up. Six patients achieved a complete response, 14 a partial response, 14 had stable disease and 17 had disease progression. Overall survival rates at 1, 2 and 3 years were 86, 58 and 47 per cent respectively. Median survival was 36 months. Extent of tumor involvement, radiographic response to treatment, extrahepatic disease and tumor grade were significant prognostic factors for overall survival.

King et al. (2008) prospectively assessed the safety and efficacy of treatment with yttrium 90 ($^{90}$Y) radioactive microspheres (SIR Spheres) in 34 patients with unresectable neuroendocrine liver metastases (NETLMs). Selective internal radiation therapy (SIRT) was administered concomitantly with 5-fluorouracil. The neuroendocrine tumors were located in the bronchus (1), medullary thyroid (2), gastrointestinal tract (15), pancreas (8) and of unknown origin (8). The tumors were classified as vipoma (1), somatostatinoma (1), glucagonoma (2), large cell (3),
carcinoid (25), and unknown origin (2). Complications after radioembolization included abdominal pain, nausea, fever and lethargy. Two patients developed radiation gastritis, 1 patient developed a duodenal ulcer and there was 1 early death from liver dysfunction and pneumonia.

Symptomatic responses were observed in 18 of 33 patients (55%) at 3 months and in 16 of 32 patients (50%) at 6 months. Radiologic liver responses were observed in 50% of patients and included 6 (18%) complete responses and 11 (32%) partial responses, and the mean overall survival was 29.4 +/- 3.4 months). The authors concluded that radioembolization with $^{90}$Y resin microspheres can achieve relatively long-term responses in some patients with nonresectable NETLMs.

Kennedy et al. (2008) reported results from 148 patients (ten institutions) treated for unresectable liver metastases originating from a variety of neuroendocrine tumors (NET). All patients had previously completed treatment of the primary tumor and metastatic disease. The median follow-up was of 42 months. All patients were evaluated at least during the 6th and 12th week’s post-microsphere treatment. After 12 weeks, patients resumed a routine schedule of labs and imaging at 3-month intervals. Imaging response was stable in 22.7%, partial response in 60.5%, complete in 2.7% and progressive disease in 4.9%. There was no acute or delayed toxicity, with fatigue the most common side effect. The median survival is 70 months. The authors stated that in comparison to published reports of other local treatments in the liver for NETs, radioembolization has a similar safety profile, improvement in debulking of tumor and survival. Further prospective trials are desired.

Liver Metastases from Other Primary Sites

In a retrospective review of a prospectively collected database, Mouli et al. (2013) evaluated the safety, antitumoral response, and survival following yttrium-90 ($^{90}$Y) radioembolization for patients with unresectable intrahepatic cholangiocarcinoma (ICC). The study included 46 patients treated with $^{90}$Y radioembolization at a single institution during an 8-year period. Ninety-two treatments were performed, with a mean of two per patient. World Health Organization (WHO) imaging findings included partial response (n = 11; 25%), stable disease (n = 33; 73%), and progressive disease (n = 1; 2%). European Association for the Study of Liver Disease (EASL) imaging findings included partial/complete response (n = 33; 73%) and stable disease (n = 12; 27%). Survival varied based on presence of multifocal (5.7 months vs 14.6 months), infiltrative (6.1 months vs 15.6 months), and bilobar disease (10.9 months vs 11.7 months). Disease was converted to resectable status in five patients, who successfully underwent curative resection. The authors concluded that radioembolization with $^{90}$Y is safe and demonstrates antitumoral response and survival benefit in select patients with ICC. Results are most pronounced in patients with solitary tumors, for whom conversion to curative resection is possible. Study limitations included a weak study design including lack of comparisons with standard therapy.

Hoffman et al. (2012) treated 33 patients with unresectable intrahepatic cholangiocarcinoma (ICC), with $^{90}$Y resin-microspheres and assessed at 3-monthly intervals. Thirty-four treatments were administered to 33 patients without major complications. Twelve patients had a partial response, 17 had stable disease and 5 had progressive disease after 3 months. The median overall survival (OS) was 22 months post-treatment and 43.7 months post-diagnosis. Median time-to-progression (TTP) was 9.8 months. The authors concluded that radioembolization is an effective and safe option for patients with unresectable ICC. The authors concluded that while promising, this treatment warrants further investigation. The study is limited by its retrospective design, small sample size, and lack of randomization into a treatment group and a control group.

The National Institute for Health and Care Excellence (NICE) states that current evidence on the safety and efficacy of selective internal radiation therapy (SIRT) for primary intrahepatic cholangiocarcinoma is limited in both quantity and quality. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research (NICE 2013a).
Kucuk et al. (2011) evaluated the success of selective intraarterial radionuclide therapy (SIRT) with yttrium-90 (90Y) microspheres in liver metastases of different tumors. Seventy-eight patients (49 M; 29 F; mean age: 62.4 ± 2.3 years) received intraarterial radionuclide therapy with 90Y microspheres for liver metastasis or primary hepatocellular carcinoma (HCC). Twenty-five patients had primary HCC. The remaining patients had unresectable multiple liver metastases of different cancers (35 colorectal, 7 gastric, 4 breast, 1 pancreas, 1 renal cell, 1 esophagus cancer, 3 neuroendocrine tumor and 1 malignant melanoma). Treatment response was evaluated by fluorine-18 fluorodeoxyglucose (F18-FDG) positron emission tomography/computed tomography (PET/CT) six weeks after treatment. Patients were divided into two groups according to the disease stage; those with only liver metastases (H) and those with metastases in other organs (EH). In the evaluation of treatment response, 43(55%) patients were responders (R) and 35 (45%) patients were non-responders (NR). The mean overall survival time of the R group was calculated as 25.63 ± 1.52 months and the NR group’s 20.45 ± 2.11. The mean overall survival time of the H group was computed as 25.66 ± 1.52 months and the EH group’s 20.76 ± 1.97. The authors concluded that SIRT is a useful treatment method which can contribute to the lengthening of survival times in patients with primary or metastatic unresectable liver malignancies. F18-FDG PET/CT is seen to be a successful imaging method in evaluating treatment response for predicting survival times in this patient group. Larger, prospective, randomized studies are needed to confirm these results.

Cao et al. (2010) examined the safety and efficacy of radioembolization with yttrium-90 microspheres for patients with liver metastases from pancreatic adenocarcinomas. After radioembolization, follow-up abdominal computed tomography scans were performed to assess response. Of the seven patients identified, five had available computed tomography follow-up. Two patients achieved a partial response and 1 had stable disease. One patient with partial response survived for nearly 15 months after radioembolization therapy. No patient experienced major post-radioembolization complications. The authors concluded that radioembolization with yttrium-90 microspheres may have a useful role in treating patients with pancreatic carcinoma liver metastases in a multimodality setting. Results of the current study warrant further investigation of this novel treatment.

Smits et al. (2013) provided a systematic overview of the current literature concerning yttrium-90 microspheres ((90)Y-RE) for breast cancer liver metastases (BCLM) patients. Six studies were included for analysis, with a total of 198 patients. Tumor response was scored in five studies using either Response Evaluation Criteria In Solid Tumors (RECIST) (n=3) or World Health Organization (WHO) criteria (n=2). Overall disease control rates (complete response, partial response and stable disease) at 2-4 months post treatment ranged from 78% to 96%. Median survival, available in four studies, ranged from 10.8 to 20.9 months. In total, gastric ulceration was reported in ten patients (5%) and treatment related mortality in three patients (2%). The authors concluded that the results from the analyzed studies consistently show that (90)Y-RE is a safe and effective treatment option for BCLM patients. According to the authors, well designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes of (90)Y-RE for BCLM patients.

In a retrospective review, Kennedy et al. (2009) reported the first results of yttrium-90 microspheres for treating ocular melanoma with liver metastases and rapid progression despite aggressive therapy. Eleven patients received 12 treatments and toxicity was minimal. PET/CT at 3 months post treatment showed a response in all patients with 1 patient showing a complete response. Further prospective studies are needed to confirm these initial results.

Sato et al. (2008) performed radioembolization on 137 patients with non-resectable liver metastases who had failed standard of care polychemotherapy. Primary sites origins of malignancy included colon (n=51), breast (n=21), neuroendocrine (n=19), and others. Clinical toxicities included fatigue (56%), vague abdominal pain (26%), and nausea (23%). At follow-up imaging, according to World Health Organization (WHO) criteria, there was a 42.8% response rate (2.1% complete response, 40.7% partial response). There was a biologic tumor response,
defined as any decrease in tumor size, of 87%. Differences in survival were seen with different tumor type, ECOG performance status, tumor burden, imaging findings (hypovascular or hypervascular tumors at angiography and cross-sectional imaging), and number of tumors. Median survival rate for patients with colorectal cancer, neuroendocrine tumors, and noncolorectal, nonneuroendocrine tumors were 457, 776, and 207 days, respectively. Survival differences by tumor type were not statistically significant.

Miller et al. (2007) conducted a retrospective review of 42 patients with unresectable liver metastases. The primary tumors included colorectal (n = 18), breast (n = 5), neuroendocrine (n = 7), renal cell (n = 2), esophageal (n = 2), sarcoma (n = 1), melanoma (n = 1), cholangiocarcinoma (n = 1), duodenal (n = 1), ovarian (n = 1), lung (n = 1), bladder (n = 1), and squamous cell carcinoma of the skin (n = 1). CT response was determined using traditional size criteria WHO and RECIST, necrosis criteria, and combined criteria (RECIST and necrosis). We compared the response on CT with the response on PET. In responding patients, the median time to response was 116 days by RECIST, 68 days by WHO criteria, 29 days by necrosis criteria, and 34 days by combined criteria. The response rate was 19% (8/42) by WHO criteria, 24% (10/42) by RECIST, 45% (19/42) by necrosis criteria, and 50% (21/42) by combined criteria. Stabilization of lesion size occurred in 50% of patients. Necrosis and combined criteria identified responders earlier than RECIST and WHO criteria.

Sato et al. (2006) prospectively evaluated the use of TheraSpheres on 19 unresectable HCC patients and 11 metastatic diseases. Tumor etiology for the metastatic lesions prior to treatment included three neuroendocrine tumors, two malignant melanomas, and one each from lung, colon, esophagus, pancreas, duodenal, and cholangiocarcinoma primary sources. Repeat diagnostic studies (CT or MRI) were performed to assess tumor response. The WHO, RECIST, and EASL tumor response criteria were used to assess the response to treatment during follow-up. Median and mean imaging follow-up times were 95 and 132 days, respectively. The objective tumor response rates for all patients were 24%, 31%, and 72% for WHO, RECIST, and EASL criteria, respectively. All of the patients tolerated the procedure without complications and were treated on an outpatient basis, and four patients had evidence of postembolization syndrome.

Professional Societies
Radioembolization Brachytherapy Oncology Consortium (REBOC)
In 2007, REBOC, an independent group of experts from the fields of interventional radiology, radiation oncology, nuclear medicine, medical oncology and surgical oncology issued clinical guidelines for 90Y microsphere brachytherapy with the purpose to standardize the indications, techniques, multimodality treatment approaches and dosimetry to be used for 90Y microsphere hepatic brachytherapy. The recommendations state that success in treatment of tumors in the liver by radioembolization relies on the presence of appropriate indications to ensure that patients receive safe and effective therapy. Because the nature of primary and secondary hepatic malignancies differs, therapy should be tailored to the disease. Patients with hepatic metastases from primary sites other than colorectal should be offered standard systemic treatment options with known survival benefit before 90Y treatment. In the case of primary liver tumors, patients should undergo a thorough evaluation to determine the optimal treatment strategy.

Key findings include the following:

- Sufficient evidence exists to support the safety and effectiveness of 90Y microsphere therapy in selected patients.
- Candidates for radioembolization are patients with unresectable primary or metastatic hepatic disease with liver-dominant tumor burden and a life expectancy >3 months.
- In metastatic colorectal cancer, radioembolization therapy can be given (1) alone after failure of first-line chemotherapy, (2) with floxuridine (FUDR) during first-line therapy or (3) during first- or second-line chemotherapy on a clinical trial.
- Initiation of clinical trials is essential to further define the safety and role of 90Y microspheres in the context of currently available therapies (Kennedy, 2007).
**American College of Radiology (ACR)**

In a joint guideline with the American Society for Radiation Oncology (ASTRO) and the Society of Interventional Radiology (SIR), ACR states that indications for radioembolization with microspheres include, but are not limited to:

- The presence of unresectable and/or medically inoperable primary or secondary liver malignancies. The tumor burden should be liver dominant, not necessarily exclusive to the liver. Patients should also have a performance status that will allow them to benefit from such therapy, i.e., an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 or Karnofsky Performance Status (KPS) of 70 or more.
- A life expectancy of at least three months (ACR, 2008).

ACR appropriateness criteria on the radiologic management of hepatic malignancies rated selective internal radiation therapy (a broad category that includes radioembolization with $^{90}\text{Y}$ microspheres) as a 5 for solitary hepatocellular tumors less than 3 cm in diameter, 7 for solitary hepatocellular tumors 5 cm in diameter and 7 for more than one hepatocellular tumor with at least one greater than 5 cm in diameter. Ratings of 4, 5 and 6 represent a treatment that may be appropriate and ratings of 7, 8 and 9 represent a treatment that is usually appropriate (ACR, 2011).

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

The FDA has approved two commercial forms of $^{90}\text{Y}$ microspheres; TheraSphere and SIR-Spheres.

SIR-Spheres (Sirtex Medical) are resin $^{90}\text{Y}$ microspheres and are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of floxuridine (FUDR). SIR-Spheres received FDA premarket approval (P990065) on March 5, 2002. Additional information is available at:


TheraSphere (Nordion) are glass $^{90}\text{Y}$ microspheres and are indicated 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. Glass $^{90}\text{Y}$ microspheres are approved by the FDA under the provisions of a Humanitarian Device Exemption (H980006). Additional information is available at:


The use of TheraSphere and SIR-Spheres is also regulated by the United States Nuclear Regulatory Commission (U.S. NRC), which grants a license for the use of these products. See the following guidance for further information:


**CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**

Medicare does not have a National Coverage Determination (NCD) for implantable beta-emitting microspheres used in the treatment of malignant tumors. Local Coverage Determinations (LCDs) do exist. Refer to the LCDs for Selective Internal Radiation Therapy (SIRT) for Primary and Secondary Hepatic Malignancy (90Y-Microsphere Hepatic Brachytherapy) and Radiopharmaceutical Agents. (Accessed September 30, 2013)
The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

<table>
<thead>
<tr>
<th>CPT® Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>37243</td>
<td>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</td>
</tr>
<tr>
<td>79445</td>
<td>Radiopharmaceutical therapy, by intra-arterial particulate administration</td>
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</table>

CPT® is a registered trademark of the American Medical Association.

<table>
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<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tr>
<td>S2095</td>
<td>Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres</td>
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</table>

REFERENCES


Implantable Beta-Emitting Microspheres for Treatment of Malignant Tumors: Medical Policy (Effective 07/01/2014)

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<tr>
<td>07/01/2014</td>
<td>• Updated list of applicable CPT codes; added 37243</td>
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<td></td>
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