RADIOACTIVE MICROSPHERES EMBOLIZATION FOR TREATMENT OF MALIGNANT TUMORS
(SIR-Spheres® or TheraSphere®)

Policy Number: 2014M0072A  Effective Date: January 1, 2015

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INSTRUCTIONS:

“Medical Policy assists in administering UCare benefits when making coverage determinations for members under our health benefit plans. When deciding coverage, all reviewers must first identify enrollee eligibility, federal and state legislation or regulatory guidance regarding benefit mandates, and the member specific Evidence of Coverage (EOC) document must be referenced prior to using the medical policies. In the event of a conflict, the enrollee’s specific benefit document and federal and state legislation and regulatory guidance supersede this Medical Policy. In the absence of benefit mandates or regulatory guidance that govern the service, procedure or treatment, or when the member’s EOC document is silent or not specific, medical policies help to clarify which healthcare services may or may not be covered. This Medical Policy is provided for informational purposes and does not constitute medical advice. In addition to medical policies, UCare also uses tools developed by third parties, such as the InterQual Guidelines®, to assist us in administering health benefits. The InterQual 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. Other Policies and Coverage Determination Guidelines may also apply. UCare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary and to provide benefits otherwise excluded by medical policies when necessitated by operational considerations.”
POLICY DESCRIPTION:

This medical policy describes intrahepatic microsphere radiation (IMR) therapy or Selective Internal Radiation Therapy (SIRT), also known as radioembolization, a palliative liver cancer therapy that consists of millions of small glass microspheres containing radioactive Y-90 targeted directly to the tumor. The Y-90 microsphere administration is a nonsurgical, minimally invasive procedure, used to treat inoperable primary and secondary liver cancer. The product is injected by physicians into the artery of the patient's liver through a catheter, which allows the treatment to be delivered directly to the tumor via blood flow.

SIRT has been used to treat or palliate unresectable primary liver cancer (e.g., hepatocellular carcinoma) and metastatic liver tumors.

COVERAGE RATIONALE / CLINICAL CONSIDERATIONS:

Selective internal radiation therapy (SIRT) or Intrahepatic Microsphere Radiation (IMR) therapy, also known as Yttrium-90 (90Y) microsphere radioembolization (SIR-Spheres® or TheraSphere®), may be considered MEDICALLY NECESSARY for the following indications:

1. As palliative treatment for individuals with unresectable metastatic liver tumors from primary colorectal cancer (CRC), with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (floxuridine), as noted in the FDA labeled indications.

2. As palliative treatment for individuals with unresectable metastatic liver tumors from neuroendocrine tumors (e.g., carcinoid tumors, pancreatic islet cell tumors, parathyroid adenomas, pituitary adenomas), when systemic therapy has failed to control symptoms such as carcinoid syndrome.

3. As radiation treatment, neoadjuvant to surgery, or as a bridge to liver transplantation in individuals with unresectable primary hepatocellular carcinoma (HCC), when all of the following criteria are met for either indication:
   - Preserved liver function, and
   - Three or fewer encapsulated nodules (each nodule is less than five centimeters in diameter), and
   - No evidence of extra-hepatic metastases, and
   - No evidence of severe renal function impairment, and
   - No evidence of portal vein occlusion.

Note: Limited evidence suggests that treatment with intrahepatic microsphere radiation therapy might shrink tumors that exceed(s) five centimeters in maximal diameter and relieve symptoms in some patients, sometimes enough to render some inoperable tumors operable. However, limited available evidence has not shown improved quality of life or survival.

Intrahepatic Microsphere Radiation (IMR) therapy (SIR-Spheres® or TheraSphere®) is considered EXPERIMENTAL AND/OR INVESTIGATIONAL and NOT MEDICALLY NECESSARY for all other indications.
Clinical Considerations:

Contraindications:
- Pre-treatment 99mTc macro-aggregated albumin (MAA) scan demonstrating the potential of 30 Gy radiation exposure to the lung or flow to the gastrointestinal tract that cannot be corrected by catheter techniques
- Limited hepatic reserve
- Irreversibly elevated bilirubin levels
- Compromised portal vein (unless selective or superselective radioembolization can be performed)
- Prior radiation therapy involving the liver

Complications:
- Lymphopenia (61%)
- Fatigue (9% to 55%)
- Abdominal pain, discomfort, or cramping (5% to 29%)
- Fever (6% to 15%)
- Nausea and/or vomiting (2% to 32%)
- Biliary necrosis (1.6%)
- Radiation-induced cholecystitis (0.6%)
- Biliary stricture (2.4%)
- Leaks and spills (1.9% to 4.8%)
- Product defect and operator error (5.7% and 8.7%)

BACKGROUND:

Hepatic tumors can arise either as primary liver cancer or by metastasis to the liver from other organs. Primary liver cancers are largely adenocarcinomas, with 2 major cell types: hepatocellular (liver cell carcinoma) and cholangiocarcinoma (intrahepatic cholangiocarcinoma). Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, accounting for approximately 90% of cases (NCI, 2014). HCC is the sixth most common cause of cancer death in men and women combined. Untreated unresectable disease has a median survival of 3 to 6 months and a 5-year survival rate of < 5%. Estimated new cases and deaths from primary liver cancer and intrahepatic bile duct cancer in the United States in 2014 are 33,190 and 23,000, respectively. Incidence and mortality rates are approximately twice as high in African Americans as in white Americans. Factors that contribute to the development of primary liver cancer include cirrhosis of the liver due to chronic viral hepatitis B and C and/or alcohol abuse and exposure to naturally occurring or industrial carcinogens.

There are 4 established treatment options for HCC: resection, transplantation, ablation, and embolization. The treatment options are determined by tumor stage and the degree of liver impairment.

The preferred treatment for liver tumors is local surgical excision with tumor-free margins. Unfortunately, at the time of diagnosis, most liver tumors, whether primary or from metastases, are unresectable due
either to: their anatomic location, size, and number of lesions; concurrent nonmalignant liver disease; insufficient hepatic reserve; or are too advanced, thus making surgery potentially unsafe and inadvisable. For inoperable liver tumors, physicians may recommend chemotherapy palliative treatments to reduce pain and improve quality of life.

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

One of these therapies, Intrahepatic Microsphere Radiation Therapy (IMRT) or Selective Internal Radiation Therapy (SIRT), also known as radioembolization, is a palliative treatment for inoperable liver tumors designed to inhibit tumor growth and preserve remaining liver function by delivering radiation locally.

Candidates for SIRT are initially examined by hepatic angiogram to identify and map the hepatic arterial system and at that time a mixture of albumin particles are 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.

During SIRT, 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 (90Y). 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. Patients tolerate 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.

SIRT has been used to treat primary liver cancer (e.g., hepatocellular carcinoma) and metastatic liver tumors. The majority of liver tumors have metastasized from another organ, most often the colon. In some cases, SIRT has been reported to shrink tumors enough to allow patients to become good candidates for tumor excision surgery or liver transplantation.

There are currently 2 commercially available beta-emitting microsphere devices, in which yttrium-90 (90Y) is incorporated: 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 (e.g., resin vs. glass), and size of commercially available doses. These 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-fluorouridine (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.

REGULATORY STATUS:

1. U.S. FOOD AND DRUG ADMINISTRATION (FDA):

The use of 90Y microspheres for the treatment of primary unresectable liver cancer is a procedure and, therefore, not subject to FDA regulation. However, any medical devices, drugs, biologics, or tests used as a part of this procedure may be subject to FDA regulation.

**SIR-Spheres® (Sirtex Medical Ltd.):** The FDA issued premarket approval (PMA) (P990065) for the SIR-Spheres® on March 5, 2002 as a Class III device under the Product Code NAW (Radionuclide Microsphere) in combination with floxuridine intrahepatic artery chemotherapy, for the treatment of unresectable metastatic liver tumors from primary colorectal cancer. Three supplemental approvals have been issued for manufacturing and labeling changes since the original approval, with the most recent (P990065 S006) on July 17, 2012.


**TheraSphere® (MDS Nordion Inc.):** The FDA issued Humanitarian Device Exemption (HDE) (H980006) status for the TheraSphere® on December 10, 1999. TheraSphere® is 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. TheraSphere® is also indicated for hepatocellular carcinoma patients with partial or branch portal vein thrombosis or occlusion.


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.


2. CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS):

No National Coverage Determination (NCD) for the use of 90Y microspheres for the treatment of unresectable liver cancer was identified on the CMS website. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

3. MINNESOTA DEPARTMENT OF HUMAN SERVICES (DHS):

Minnesota DHS does not have a policy statement regarding the use of 90Y microspheres for the treatment of unresectable liver cancer in its Provider Manual or other specific provider references.

CLINICAL EVIDENCE:

1. EXTERNAL SOURCES/ GROUPS POLICY:

**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 90Y 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).

**The National Comprehensive Cancer Network (NCCN):** 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, 2012a).

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, 2013a; NCCN 2013b).

**SUMMARY:**

Most studies addressing the use of SIRT for hepatic tumors are uncontrolled and have relatively short-term follow-up. However, there is some evidence that yttrium-90 (90Y) microsphere therapy may offer a safe palliative treatment for unresectable primary liver cancer, provided patients are selected appropriately and target delivery is performed meticulously. The treatment was associated with favorable tumor response rates with a low toxicity profile, and a potential survival benefit. There is also some evidence that for a small part of the patient population, this therapy can be used to bridge and downstage patients to resection, ablation or transplantation. In addition, 90Y microsphere therapy seemed to be safe for patients with portal vein thrombosis, who are generally excluded from other embolic liver-directed intra-arterial therapies. However, the encouraging findings of these studies must be considered in the context of the limitations of the reported studies. There have been no direct comparisons of 90Y microsphere therapy with existing therapies for unresectable hepatocellular carcinoma to confirm efficacy and potential survival benefits. Moreover, the quality of evidence from the selected studies was weakened by retrospective stratification of patient groups, small study sizes, a heterogeneous study population and a limited number of treatment centers (Hayes, 2008a; updated 2012).

The strength of selective internal radiation therapy (SIRT) with 90Y microspheres is the high dose of targeted radiation that can be delivered to liver tumors while sparing normal liver tissue. The selected studies provide some evidence of high tumor response rates among patients with unresectable hepatic metastases. SIRT appears to be most promising for patients who had failed all available treatment options for metastatic liver cancer. In addition, as adjunct treatment of chemotherapy, SIRT appeared to increase response and survival rates compared with chemotherapy alone. Although 90Y microsphere therapy was well tolerated by the liver, occasional serious adverse events associated with inadvertent delivery of microspheres to the gastroduodenum were reported, despite careful planning and proper techniques.

Most studies lacked a comparative arm, which limits the conclusions that can be drawn regarding equivalence or superiority of this treatment as a nonsurgical therapy for secondary liver cancer. Comparing this treatment modality with alternative approaches is hampered by differences in patient selection criteria for each treatment, lack of alternative treatments for this patient population, and ethical restrictions.

There were several other factors that weakened the overall quality of evidence regarding 90Y microsphere, including retrospective stratification of patient groups and analysis of data, small sample sizes, single-center experiences, lack of controlled treatment protocol, use of nonuniform tumor response assessment criteria, and the heterogeneous study population (Hayes, 2008b; updated 2012).
### APPLICABLE CODES:

The Current Procedural Terminology (CPT®) codes and HCPCS 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. The inclusion of a code does not imply any right to reimbursement or guarantee claims payment. Other medical policies and coverage determination guidelines may apply.

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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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<th>ICD-9 Codes</th>
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<tr>
<td>92.15</td>
<td>Malignant neoplasm of liver, primary</td>
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<tr>
<td>99.25</td>
<td>Malignant neoplasm of intrahepatic bile ducts</td>
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<tr>
<td>155.0</td>
<td>Malignant neoplasm of liver, not specified as primary or secondary</td>
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<tr>
<td>209.70-209.79</td>
<td>Secondary neuroendocrine tumors</td>
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<td>251.0-251.2</td>
<td>Hypoglycemia</td>
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<td>251.4-251.9</td>
<td>Abnormality of secretion of glucagon, gastrin (Zollinger-Ellison syndrome), other disorders of pancreatic internal secretion</td>
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<td>259.2</td>
<td>Malignant neoplasms</td>
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<tr>
<td>209.00-209.36</td>
<td>Malignant carcinoid tumors</td>
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<td>140.0-199.2</td>
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<td>209.70-209.79</td>
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<td>Malignant neoplasms</td>
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<td>E16.0-E16.2</td>
<td>Drug-induced, other and unspecified hypoglycemia</td>
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<td>E16.4</td>
<td>Increased secretion of gastrin (Zollinger-Ellison syndrome)</td>
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<th>CPT® Codes</th>
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<tr>
<td>37204</td>
<td>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</td>
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<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>
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<tr>
<td>79445</td>
<td>Radiopharmaceutical therapy, by intra-arterial particulate administration</td>
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