



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject **Radioembolization with Yttrium-90 (⁹⁰Y) Microspheres**

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Coverage Policy

CIGNA covers yttrium-90 (90Y) microsphere radioembolization (SIR-Spheres® or TheraSpheres®) as medically necessary for ANY of the following indications:

- unresectable metastatic liver tumors from primary colorectal cancer (CRC)
- unresectable liver-only or liver-dominant metastases from neuroendocrine tumors (NET) (e.g., carcinoid, islet cell tumor/pancreatic endocrine tumor)
- unresectable primary hepatocellular carcinoma (HCC)

CIGNA does not cover ⁹⁰Y microsphere radioembolization for any other indication because it is considered experimental, investigational or unproven.

General Background

Treatment options for primary or secondary liver cancer may include surgery, ablation, embolization, targeted therapy, radiation therapy, and chemotherapy. At the time of diagnosis, most hepatic tumors, whether primary or from metastases, are usually unresectable, and chemotherapy is generally provided only as a palliative measure. Prognosis is usually poor and depends on the degree of local tumor replacement and the extent of liver function impairment. A few patients may be candidates for liver transplantation, but the limited availability of livers for transplantation restricts the use of this approach.

Embolization therapy may include chemoembolization, bland embolization, or radioembolization and were developed as alternatives to conventional therapies such as systemic chemotherapy for the treatment of liver cancer. Bland embolization is the injection of an embolic agent only. Chemoembolization, also referred to transcatheter arterial chemoembolization (TACE), involves the injection of a chemotherapy agent then an embolic material. Radioembolization is the intra-arterial (hepatic artery) injection of an embolic agent and radioactive isotope yttrium-90 (⁹⁰Y) in a resin or glass microsphere.

Radioembolization, also called selective internal radiation therapy (SIRT), is designed to inhibit tumor growth and preserve remaining liver function. It may shrink tumors enough to allow patients to become good candidates for tumor excision surgery or liver transplantation. This therapy is used to treat both primary and metastatic liver tumors. Radioembolization is not a curative treatment, but patients benefit by extending their lives and improving their quality of life. Careful evaluation of the arterial anatomy of each patient's liver must occur prior to radioembolization because non-target embolization can result in serious injury. It is generally performed on an outpatient basis and is reported comparable to TACE in safety and efficacy (Carr, et al., 2010).

U.S. Food and Drug Administration (FDA)

⁹⁰Y microsphere products are available in two forms, resin and glass:

- Resin ⁹⁰Y microspheres (SIR-Spheres[®], Sirtex Medical, Lane Cove, Australia) have received FDA premarket approval for unresectable liver metastases from colorectal cancer, with adjuvant intrahepatic artery chemotherapy of fluorodeoxyuridine (FUdR).
- Glass ⁹⁰Y microspheres (TheraSphere[®], MDS Nordion, Kanata, Canada) are approved by the FDA under the provisions of a "Humanitarian Device Exemption" for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters. In January 2007, the HDE for TheraSpheres was expanded to include patients with hepatocellular carcinoma who have partial or branch portal vein thrombosis and have been identified as suitable candidates by their physicians.

Literature Review

Vente et al. (2009) conducted a meta-analysis on tumor response and survival in patients who underwent ⁹⁰Y radioembolization. Thirty articles (n=1217 patients) were included in the meta-analysis. The proportion of 'any response' (AR) for HCC and liver mCRC combined, varied between 0.29 and 1.00 with a median value of 0.82. Treatment with glass microspheres showed a lower response (AR=0.77) than treatment with resin microspheres (AR=0.85) (p=0.07). The AR category comprises all patients originally from the categories complete response, partial response, and stable disease. Vente et al. noted that complications have been reported when microspheres were inadvertently deposited in excessive amounts in organs other than the liver. For liver mCRC, in a salvage setting, response was 79% for ⁹⁰Y radioembolization combined with 5-fluorouracil/leucovorin (5-FU/LV), and 79% when combined with 5-FU/LV/oxaliplatin or 5-FU/LV/irinotecan, and in a first-line setting 91% and 91%, respectively. For HCC, response was 89% for resin microspheres and 78% for glass microspheres. In patients with liver mCRC, the tumor response of ⁹⁰Y radioembolization is high, with AR rates of approximately 80% in a salvage setting, and over 90% when used as first-line treatment, as neoadjuvant to chemotherapy. Resin (SIR-Spheres) microspheres were significantly more effective in treating HCC than glass (Theraspheres) microspheres (AR 89% vs. 78% [p=0.02]). Vente et al. stated that this was a rather unexpected finding, because only the glass microspheres are FDA-approved for treating HCC, whereas the resin microspheres are approved for liver mCRC, not HCC. For liver mCRC, median survival after ⁹⁰Y-RE, irrespective of differences in determinants (microspheres type, chemotherapy protocol, and stage: salvage or first-line), varied from 6.7 to 17.0 months. The reported median survival from diagnosis of liver mCRC ranged from 10.8 to 29.4 months. For 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 author concluded that ⁹⁰Y radioembolization is associated with high response rates, both in salvage and first-line settings; noting true impact on survival will only become known after publication of Phase III studies.

Evidence in the published, peer-reviewed scientific literature suggests ⁹⁰Y radioembolization is safe and effective in patients with: unresectable metastatic liver tumors from primary colorectal cancer (CRC) (Hendlisz, et al., 2010; Cianni, et al., 2010; Kennedy, et al., 2009; Mulcahy, et al., 2009; Hong, et al., 2009; Sato, et al., 2008; Miller, et al., 2007; Kennedy, et al., 2006; Lim, et al., 2005; Van Hazel, et al., 2004; Gray, et al., 2001; Stubbs, et al., 2001); unresectable liver-only or liver-dominant metastases from neuroendocrine tumors (NET) (e.g., carcinoid, islet cell tumor/pancreatic endocrine tumor) (Cao, et al., 2010; Kennedy, et al., 2009; Kennedy, et al., 2008; Sato, et al., 2008; Rhee, et al., 2008); and unresectable hepatocellular carcinoma (HCC) (Salem, et al., 2010; Atassi, et al., 2008; Kulik, et al., 2008; Kulik, et al., 2006; Sato, et al. 2006; Salem, et al., 2005; Goin, et al., 2005; Carr, et al., 2004; Geschwind, et al., 2004; Dancey, et al., 2000; Lau, et al., 1998).

Liver Metastases From Primary Sites Other Than Colorectal or Neuroendocrine: There is insufficient evidence in the peer-reviewed scientific literature to support the safety and effectiveness of ⁹⁰Y microsphere radioembolization for liver metastases from any primary site other than colorectal or neuroendocrine, including but not limited to breast cancer, cholangiocarcinoma, and pancreatic cancer (Sato, et al., 2008; Atassi, et al., 2008; Coldwell, et al., 2007). Although the studies reported tumor response and/or survival, they are primarily very small retrospective reviews involving various, mixed types of primary cancers with short-term follow-ups.

Professional Societies/Organizations

National Comprehensive Cancer Network[®] (NCCN[®]): The NCCN Clinical Practice Guideline in Oncology[™] for Hepatobiliary Cancers (v.1.2011) states under HCC Principals of Locoregional Therapy, "All tumors irrespective of their location may be amenable to embolization (chemoembolization, bland embolization, radioembolization) provided that the arterial blood supply to the tumor may be isolated without non-target embolization." Under HCC heading, the NCCN states that general patient selection criteria for embolization procedures include unresectable/inoperable disease with tumors not amenable to ablation therapy only, and the absence of extrahepatic disease. Patients with unresectable/inoperable disease who are eligible to undergo embolization therapy and have tumor lesions > 5 centimeters (cm), should be treated using arterial embolic approaches; whereas those patients with lesions 3 – 5 cm can be considered for combination therapy with ablation and arterial embolization.

The NCCN Guidelines[™] for Colon Cancer (v.3.2011) state there was no consensus of the panel regarding the use of radioembolization. A number of non-extirpative liver-directed therapies exist, although their role in the treatment of colorectal metastases is controversial. These therapies include radioembolization and external beam radiation therapy. The NCCN Guidelines[™] for Rectal Cancer (v.4.2011) state a number of non-extirpative liver-directed therapies are available for the treatment of unresectable metastatic disease in highly selected patients, although the role of such therapies of colorectal metastases is controversial.

The NCCN Guidelines[™] for Neuroendocrine Tumors (v.2.2010) list radioembolization as one of several options under carcinoid tumor for unresectable liver metastases and under islet cell tumors for incurable liver metastases with dominant metastases.

American College of Radiology (ACR): The ACR Practice Guideline for Radioembolization with Microsphere Brachytherapy Device (RMBD) for Treatment of Liver Malignancies (2008) states indications 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

Radioembolization Brachytherapy Oncology Consortium (REBOC): REBOC is an independent group of experts from the fields of interventional radiology, radiation oncology, nuclear medicine, medical oncology, and surgical oncology involved with ⁹⁰Y microsphere therapy. They convened in 2006 and published a consensus panel report in 2007 (Kennedy, et al., 2007). Specifically, the consortium states that patients considered for radioembolization therapy would include those with (1) unresectable hepatic primary or metastatic cancer, (2) liver-dominant tumor burden, and (3) a life expectancy of at least 3 months. In metastatic colorectal cancer,

radioembolization therapy can be given (1) alone after failure of first-line chemotherapy, (2) with FUDR during first-line therapy, or (3) during first- or second-line chemotherapy on a clinical trial. It should be noted that the American College of Radiation Oncology, American Brachytherapy Society, Society of Interventional Radiologists, Society of Nuclear Medicine, and the Cardiovascular and Interventional Radiologic Society of Europe had representatives in the panel; however, “the report represents the opinions of the individual panel members and does not necessarily imply an official endorsement by the represented societies.”

Summary

The evidence in the published, peer-reviewed scientific literature supports the safety and effectiveness of yttrium-90 (⁹⁰Y) radioembolization for the treatment of unresectable metastatic liver tumors from primary colorectal cancer (CRC), unresectable liver-only or liver-dominant metastases from neuroendocrine tumors (NET) (e.g., carcinoid, islet cell tumor/pancreatic endocrine tumor), and unresectable primary hepatocellular carcinoma (HCC). There is currently insufficient evidence in the peer-reviewed literature evaluating ⁹⁰Y radioembolization for use in any other indication. Tumor response and/or survival results specific to radioembolization for liver metastases other than from colorectal and neuroendocrine primary cancers, remain unknown.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT ^{®*} Codes	Description
37204	Transcatheter occlusion or embolization (eg, for tumor destruction, to achieve hemostasis, to occlude a vascular malformation), percutaneous, any method, non-central nervous system, non-head or neck
79445	Radiopharmaceutical therapy, by intra-arterial particulate administration

HCPCS Codes	Description
C2616	Brachytherapy source, non-stranded, yttrium-90, per source
S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres

ICD-9-CM Diagnosis Codes	Description
155.0	Malignant neoplasm of liver and intrahepatic bile ducts. Liver; primary
155.2	Malignant neoplasm of liver and intrahepatic bile ducts, Liver, not specified as primary or secondary
197.7	Secondary malignant neoplasm of respiratory and digestive systems, Liver; specified as secondary
209.72	Secondary neuroendocrine tumor of liver

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
	All other codes

*Current Procedural Terminology (CPT[®]) © 2010 American Medical Association: Chicago, IL.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	5/15/2008	0081	Selective Internal Radiation Therapy (SIRT)

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