



EFFECTIVE DATE: 10|06|2009

POLICY LAST UPDATED: 08|16|2023

OVERVIEW

Radioembolization (RE), also referred to as selective internal radiotherapy, delivers small beads (microspheres) impregnated with yttrium 90 intra-arterially via the hepatic artery. The microspheres, which become permanently embed, are delivered to tumors preferentially because the hepatic circulation is uniquely organized, whereby tumors greater than 0.5 cm rely on the hepatic artery for blood supply while the normal liver is primarily perfused via the portal vein. Radioembolization has been proposed as a therapy for multiple types of primary and metastatic liver tumors.

MEDICAL CRITERIA

Radioembolization may be considered medically necessary as a treatment for any of the following:

- Primary hepatocellular carcinoma that is unresectable and limited to the liver.
- In primary hepatocellular carcinoma as a bridge to liver transplantation.
- Hepatic metastases from neuroendocrine tumors (carcinoid and noncarcinoid) with diffuse and symptomatic disease when systemic therapy has failed to control symptoms.
- Unresectable hepatic metastases from colorectal carcinoma, melanoma (ocular or cutaneous), or breast cancer that are both progressive and diffuse, in individuals with liver-dominant disease who are refractory to chemotherapy or are not candidates for chemotherapy.
- Primary intrahepatic cholangiocarcinoma in individuals with unresectable tumors.

PRIOR AUTHORIZATION

Prior authorization is required for Medicare Advantage Plan members and recommended for Commercial products.

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

Radioembolization is considered medically necessary when the medical criteria have been met.

Radioembolization is considered not covered for Medicare Advantage Plans and not medically necessary for Commercial products for all other indications.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for the applicable radiology benefits.

BACKGROUND

Treatments for Hepatic and Neuroendocrine Tumors

The use of external beam radiotherapy and the application of more advanced radiotherapy approaches (e.g., intensity-modulated radiotherapy) may be of limited use in patients with diffuse, multiple lesions due to the low tolerance of the normal liver to radiation compared with the higher doses of radiation needed to kill the tumor.

Various nonsurgical ablative techniques have been investigated that seek to cure or palliate unresectable hepatic tumors by improving locoregional control. These techniques rely on extreme temperature changes

(cryosurgery or radiofrequency ablation), particle and wave physics (microwave or laser ablation), or arterial embolization therapy including chemoembolization, bland embolization, or radioembolization.

Radioembolization

Radioembolization (referred to as selective internal radiotherapy in older literature) delivers small beads (microspheres) impregnated with yttrium-90 (Y90) intra-arterially via the hepatic artery. The microspheres, which become permanently embedded, are delivered to tumors preferentially because the hepatic circulation is uniquely organized, whereby tumors greater than 0.5 cm rely on the hepatic artery for blood supply while the normal liver is primarily perfused via the portal vein. Y90 is a pure beta-emitter with a relatively limited effective range and short half-life that helps focus the radiation and minimize its spread. Candidates for radioembolization are initially examined by hepatic angiogram to identify and map the hepatic arterial system. At that time, a mixture of technetium 99-labeled albumin particles is delivered via the hepatic artery to simulate microspheres. Single photon emission computed tomography imaging is used to detect possible shunting of the albumin particles into the gastrointestinal or pulmonary vasculature.

Currently, 2 commercial forms of Y90 microspheres are available: a glass sphere (TheraSphere) and a resin sphere (SIR-Spheres). Noncommercial forms are mostly used outside the U.S. While the commercial products use the same radioisotope (Y90) and have the same target dose (100 gray), they differ in microsphere size profile, base material (ie, resin vs glass), and size of commercially available doses. The physical characteristics of the active and inactive ingredients affect the flow of microspheres during injection, their retention at the tumor site, spread outside the therapeutic target region, and dosimetry calculations. The U.S. Food and Drug Administration (FDA) granted premarket approval of SIR-Spheres for use in combination with 5-fluorouridine chemotherapy by hepatic arterial infusion to treat unresectable hepatic metastases from colorectal cancer. In contrast, TheraSphere's glass sphere was approved under a humanitarian device exemption for use as monotherapy to treat unresectable hepatocellular carcinoma. In 2007, this humanitarian device exemption was expanded to include patients with hepatocellular carcinoma who have partial or branch portal vein thrombosis. For these reasons, results obtained with a product do not necessarily apply to another commercial (or non-commercial) products.

Regulatory Status

Currently, 2 forms of yttrium-90 microspheres have been approved by FDA.

In 1999, TheraSphere® (Boston Scientific; previously manufactured by Nordion, under license by BTG International), a glass sphere system, was approved by the FDA through the humanitarian drug exemption process for radiotherapy or as a neoadjuvant treatment to surgery or transplantation in patients with unresectable hepatocellular carcinoma who can have placement of appropriately positioned hepatic arterial catheters.

On March 17, 2021, TheraSphere received approval through the premarket approval process for use as selective internal radiation therapy (SIRT) for local tumor control of solitary tumors (1-8 cm in diameter), in patients with unresectable hepatocellular carcinoma, Child-Pugh Score A cirrhosis, well-compensated liver function, no macrovascular invasion, and good performance status.

In 2002, SIR-Spheres® (ex Medical), a resin sphere system, was approved by the FDA through the premarket approval process for the treatment of inoperable colorectal cancer metastatic to the liver.

For individuals who have unresectable hepatocellular carcinoma (HCC) who receive radioembolization (RE) or RE with a liver transplant, the evidence includes primarily retrospective and prospective nonrandomized studies, with limited evidence from randomized controlled trials (RCTs). Relevant outcomes are overall survival (OS), functional outcomes, quality of life, and treatment-related morbidity. Nonrandomized studies have suggested that RE has high response rates compared with historical controls. Two small pilot RCTs have compared RE with alternative therapies for HCC, including transarterial chemoembolization and transarterial chemoembolization with drug-eluting beads. Both trials reported similar

outcomes for RE compared with alternatives. Evidence from nonrandomized studies has demonstrated that RE can permit successful liver transplantation in certain patients. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable intrahepatic cholangiocarcinoma (ICC) who receive RE, the evidence includes phase 2 studies and case series. Relevant outcomes are OS, functional outcomes, quality of life, and treatment-related morbidity. Comparisons of these case series to case series of alternative treatments have suggested that RE for primary ICC has response rates similar to those seen with standard chemotherapy. Due to high study heterogeneity, it is difficult to identify patients that are most likely to benefit from treatment. A phase 2 study of RE with chemotherapy in the first-line setting reported a response rate of 39% and a disease control rate of 98%. The efficacy of RE in the neoadjuvant setting is being evaluated in an ongoing follow-up RCT. Another phase 2 study evaluating RE with or without subsequent chemotherapy in patients without prior treatment with chemotherapy or radiation found overall response rates of 25% and 16.7% in those who received RE with and without chemotherapy, respectively; the disease control rates were 75% and 58.3% amongst those who received RE with and without chemotherapy, respectively. However, at this time, the evidence is not yet sufficiently robust to draw definitive conclusions about treatment efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable neuroendocrine tumors who receive RE, the evidence includes an open-label phase 2 study, retrospective reviews, and case series, some of which have compared RE with other transarterial liver-directed therapies. Relevant outcomes are OS, functional outcomes, quality of life, and treatment-related morbidity. This evidence has suggested that RE provides outcomes similar to standard therapies and historical controls for patients with neuroendocrine tumor-related symptoms or progression of the liver tumor. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable intrahepatic metastases from colorectal cancer and prior treatment failure who receive RE, the evidence includes several small- to moderate-sized RCTs, prospective trials, and retrospective studies using a variety of comparators, as well as systematic reviews of these studies. Relevant outcomes are OS, functional outcomes, quality of life, and treatment-related morbidity. While studies of patients with prior chemotherapy failure have methodologic problems and have not shown definitive superiority of RE compared with alternatives in terms of survival benefit, they tend to show greater tumor response and significantly delayed disease progression, particularly with combined use of RE and chemotherapy. For example, the Efficacy Evaluation of TheraSphere Following Failed First Line Chemotherapy in Metastatic Colorectal Cancer (EPOCH) RCT found significantly prolonged primary endpoints of progression-free survival (PFS) (hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.54 to 0.88) and hepatic PFS (HR, 0.59; 95% CI, 0.46 to 0.77) with combined RE and chemotherapy in patients who had progressed on first-line chemotherapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable intrahepatic metastases from other cancers (eg, breast, melanoma, pancreatic) who receive RE, the evidence includes nonrandomized studies. Relevant outcomes are OS, functional outcomes, quality of life, and treatment-related morbidity. These studies have shown significant tumor response; however, improvement in survival has not been demonstrated in controlled comparative studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Clinical input obtained in 2010, 2011, and 2015 has supported the use of RE for primary hepatocellular carcinoma, intrahepatic cholangiocarcinoma, hepatic metastases from neuroendocrine tumors, chemorefractory colorectal carcinoma, chemorefractory breast cancer, and chemorefractory melanoma. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

CODING

Medicare Advantage Plans and Commercial Products

There are no specific CPT codes describing radioembolization therapy. Providers should file using the unlisted CPT code:

77399 Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services

RELATED POLICIES

Unlisted Procedures

PUBLISHED

Provider Update, October 2023

Provider Update, November 2022

Provider Update, November 2021

Provider Update, November 2020

Provider Update, October 2019

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