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FEP Medical Policy Manual

FEP 8.01.43 Radioembolization for Primary and Metastatic Tumors of the Liver

Effective Policy Date: October 1, 2023

Original Policy Date: June 2012

Related Policies:

7.01.133 - Microwave Tumor Ablation
7.01.75 - Cryosurgical Ablation of Primary or Metastatic Liver Tumors
7.01.91 - Radiofrequency Ablation of Primary or Metastatic Liver Tumors
8.01.11 - Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

Radioembolization for Primary and Metastatic Tumors of the Liver

Description

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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 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. Radioembolization has been proposed as a therapy for multiple types of primary and metastatic liver tumors.

OBJECTIVE

The objective of this evidence review is to determine whether radioembolization improves the net health outcome in individuals with primary or metastatic liver tumors.

POLICY STATEMENT

Radioembolization may be considered **medically necessary** to treat primary hepatocellular carcinoma that is unresectable and limited to the liver (see Policy Guidelines section).

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

Radioembolization may be considered **medically necessary** to treat primary intrahepatic cholangiocarcinoma in individuals with unresectable tumors.

Radioembolization may be considered **medically necessary** to treat hepatic metastases from neuroendocrine tumors (carcinoid and noncarcinoid) with diffuse and symptomatic disease when systemic therapy has failed to control symptoms.

Radioembolization may be considered **medically necessary** to treat 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 or other systemic therapies.

Radioembolization is considered **investigational** for all other hepatic metastases except as noted above.

Radioembolization is considered **investigational** for all other indications not described above.

POLICY GUIDELINES

In general, radioembolization is used for unresectable hepatocellular carcinoma that is greater than 3 cm.

There is little information on the safety or efficacy of repeated radioembolization treatments or on the number of treatments that should be administered.

Radioembolization should be reserved for individuals with adequate functional status (Eastern Cooperative Oncology Group Performance Status 0 to 2), adequate liver function and reserve, Child-Pugh class A or B, and liver-dominant metastases.

Symptomatic disease from metastatic neuroendocrine tumors refers to symptoms related to excess hormone production.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

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-floxuridine 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 (see Regulatory Status section).

Regulatory Status

Currently, 2 forms of Y90 microspheres have been approved by the 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 (H980006).

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 to 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 (P200029).

In 2002, SIR-Spheres (Sirtex 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 (P990065).

FDA product code: NAW.

RATIONALE

Summary of Evidence

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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Radiology et al

In 2021, the American College of Radiology issued a practice parameter jointly developed with the American Brachytherapy Society, the American College of Nuclear Medicine, the American Society for Radiation Oncology, the Society of Interventional Radiology, and the Society of Nuclear Medicine and Molecular Imaging addressing the use of RE for the treatment of liver malignancies with glass- or resin-based yttrium-90 microspheres.[100,] The guidelines provided indications and contraindications for treatment as follows:

- "Indications for both agents include but are not limited to the following:
    1. The presence of unresectable or inoperable primary or secondary liver malignancies (particularly colorectal cancer and neuroendocrine tumor metastases). 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.
    2. A life expectancy of at least 3 months."
- "Absolute contraindications include the following:
    1. Inability to catheterize the hepatic artery
    2. Fulminant liver failure
    3. Initial mapping angiography and/or technetium-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy demonstrating nontarget deposition to the gastrointestinal organs that cannot be corrected by angiographic techniques.
    4. Pretreatment hepatic arterial administration with technetium-99m MAA demonstrative of unfavorable (or unacceptable) shunt function between the liver and the pulmonary parenchyma. This shunt fraction must not be greater than acceptable limits specific to each brachytherapy device.
    5. Active hepatic infection
    6. Therapy during pregnancy may possibly be an option in extraordinary circumstances and with multidisciplinary consult and considerations."
- "Relative contraindications include the following:
    1. Excessive tumor burden in the liver with greater than 50 to 70% of the parenchyma replaced by tumor. In the setting of more extensive tumor burden, treatment can be considered if synthetic hepatic function is preserved.

2. Total bilirubin greater than 2 mg/dL (in the absence of obstructive cause), which indicates severe liver function impairment. Nonobstructive bilirubin elevations may indicate that liver metastases have caused liver impairment to the degree that risks outweigh benefits for this therapy. In contrast, patients with hepatocellular carcinoma (HCC) and elevated bilirubin may be treated with radioembolization if a segmental or subsegmental infusion can be performed.
3. Prior radiation therapy to the liver or upper abdomen that included a significant volume of the liver (clinical judgment by the [authorized user] required).
4. Care must be employed when patients are on systemic therapies that may potentiate or may alter the impact of radioembolization and should use caution when combining therapies."

American Society of Clinical Oncology

The 2023 American Society of Clinical Oncology (ASCO) guidelines for the treatment of metastatic colorectal cancer (mCRC) makes the following relevant recommendation: [101,]

- "SIRT [selective internal radiation therapy] is not routinely recommended for patients with mCRC and unilobar or bilobar metastases of the liver (Type: Evidence-based, harms outweigh benefits; Evidence quality: Low; Strength of recommendation: Weak)."

National Comprehensive Cancer Network

Primary Hepatocellular Carcinoma

The National Comprehensive Cancer Network (NCCN) guidelines (v.1.2023) on the treatment of hepatocellular carcinoma indicate that the use of arterially directed therapies, including transarterial bland embolization, transarterial chemoembolization, and drug-eluting beads transarterial chemoembolization, and RE with yttrium-90 microspheres may be appropriate provided that the arterial blood supply can be isolated without excessive nontarget treatment. Patients should be considered for locoregional therapy if they are not candidates for potential curative treatments (resection, transplantation, and for small lesions, ablative strategies). RE with yttrium-90 microspheres has an increased risk of radiation-induced liver disease in patients with bilirubin levels greater than 2 mg/dL. Delivery of 205 Gy or more to the tumor may be associated with increased overall survival. A dose of greater than 400 Gy to 25% of the liver or less in patients with Child-Pugh A liver function is recommended. RE may be more appropriate in some patients with advanced HCC, specifically patients with segmental or lobar portal vein, rather than main portal vein thrombosis.[29,]

Metastatic Neuroendocrine Tumors

The NCCN guidelines (v.2.2022) on the treatment of neuroendocrine tumors recommend consideration of transarterial radioembolization (TARE) for lobar or segmental disease distribution and in patients with prior Whipple surgery or biliary tract instrumentation.[102,]TARE is better tolerated than transarterial embolization/transarterial chemoembolization, but late radioembolization-induced chronic hepatotoxicity may occur in long-term survivors, and is particularly a concern among patients undergoing bilobar radioembolization.

Metastatic Colon Cancer

The NCCN guidelines (v.2.2023) on the treatment of colon cancer provides a consensus recommendation that: "...arterial-directed catheter therapy, in particular yttrium-90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases." RE may also be considered "when hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume..." The guidelines also note that "further investigation is necessary to identify the role of radioembolization at earlier stages of disease, particularly in patients with right-sided primary origin."[103,]

Metastatic Uveal Melanoma

The NCCN guidelines (v.1.2023) on the treatment of uveal melanoma state the following regarding RE: "Further study is required to determine the appropriate patients for and risks and benefits of this approach." [National Comprehensive Cancer Network. Melanoma: U.... al.pdf. Accessed May 23, 2023.

National Institute for Health and Care Excellence

Primary Hepatobiliary Carcinoma

The July 2013 NICE interventional procedures guidance on selective internal radiation therapy for primary hepatocellular carcinoma states that the evidence for efficacy and safety are adequate for use with normal arrangements. However, "uncertainties remain about its comparative effectiveness, and clinicians are encouraged to enter eligible patients into trials comparing the procedure against other forms of treatment."[105,]

In March 2021, a NICE technology appraisal guidance on selective internal radiation therapies (SIRTs) for treating hepatocellular carcinoma was published, providing specific evidence-based recommendations for the use of SIR-Spheres (Sirtex), TheraSphere (Boston Scientific), and QuiremSpheres (Quirem Medical).[106,] The guidance states that RE with SIR-Spheres or TheraSphere is recommended as an option for treating unresectable advanced hepatocellular carcinoma in adults only if "used for people with Child-Pugh grade A liver impairment when conventional transarterial therapies are inappropriate, and the company provides [the microspheres] according to the commercial arrangement." The guidance also stated that "clinical trial data for these SIRTs compared with other treatment options are limited. But, compared with sorafenib, SIRTs may have fewer and more manageable adverse effects, which can improve quality of life." The use of QuiremSpheres, imageable holmium-166 microspheres, was not recommended due to reduced clinical efficacy compared to sorafenib and higher cost. QuiremSpheres received its CE mark in April 2015 in Europe and is not commercially available in the U.S.

Primary Intrahepatic Cholangiocarcinoma

The October 2018 NICE interventional procedures guidance on selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma state that there are "well-recognized, serious but rare safety concerns. Evidence on its efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research."[107,]

Metastatic Colon Cancer

The March 2020 NICE interventional procedures guidance on selective internal radiation therapy for unresectable colorectal metastases in the liver states that "in people who cannot tolerate chemotherapy or have liver metastases that are refractory to chemotherapy, there is evidence of efficacy but this is limited, particularly for important outcomes such as quality of life. Therefore, in these people, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research."[108,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
June 2012	New policy	
June 2013	Replace policy	Policy updated with literature review through February 2013. New investigational policy statement on intrahepatic cholangiocarcinoma added. References updated. Ongoing and unpublished clinical trials updated.
June 2014	Replace policy	Policy updated with literature review. Added policy statement indicating all other indications not described are investigational. References 15-16, 22-23, 32, 42-43, 48 and 51 added. References 4- 6 and 49-51 updated.
September 2015	Replace policy	Policy updated with literature review. References 10-11, 14-15, 18, 29, 21, 24-25, 31-32, 36, 45, 47-48, 51, 54-55, and 61-62 added. Rationale extensively reorganized. Policy revised to add Medically Necessary statements for unresectable metastatic breast cancer and melanoma with liver-dominant disease and unresectable intrahepatic cholangiocarcinoma.
December 2016	Replace policy	Policy updated with literature review through June 10, 2016; references 12-13, 47, and 49 added.
September 2018	Replace policy	Policy updated with literature review through May 10, 2018; references 8-11, 15-16, 21, 28, 31-32, 56 and 73 added. Policy statements unchanged except "not medically necessary, corrected to "investigational, for non-FDA approved indications.
September 2019	Replace policy	Policy updated with literature review through May 6, 2019; references on NCCN updated. Policy statements unchanged.
September 2020	Replace policy	Policy updated with literature review through May 21, 2020; references added. Policy statements unchanged.
September 2021	Replace policy	Policy updated with literature review through May 27, 2021; references added. Policy statements unchanged.
September 2022	Replace policy	Policy updated with literature review through June 22, 2022; references added. NCCN and NICE guidelines updated. Policy statements unchanged.
September 2023	Replace policy	Policy updated with literature review through May 26, 2023; references added. Minor editorial refinements to policy statements; intent unchanged.