Medical Coverage Policy | Radioembolization of Primary and Metastatic Tumors of the Liver

EFFECTIVE DATE: 10|06|2009
POLICY LAST UPDATED: 09|15|2021

OVERVIEW

Radioembolization (RE), also referred to as selective internal radiotherapy, delivers small beads (microspheres) impregnated with yttrium 90 intra-arterially via the hepatic artery. 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 patients with liver-dominant disease who are refractory to chemotherapy or are not candidates for chemotherapy.
- Primary intrahepatic cholangiocarcinoma in patients 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 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.

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 HCC who receive RE or RE with a liver transplant, the evidence includes primarily retrospective and prospective nonrandomized studies, with limited evidence from RCTs. Relevant outcomes are 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 TACE and DEB-TACE. 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 ICC who receive RE, the evidence includes a phase 2 study 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. 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 overall survival, 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 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 overall survival, functional outcomes, quality of life, and treatment-related morbidity. RCTs of patients with prior treatment failure have methodologic problems, do not show definitive superiority of RE compared with alternatives, but tend to show greater tumor response with RE. 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. RCTs of patients with prior treatment failure have methodologic problems, do not show definitive superiority of RE compared with alternatives but tend to show greater tumor response with RE. 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.

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

RELATED POLICIES

Not applicable

PUBLISHED

Provider Update, November 2021
Provider Update, November 2020

Provider Update, October 2019
Provider Update, November 2018
Provider Update, November 2017

REFERENCES

1. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet*. May 18 2002;359(9319):1734-1739. PMID 12049862
2. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology*. May 2002;35(5):1164-1171. PMID 11981766
3. Tao R, Li X, Ran R, et al. A mixed analysis comparing nine minimally invasive surgeries for unresectable hepatocellular carcinoma patients. *Oncotarget*. Jan 17 2017;8(3):5460-5473. PMID 27705924
4. Ludwig JM, Zhang D, Xing M, et al. Meta-analysis: adjusted indirect comparison of drug-eluting bead transarterial chemoembolization versus 90Y-radioembolization for hepatocellular carcinoma. *Eur Radiol*. May 2017; 27(5):2031-2041. PMID 27562480
5. Lobo L, Yakoub D, Picado O, et al. Unresectable hepatocellular carcinoma: radioembolization versus chemoembolization: a systematic review and meta-analysis. *Cardiovasc Intervent Radiol*. Nov 2016;39(11):1580-1588. PMID 27586657
6. Facciorusso A, Serviddio G, Muscatiello N. Transarterial radioembolization vs chemoembolization for hepatocarcinoma patients: A systematic review and meta-analysis. *World J Hepatol*. Jun 28 2016;8(18):770-778. PMID 27366304
7. Vente MA, Wondergem M, van der Tweel I, et al. Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis. *Eur Radiol*. Nov 2009;19(4):951-959. PMID 18989675
8. Kolligs FT, Bilbao JI, Jakobs T, et al. Pilot randomized trial of selective internal radiation therapy vs. chemoembolization in unresectable hepatocellular carcinoma. *Liver Int*. Jun 2015;35(6):1715-1721. PMID 25443863
9. Pitton MB, Kloeckner R, Ruckes C, et al. Randomized comparison of selective internal radiotherapy (SIRT) versus drug-eluting bead transarterial chemoembolization (DEB-TACE) for the treatment of hepatocellular carcinoma. *Cardiovasc Intervent Radiol*. Apr 2015;38(2):352-360. PMID 25373796
10. Padia SA, Johnson GE, Horton KJ, et al. Segmental Yttrium-90 radioembolization versus segmental chemoembolization for localized hepatocellular carcinoma: results of a single-center, retrospective, propensity score-matched study. *J Vasc Interv Radiol*. Jun 2017;28(6):777-785 e771. PMID 28365172
11. Soydal C, Arslan MF, Kucuk ON, et al. Comparison of survival, safety, and efficacy after transarterial chemoembolization and radioembolization of Barcelona Clinic Liver Cancer stage B-C hepatocellular cancer patients. *Nucl Med Commun*. Jun 2016;37(6):646-649. PMID 26905317
12. Oladeru OT, Miccio JA, Yang J, et al. Conformal external beam radiation or selective internal radiation therapy-a comparison of treatment outcomes for hepatocellular carcinoma. *J Gastrointest Oncol*. Jun 2016;7(3):433-440. PMID 27284477
13. El Fouly A, Ertle J, El Dorry A, et al. In intermediate stage hepatocellular carcinoma: radioembolization with yttrium 90 or chemoembolization? *Liver Int*. Feb 2015;35(2):627-635. PMID 25040497
14. Gramenzi A, Golfieri R, Mosconi C, et al. Yttrium-90 radioembolization vs sorafenib for intermediate-locally advanced hepatocellular carcinoma: a cohort study with propensity score analysis. *Liver Int*. Mar 2015;35(3):1036-1047. PMID 24750853
15. Carr BI, Kondragunta V, Buch SC, et al. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. *Cancer*. Mar 1 2010;116(5):1305-1314. PMID 20066715
16. Kulik L, Heimbach JK, Zaiem F, et al. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis. *Hepatology*. Jan 2018;67(1):381-400. PMID 28859222
17. Salem R, Gordon AC, Mouli S, et al. Y90 Radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology*. Dec 2016;151(6):1155-1163 e1152. PMID 27575820

18. Kulik L, Vouche M, Koppe S, et al. Prospective randomized pilot study of Y90+/-sorafenib as bridge to transplantation in hepatocellular carcinoma. *J Hepatol.* Aug 2014;61(2):309-317. PMID 24681342
19. Tohme S, Sukato D, Chen HW, et al. Yttrium-90 radioembolization as a bridge to liver transplantation: a single-institution experience. *J Vasc Interv Radiol.* Nov 2013;24(11):1632-1638. PMID 24160821
20. Ramanathan R, Sharma A, Lee DD, et al. Multimodality therapy and liver transplantation for hepatocellular carcinoma: a 14-year prospective analysis of outcomes. *Transplantation.* Jul 15 2014;98(1):100-106. PMID 24503764
21. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. *Am J Transplant.* Aug 2009;9(8):1920-1928. PMID 19552767
22.National Comprehensive Cancer Network. Hepatobiliary cancers. Version 2.2020. Accessed May 27, 2020. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf
23.National Comprehensive Cancer Network. Neuroendocrine tumors. Version 1.2019. Accessed May 27, 2020. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf.
24.National Comprehensive Cancer Network. Colon Cancer. Version 3.2020. Accessed May 27, 2020. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
25.National Comprehensive Cancer Network. Melanoma: Uveal. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf. Accessed June 28, 2021
26.National Institute for Health and Care Excellence. Selective internal radiation therapy for primary hepatocellular carcinoma Interventional procedures guidance [IPG460]. July, 2013. https://www.nice.org.uk/guidance/ipg460. Accessed June 25, 2021.
27.National Institute for Health and Care Excellence. Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma Interventional procedures guidance [IPG630]. October, 2018. https://www.nice.org.uk/guidance/ipg630. Accessed June 26, 2021.
28.National Institute for Health and Care Excellence. Selective internal radiation therapy for unresectable colorectal metastases in the liver Interventional procedures guidance [IPG672]. March, 2020. https://www.nice.org.uk/guidance/ipg672. Accessed June 27, 2021.
29.Michl M, Haug AR, Jakobs TF, et al. Radioembolization with Yttrium-90 microspheres (SIRT) in pancreatic cancer patients with liver metastases: efficacy, safety and prognostic factors. Oncology. 2014; 86(1): 24-32. PMID 24401529
30.Miller MD, Sze DY, Padia SA, et al. Response and Overall Survival for Yttrium-90 Radioembolization of Hepatic Sarcoma: A Multicenter Retrospective Study. J Vasc Interv Radiol. Jun 2018; 29(6): 867-873. PMID 29724518