Protocol

Radioembolization for Primary and Metastatic Tumors of the Liver

(80143)

Medical Benefit		**Effective Date**: 10/01/15	**Next Review Date**: 07/23
Preauthorization	No	**Review Dates**: 07/07, 07/08, 05/09, 05/10, 09/10, 07/11, 07/12, 07/13, 07/14, 07/15, 07/16, 07/17, 07/18, 07/19, 07/20, 07/21, 07/22	

Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

RELATED PROTOCOLS

Cryosurgical Ablation of Primary or Metastatic Liver Tumors

Microwave Tumor Ablation

Radiofrequency Ablation of Primary or Metastatic Liver Tumors

Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

Populations	Interventions	Comparators	Outcomes
Individuals: • With unresectable hepatocellular carcinoma	Interventions of interest are: • Radioembolization • Radioembolization and liver transplant	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With unresectable intrahepatic cholangiocarcinoma	Interventions of interest are: • Radioembolization	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With unresectable neuroendocrine tumors	Interventions of interest are: • Radioembolization	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With unresectable intrahepatic metastases from colorectal cancer and prior treatment failure	Interventions of interest are: • Radioembolization	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Functional outcomes • Quality of life • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With unresectable intrahepatic metastases from other cancers (e.g., breast, melanoma, pancreatic)	Interventions of interest are: • Radioembolization	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Functional outcomes • Quality of life • Treatment-related morbidity

DESCRIPTION

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.

SUMMARY OF EVIDENCE

For individuals who have unresectable hepatocellular carcinoma who receive 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 hepatocellular carcinoma, 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 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 intrahepatic cholangiocarcinoma 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 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 retro-

spective 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 (e.g., 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.

POLICY

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

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 patients with unresectable tumors.

Radioembolization may be considered **medically necessary** to treat hepatic metastases from neuroendocrine tumors (carcinoid and non-carcinoid) 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 patients 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 (HCC) that is greater than 3 cm.

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

Radioembolization should be reserved for patients with adequate functional status (Eastern Cooperative Oncology Group [ECOG] Performance Status 0-2), 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

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 multiple diffuse 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 a 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 are delivered via the hepatic artery to simulate microspheres. Single-photon emission computed tomography 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 (i.e., 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 (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 (1-8 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® (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 (P990065).

FDA product code: NAW.

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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