Radioembolization for Primary and Metastatic Tumors of the Liver

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

FDA REGULATORY STATUS
Currently 2 forms of yttrium-90 microspheres have been approved by the U.S. Food and Drug Administration (FDA).
In 1999, TheraSphere® (manufactured by Nordion, Ontario, under license by BTG International), a glass sphere system, was approved by FDA through the humanitarian drug exemption process for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma who can have placement of appropriately positioned hepatic arterial catheters (H980006).
In 2002, SIR-Spheres® (Sirtex Medical, Lake Forest, IL), a resin sphere system, was approved by FDA through the premarket approval process for the treatment of inoperable colorectal cancer metastatic to the liver.
FDA product code: NAW.

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 patients 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.
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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 **not medically necessary** for all other hepatic metastases except as noted above.

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

**POLICY GUIDELINES (IF NEEDED)**

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 about the number of treatments that should be administered.

Radioembolization should be reserved for patients with adequate functional status (Eastern Cooperative Oncology Group 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 production.

**BENEFIT APPLICATION**

FDA approved devices under Premarket Approval (PMA) cannot be denied on the basis of experimental or investigational.

**RATIONALE**

### Summary of Evidence

For individuals who have hepatocellular carcinoma (HCC) who receive radioembolization (RE) or RE with liver transplant, the evidence includes primarily retrospective and prospective observational studies, with limited evidence from randomized controlled trials (RCTs). Relevant outcomes are overall survival, functional outcomes, quality of life, and treatment-related morbidity. Observational 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 (TACE) and TACE with drug-eluting beads. Both trials demonstrated similar outcomes for RE compared with alternatives. Evidence from observational studies has demonstrated that RE can allow successful liver transplantation in certain patients. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in net health outcome.

For individuals who have unresectable intrahepatic cholangiocarcinoma who receive RE, the evidence includes case series. Relevant outcomes are overall survival, 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. RE may play a role for patients with unresectable tumors that are chemorefractory or who are unable to tolerate systemic chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have unresectable neuroendocrine tumors who receive RE, the evidence includes 1 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 shown that RE has similar outcomes to standard therapies and historical controls for patients with neuroendocrine tumor-related symptoms or progression of liver tumor. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in net health outcome.
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For individuals who have unresectable intrahepatic metastases from colorectal cancer (CRC) 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, along with 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 to alternatives, but tend to show greater tumor response with RE. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in net health outcome.

For individuals who have unresectable intrahepatic metastases from miscellaneous cancers (eg, breast cancer, melanoma) who receive RE, the evidence includes observational studies. Relevant outcomes are overall survival, functional outcomes, quality of life, and treatment-related morbidity. These studies generally have shown significant tumor response. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Primary Hepatocellular Carcinoma

National Comprehensive Cancer Network (NCCN) guidelines (v.2.2016) for the treatment of primary HCC mention the use of arterially directed therapies, including transarterial bland embolization, transarterial chemoembolization (TACE), and drug-eluting beads TACE, and RE with yttrium-90 microspheres for specific categories of patients. The guidelines did not distinguish between the different arterially directed therapies, and all statements were category 2A recommendations.

Primary Cholangiocarcinoma

NCCN guidelines for the treatment of primary intrahepatic cholangiocarcinoma recommend locoregional therapy for unresectable or metastatic disease, or for residual local disease after resection (category 2B recommendation). The guidelines note that no RCTs of radiofrequency ablation, TACE, or RE exist.

Metastatic Neuroendocrine Tumors

NCCN guidelines (v.2.2016) for the treatment of metastatic neuroendocrine tumors give a category 2B recommendation for hepatic regional therapy (arterial embolization, chemoembolization, RE) in certain clinical situations.

Metastatic Colon Cancer

NCCN guidelines (v.2.2016) for the treatment of colon cancer state: “The use of arterial-directed therapies such as radioembolization in highly select patients … remains a category 3 recommendation based on the relatively limited amount of evidence and different institutional practices.”

Metastatic Breast Cancer

NCCN guidelines (v.2.2016) for the treatment of breast cancer do not address the use of RE in the treatment of metastatic breast cancer.

Metastatic Melanoma

NCCN guidelines (v.2.2016) for the treatment of melanoma do not address the use of RE in the treatment of metastatic melanoma.
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RE Brachytherapy Oncology Consortium
The Radioembolization Brachytherapy Oncology Consortium was convened as independent group of experts in interventional radiology, radiation oncology, nuclear medicine, medical oncology, and surgical oncology. In 2007, the panel made 14 recommendations with level 2A evidence (panel consensus with low-level evidence). Some of the consortium’s recommendations about specific indications for RE therapy were as follows:

- The panel believes that there is sufficient evidence to support the safety and effectiveness of yttrium-90 (Y90) microsphere therapy in selected patients.
- Candidates for radioembolization are patients with unresectable primary or metastatic hepatic disease with liver-dominant tumor burden and a life expectancy greater than 3 months.
- Absolute contraindications to Y90 microsphere treatment include pretreatment 99mTc macrogaggregated albumin (MAA) scan demonstrating the potential of 30 Gy radiation exposure to the lung or flow to the gastrointestinal tract that cannot be corrected by catheter techniques.
- Relative contraindications to Y90 microsphere treatment include limited hepatic reserve, irreversibly elevated bilirubin levels, compromised portal vein (unless selective or superselective radioembolization can be performed), and prior radiation therapy involving the liver.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES
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POLICY HISTORY

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<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>June 2013</td>
<td>Update Policy</td>
<td>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.</td>
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<tr>
<td>December 2016</td>
<td>Replace policy</td>
<td>Policy updated with literature review through June 10, 2016; references 12-13, 47, and 49 added.</td>
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Signature on File

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