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 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.

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 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 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

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

FDA REGULATORY STATUS

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.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
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 Food and Drug Administration (FDA) granted premarket approval of SIR-Spheres for use in combination with 5-fluorouracil 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.

Currently, 2 forms of Y90 microspheres have been approved by the FDA.

In 1999, TheraSphere (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).

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 observational studies, with limited evidence from randomized controlled trials (RCTs). The relevant outcomes are overall survival (OS), functional outcomes, quality of life (QOL), 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 bead (DEB). Both trials reported similar outcomes for RE compared with alternatives. Evidence from observational studies has demonstrated that RE can permit successful liver transplantation in certain patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have unresectable intrahepatic cholangiocarcinoma (ICC) who receive RE, the evidence includes case series. The relevant outcomes are OS, functional outcomes, QOL, 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. RE may play a role for patients with unresectable tumors that are chemorefractory or who are unable to tolerate systemic chemotherapy. However, the evidence is not yet sufficiently robust to draw definitive conclusions about treatment efficacy. 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 an open-label phase 2 study, retrospective reviews, and case series, some of which have compared RE with other transarterial liver-directed therapies. The relevant outcomes are OS, functional outcomes, QOL, 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 a meaningful improvement in the net health outcome.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
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, as well as systematic reviews of these studies. The relevant outcomes are OS, functional outcomes, QOL, 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 a meaningful 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 observational studies. The relevant outcomes are OS, functional outcomes, QOL, 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 the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Primary Hepatobiliary Carcinoma

The NCCN guidelines (v.1.2019) on the treatment of hepatobiliary 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.74.

Metastatic Neuroendocrine Tumors

The NCCN guidelines (v.2.2019) on the treatment of neuroendocrine tumors give a category 2B recommendation for hepatic regional therapy (arterial embolization, chemoembolization, RE) in the setting of advanced locoregional disease.75.

Metastatic Colon Cancer

The NCCN guidelines (v.2.2019) 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."76.

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.

REFERENCES


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.


45. Tice J. Selective internal radiation therapy or radioembolization for inoperable liver metastases from colorectal cancer San Francisco, CA: California Technology Assessment Forum; 2010.


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
### POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2013</td>
<td>Replace 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>
</tr>
<tr>
<td>September 2015</td>
<td>Replace policy</td>
<td>Policy updated with literature review through May 6, 2019; references on NCCN updated. Policy statements unchanged.</td>
</tr>
<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>
</tr>
<tr>
<td>September 2018</td>
<td>Replace policy</td>
<td>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.</td>
</tr>
</tbody>
</table>

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.