**Protocol**

Radioembolization for Primary and Metastatic Tumors of the Liver

(80143)

<table>
<thead>
<tr>
<th>Medical Benefit</th>
<th>Effective Date: 10/01/15</th>
<th>Next Review Date: 07/18</th>
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</thead>
<tbody>
<tr>
<td>Preauthorization</td>
<td>Yes</td>
<td>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</td>
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</tbody>
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**Preauthorization is 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.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals: • With unresectable hepatocellular cancer</td>
<td>Interventions of interest are: • Radioembolization • Radioembolization and liver transplant</td>
<td>Comparators of interest are: • Standard of care</td>
<td>Relevant outcomes include: • Overall survival • Functional outcomes • Quality of life • Treatment-related morbidity</td>
</tr>
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</tr>
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</tr>
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</tr>
</tbody>
</table>

**Description**

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.

**Summary of Evidence**

For individuals who have hepatocellular carcinoma (HCC) who receive 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 one 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.

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 other cancers (e.g., breast cancer, melanoma, pancreatic) 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; 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.
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 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 HCC that is greater than three cm.
There is little information about the safety or efficacy of repeated RE 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 [ECOG] Performance Status 0-2), adequate liver function and reserve, Child Pugh score A or B, and liver-dominant metastases.
Symptomatic disease from metastatic neuroendocrine tumors refers to symptoms related to excess hormone production.

Background
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 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 [RFA]), particle and wave physics (microwave or laser ablation), or arterial embolization therapy including chemoembolization, bland embolization, or radioembolization.
Radioembolization (referred to as selective internal radiotherapy in older literature) 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. Yttrium-90 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-labelled 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 gastrointestinal or pulmonary vasculature.

Currently, two commercial forms of yttrium-90 microspheres are available: a glass sphere (TheraSphere) and a resin sphere (SIR-Spheres). Noncommercial forms are mostly used outside the United States. While the commercial products use the same radioisotope (yttrium-90) 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 Food and Drug Administration granted premarket approval of SIR-Spheres for use in combination with 5-flourouridine chemotherapy by hepatic arterial infusion to treat unresectable hepatic metastases from colorectal cancer (CRC). In contrast, TheraSphere was approved by humanitarian device exemption (HDE) for use as monotherapy to treat unresectable HCC. In January 2007, this HDE was expanded to include patients with HCC who have partial or branch portal vein thrombosis. For these reasons, results obtained with one product do not necessarily apply to other commercial (or noncommercial) products (see Regulatory Status section).

**Unresectable Primary HCC**

Most patients with HCC present with unresectable disease, and treatment options are limited secondary to the chemoresistance of HCC and the intolerance of normal liver parenchyma to tumoricidal radiation doses. Results of two randomized controlled trials have shown a survival benefit for transarterial chemoembolization (TACE) therapy compared to supportive care in patients with unresectable HCC.1, 2 One study randomized patients to TACE, transarterial embolization (TAE), or supportive care. One-year survival rates for TACE, TAE, and supportive care were 82%, 75%, and 63%, respectively; two-year survival rates were 63%, 50%, and 27%, respectively. Targeted therapies have been investigated for HCC. For example, sorafenib was associated with improved overall survival (OS) in a randomized phase three trial with 602 patients.3

**Unresectable Intrahepatic Cholangiocarcinoma**

Cholangiocarcinomas are tumors that arise from the epithelium of the bile duct and are separated into intrahepatic and extrahepatic types. Intrahepatic cholangiocarcinomas appear in the hepatic parenchyma and are also known as peripheral cholangiocarcinomas. Resection is the only treatment with the potential for cure, and five-year survival rates have been in the range of 20% to 43%.3 Patients with unresectable disease may select among fluoropyrimidine-based or gemcitabine-based chemotherapy, fluoropyrimidine chemoradiation, or best supportive care.

**Unresectable Metastatic Colorectal Cancer**

Fifty to sixty percent of patients with CRC will develop metastases, either synchronously or metachronously. Select patients with liver-only metastases that are surgically resectable can be cured, with some reports showing five-year survival rates exceeding 50%. The emphasis of treating these patients with potentially curable disease is on complete removal of all tumor with negative surgical margins. Most patients diagnosed with metastatic colorectal disease are initially classified as having unresectable disease. In patients with metastatic disease limited to the liver, preoperative chemotherapy is sometimes used to downsize the metastases to convert the metastatic lesions to a resectable status (conversion chemotherapy).

In patients with unresectable disease, the primary treatment goal is palliative, with survival benefit shown with both second- and third-line systemic chemotherapy.4 Recent advances in chemotherapy, including oxaliplatin, irinotecan, and targeted antibodies like cetuximab, have doubled the median survival in this population from less than one year to more than two years.4 Palliative chemotherapy using combined systemic and hepatic arterial infusion may increase disease-free intervals for patients with unresectable hepatic metastases from CRC.
RFA has been found inferior to resection in local recurrence rates and five-year OS and is generally reserved for patients with potentially resectable disease that cannot be completely resected due to patient comorbidities, location of metastases (i.e., adjacent to a major vessel), or an estimate of inadequate liver reserve following resection. RFA is generally recommended when the goal is complete resection with curative intent. The role of local (liver-directed) therapy (including radioembolization, chemoembolization, and conformal radiotherapy) in debulking unresectable metastatic disease remains controversial.

**Unresectable Metastatic Neuroendocrine Tumors**

Neuroendocrine tumors are an uncommon, heterogeneous group of mostly slow-growing, hormone-secreting malignancies, with an average patient age of 60 years. Primary neuroendocrine tumors vary in location, but most are either carcinoids (which most commonly arise in the midgut) or pancreatic islet cells. Carcinoid tumors, particularly if they metastasize to the liver, can result in excessive vasoactive amine secretion including serotonin and are commonly associated with the carcinoid syndrome (diarrhea, flush, bronchoconstriction, right valvular heart failure).

Although they are considered to be indolent tumors, at the time of diagnosis, up to 75% of patients have liver metastases, and with metastases to the liver, five-year survival rates are less than 20%. Surgical resection of the metastases is considered the only curative option; however, less than 10% of patients are eligible for resection, because most patients have diffuse, multiple lesions.

Conventional therapy is largely considered to be palliative supportive care, to control, eradicate, or debulk hepatic metastases, often to palliate carcinoid syndrome or local pain from liver capsular stretching. Therapies for unresectable metastatic neuroendocrine tumors include medical (somatostatin analogues like octreotide), systemic chemotherapy, ablation (radiofrequency or cryotherapy), TAE or TACE, or radiation. Although patients often achieve symptom relief with octreotide, the disease eventually becomes refractory, with a median duration of symptom relief of approximately 13 months, with no known effect on survival. Systemic chemotherapy for these tumors has shown modest response rates of limited duration, is better for pancreatic neuroendocrine tumors than carcinoids, and is frequently associated with significant toxicity. Chemoembolization has shown response rates of nearly 80%, but the effect is of short duration and a survival benefit has not been demonstrated.

**Miscellaneous Metastatic Tumors**

Case reports have been published on the use of radioembolization in many other types of cancer with hepatic metastases, including breast, melanoma, head, and neck (including parotid gland), pancreaticobiliary, anal, thymic, thyroid, endometrial, lung, kidney, gastric, small bowel, esophageal, ovarian, cervical, prostatic, bladder, and for sarcoma and lymphoma.

**Regulatory Status**

Currently two 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 radiotherapy or as a neoadjuvant to surgery or transplantation in patients with unresectable HCC 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 (P990065).

FDA product code: NAW.
Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment 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.

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


