Medical Policy
Radioembolization for Primary and Metastatic Tumors of the Liver

Table of Contents
- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References

Policy Number: 292
BCBSA Reference Number: 8.01.43
NCD/LCD: N/A

Related Policies
- Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors, #259
- Cryosurgical Ablation of Primary or Metastatic Liver Tumors, #633
- Transcatheter Arterial Chemoembolization (TACE) to Treat Primary or Metastatic Liver Malignancies, #634
- Radiofrequency Ablation of Primary or Metastatic Liver Tumors, #286

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

Radioembolization may be considered MEDICALLY NECESSARY to treat primary hepatocellular carcinoma that is unresectable and limited to the liver.

Radioembolization may be considered MEDICALLY NECESSARY in primary hepatocellular carcinoma as a bridge to liver transplantation.

Radioembolization may be considered MEDICALLY NECESSARY to treat hepatic metastases from neuroendocrine tumors (carcinoid and noncarcinoid, as classified on pathology report or by WHO classification) with diffuse and symptomatic disease when systemic therapy has failed to control symptoms*.

*Symptomatic disease from metastatic neuroendocrine tumors refers to symptoms related to excess hormone production.

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 may be considered **MEDICALLY NECESSARY** to treat primary intrahepatic cholangiocarcinoma in patients with unresectable tumors.

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

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.

**Prior Authorization Information**

Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required for outpatient services.

Yes indicates that prior authorization is required.

No indicates that prior authorization is not required.

N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>No</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>No</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>No</td>
</tr>
</tbody>
</table>

**CPT Codes / HCPCS Codes / ICD Codes**

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

**HCPCS Codes**

<table>
<thead>
<tr>
<th>HCPCS codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S2095</td>
<td>Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres</td>
</tr>
</tbody>
</table>

The following ICD Diagnosis Codes are considered medically necessary when submitted with the HCPCS code above if medical necessity criteria are met:

**ICD-9 Diagnosis Codes**

<table>
<thead>
<tr>
<th>ICD-9-CM diagnosis codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>155.0</td>
<td>Malignant neoplasm of liver, primary</td>
</tr>
</tbody>
</table>
Malignant neoplasm of intrahepatic bile ducts
Malignant neoplasm of liver, secondary
Secondary neuroendocrine tumor of liver

ICD-10 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C22.0</td>
<td>Liver cell carcinoma</td>
</tr>
<tr>
<td>C22.1</td>
<td>Intrahepatic bile duct carcinoma</td>
</tr>
<tr>
<td>C22.2</td>
<td>Hepatoblastoma</td>
</tr>
<tr>
<td>C22.3</td>
<td>Angiosarcoma of liver</td>
</tr>
<tr>
<td>C22.4</td>
<td>Other sarcomas of liver</td>
</tr>
<tr>
<td>C22.7</td>
<td>Other specified carcinomas of liver</td>
</tr>
<tr>
<td>C22.8</td>
<td>Malignant neoplasm of liver, primary, unspecified as to type</td>
</tr>
<tr>
<td>C78.7</td>
<td>Secondary malignant neoplasm of liver and intrahepatic bile duct</td>
</tr>
<tr>
<td>C7B.02</td>
<td>Secondary carcinoid tumors of liver</td>
</tr>
</tbody>
</table>

Description

The use of external beam radiotherapy and the application of more advanced radiotherapy approaches (eg, 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 ablatvie 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 RE.

RE, referred to as SIRT 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 tumor preferentially to normal liver, as 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 RE 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, 2 commercial forms of yttrium-90 microspheres are available: a glass sphere, TheraSphere® (manufactured by Nordion, Ontario, Canada, under license by BTG International) and a resin sphere, SIR-Spheres® (Sirtex Medical, Lake Forest, IL). 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 Gy), 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. FDA granted premarket approval (PMA) of SIR-Spheres® for use in combination with 5-fluorouridine chemotherapy by hepatic arterial infusion (HAI) to treat unresectable hepatic metastases from 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 1 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 2 (RCTs have shown a survival benefit for TACE therapy compared with supportive care in patients with unresectable HCC.1,2 In 1 study, patients were randomly assigned to TACE, transarterial embolization (TAE), or supportive care. One-year survival rates for TACE, TAE, and supportive care were 82%, 75%, and 63%, respectively, and 2-year survival rates were 63%, 50%, and 27%, respectively. Targeted therapies have been investigated for HCC. For example, sorafenib was associated with improved OS in a randomized phase 3 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 5-year survival rates have been in the range of 20% to 43%.4 Patients with unresectable disease may select among fluoropyrimidine-based or gemcitabine-based chemotherapy, fluoropyrimidine chemoradiation or best supportive care.

Unresectable Metastatic CRC
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 5-year survival rates exceeding 50%. Emphasis on 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 in an attempt to downsize the metastases to convert the metastatic lesions to a resectable status (conversion chemotherapy).

In patients with unresectable disease that cannot be converted to resectable disease, the primary treatment goal is palliative, with survival benefit shown with both second- and third-line systemic chemotherapy.5 Recent advances in chemotherapy, including oxaliplatin, irinotecan, and targeted antibodies like cetuximab, have doubled the median survival in this population from less than 1 year to more than 2 years.5 Palliative chemotherapy by combined systemic and HAI may increase disease-free intervals for patients with unresectable hepatic metastases from CRC.

RFA has been shown to be inferior to resection in local recurrence rates and 5-year OS and is generally reserved for patients with potentially resectable disease that cannot be completely resected due to patient comorbidities, location of metastases (ie, adjacent to a major vessel), or an estimate of inadequate liver reserve following resection. RFA is generally recommended to be used with the goal of complete resection with curative intent.6 The role of local (liver-directed) therapy (including RE, chemoembolization, and conformal radiotherapy) in debulking unresectable metastatic disease remains controversial.6

Unresectable Metastatic Neuroendocrine Tumors
Neuroendocrine tumors are an uncommon, heterogeneous group of mostly slow-growing, hormonese-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, 5-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, as 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 analogs 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 compared with carcinoids, and is frequently associated with significant toxicity.7 Chemoembolization has shown response rates of nearly 80%, but the effect is of short duration and a survival benefit has not been demonstrated.7

Miscellaneous Metastatic Tumors
Small case reports have been published on the use of RE 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 sarcoma and lymphoma.8

Summary
Radioembolization (RE), also referred to as selective internal radiotherapy (SIRT), 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 tumor preferentially to normal liver, as 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.

The available evidence for the use of RE for the treatment of primary and metastatic liver tumors varies depending on the tumor type.

For the use of RE in the treatment of hepatocellular carcinoma (HCC), the evidence consists primarily of retrospective and prospective observational studies, with limited evidence from randomized controlled trials (RCTs). Observational studies suggest 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 of which demonstrated similar outcomes for RE. Evidence from observational studies demonstrates that RE can allow successful liver transplantation in certain patients. The available evidence, including clinical input, is sufficient to draw conclusions and to determine that outcomes are improved for the use of RE for the treatment of primary HCC that is unresectable and limited to the liver or as a bridge to liver transplantation.

For the use of RE in the treatment of hepatic metastases from neuroendocrine tumors, the evidence consists of 1 open-label phase 2 study, retrospective reviews, and case series, some of which compare RE with other transarterial liver-directed therapies. This evidence suggests that RE has similar outcomes to standard therapies and historical controls for patients with neuroendocrine tumor-related symptoms or progression of liver tumor burden. There was support from clinical input for the use of RE for the treatment of hepatic metastases from neuroendocrine tumors. Therefore, the available evidence is sufficient to determine that RE is associated with improved outcomes for the treatment of hepatic metastases from neuroendocrine tumors.

A major cause of morbidity and mortality in patients with colorectal disease metastatic to the liver is liver failure, as this disease tends to progress to diffuse, liver-dominant involvement. For the use of RE in the treatment of unresectable metastases from colorectal carcinoma (CRC), the evidence consists of several small- to moderate-sized RCTs, prospective trials, and retrospective studies using a variety of comparators, along with systematic reviews of these studies. Although this evidence describes wide ranges of clinical response to therapy, there was strong support from clinical input for the use of RE for the treatment of hepatic metastases from CRC; the use of RE to decrease tumor bulk, and/or halt the time to tumor progression and liver failure, may lead to prolonged progression-free and overall survival (OS) in patients with no other treatment options (ie, those with chemotherapy refractory liver-dominant disease). Other uses include palliation of symptoms from tumor bulk. Therefore, the available evidence is
sufficient to determine that RE is associated with improved outcomes for the treatment of CRC liver metastases with liver-dominant disease.

For the use of RE for the treatment of intrahepatic cholangiocarcinoma, the evidence consists of retrospective and prospective observational studies, some of which compare RE with alternative therapies. Although no randomized trials are available, there is some suggestion that RE for primary intrahepatic cholangiocarcinoma has response rates similar to those seen with standard chemotherapy. RE may play a role in patients with unresectable tumors that are chemorefractory or unable to tolerate systemic chemotherapy. Clinical input in 2015 supported the use of RE for intrahepatic cholangiocarcinoma. Given the low likelihood of large-scale clinical trials for this rare tumor, the available evidence is sufficient to conclude that RE is associated with improved outcomes for patients with primary intrahepatic cholangiocarcinoma.

Similarly, for other tumors metastatic to the liver, including breast cancer and melanoma, the evidence consists of observational studies. In 2015, clinical input supported the use of RE for the treatment of liver-dominant metastases from breast cancer and melanoma in patients who are not candidates for or who have not responded to systemic therapies. Given the clinical input, the available evidence is sufficient to conclude that RE is associated with improved outcomes for patients with hepatic metastases from breast cancer and melanoma with liver-dominant disease.

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
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<tbody>
<tr>
<td>8/2017</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>8/2016</td>
<td>Policy statement on neuroendocrine tumors clarified to indicate carcinoid and noncarcinoid, as classified on pathology report or by WHO classification. 8/1/2016</td>
</tr>
<tr>
<td>5/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
</tr>
<tr>
<td>1/2014</td>
<td>Coding information clarified.</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

**References**


