Protocol

Radioembolization for Primary and Metastatic Tumors of the Liver

(80143)

Medical Benefit		**Effective Date**: 10/01/14	**Next Review Date**: 07/15
Preauthorization	Yes	**Review Dates**: 07/07, 07/08, 05/09, 05/10, 09/10, 07/11, 07/12, 07/13, 07/14	

The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. ***Preauthorization is required.*** *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.*

Description

Radioembolization (RE), referred to as selective internal radiation therapy (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.

Hepatic tumors can arise either as primary liver cancer or by metastasis to the liver from other organs. Local therapy by surgical resection with tumor-free margins or liver transplantation is the only potentially curative treatment. Unfortunately, most hepatic tumors are unresectable at diagnosis, due either to their anatomic location, size, number of lesions, concurrent nonmalignant liver disease, or insufficient hepatic reserve.

Background

The use of external beam radiotherapy (EBRT) and the application of more advanced radiotherapy approaches (e.g., intensity-modulated radiotherapy [IMRT]) 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 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, and at that time, a mixture of albumin particles is delivered via the hepatic artery to simulate microspheres. After, single-photon emission computed tomography (SPECT) gamma 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® (MDS Nordion Inc., Ontario, Canada) and a resin sphere, SIR-Spheres® (Sirtex Medical Limited; Lake Forest, IL).

Noncommercial forms are mostly used outside the U.S. 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 (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. Note also that the U.S. Food and Drug Administration (FDA) granted premarket approval of SIR-Spheres® for use in combination with 5-floxuridine (5-FUDR) chemotherapy by hepatic arterial infusion (HAI) 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 hepatocellular carcinoma (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.

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 (RCTs) have shown a survival benefit using transarterial chemoembolization (TACE) therapy versus supportive care in patients with unresectable HCC. (1, 2) In one study, patients were randomly assigned to TACE, TAE, or supportive care. One-year survival rates for TACE, TAE, and supportive care were 82%, 75%, and 63%, respectively, and two-year survival rates were 63%, 50%, and 27%, respectively. A recent multicenter, randomized, double-blind placebo controlled Phase III trial that enrolled 602 patients with advanced HCC randomly assigned patients to receive sorafenib versus placebo. (3) Overall survival (OS) was significantly longer in the sorafenib group compared with placebo (10.7 vs. 7.9 months, respectively; hazard ratio [HR] for sorafenib, 0.69; $p < 0.001$).

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%. (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 five-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 one year to more than two years. (5) Palliative chemotherapy by combined systemic and HAI may increase disease-free (DF) intervals for patients with unresectable hepatic metastases from colorectal cancer.

RFA has been shown to be 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 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 radiation therapy) in debulking unresectable metastatic disease remains controversial. (6)

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, 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 for sarcoma and lymphoma. (8)

Related Protocols

Cryosurgical Ablation of Primary or Metastatic Liver Tumors

Radiofrequency Ablation of Primary or Metastatic Liver Tumors

Microwave Tumor Ablation

Transcatheter Arterial Chemoembolization (TACE) to Treat Primary or Metastatic Liver Malignancies

Policy (Formerly Corporate Medical Guideline)

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 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 that are both progressive and diffuse, in patients with liver-dominant disease who are refractory to chemotherapy or are not candidates for chemotherapy.

Radioembolization is considered **investigational** for all other hepatic metastases except as noted above.

Radioembolization is considered **investigational** to treat primary intrahepatic cholangiocarcinoma.

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 3 cm.

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

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.**

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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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