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# MEDICAL POLICY – 8.01.521

# Radioembolization for Primary and Metastatic Tumors of the Liver

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| BCBSA Ref. Policy: | 8.01.43 |
| Effective Date: | Oct. 1, 2024 |
| Last Revised: | Sept. 9, 2024 |
| Replaces: | 8.01.43 |

RELATED MEDICAL POLICIES:

| | |
|---|---|
| 7.01.95 | Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors |
| 7.01.133 | Microwave Tumor Ablation |
| 8.01.11 | Transcatheter Arterial Chemoembolization (TACE) to Treat Primary or Metastatic Liver Malignancies |

**Select a hyperlink below to be directed to that section.**

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

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## Introduction

Embolization is a procedure to block blood flow. Combined with radiation, it is a way to treat cancer in the liver in some situations. In this procedure a catheter (a long, thin, hollow tube) is inserted in an artery near the groin. It's threaded to the tumor's blood supply. Tiny radioactive particles are released into the artery that feeds the tumor. The particles travel into the tumor and block off — embolize — the blood supply feeding the tumor, causing it to shrink. The radiation works to kill the cancer cells. The radiation dissipates in a few weeks and the particles stay in the liver permanently. The radiation usually doesn't affect the healthy liver tissue around the tumor very much. This policy describes when radioembolization may be considered medically necessary.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria

| Service | Medical Necessity |
|---|---|
| **Radioembolization** | **Radioembolization may be considered medically necessary in the following situations:**<br>• Treatment of primary hepatocellular carcinoma that is unresectable and limited to the liver (size of tumor(s) does not exceed total tumor size of 8 cm, and individual with good performance status)<br>**OR**<br>• Treatment of primary hepatocellular carcinoma as a bridge to liver transplantation<br>**OR**<br>• Treatment of primary intrahepatic cholangiocarcinoma in individuals with unresectable tumors<br>**OR**<br>• Treatment of hepatic metastases from neuroendocrine tumors (carcinoid and noncarcinoid) with diffuse and symptomatic disease when systemic therapy has failed to control symptoms (symptoms related to excess hormone production)<br>**OR**<br>• Treatment of unresectable hepatic metastases from colorectal carcinoma, melanoma (ocular or cutaneous), or breast cancer with the following characteristics:<br>  ○ That are both progressive and diffuse in individuals with liver-dominant disease, **and**<br>  ○ That are refractory to chemotherapy or are not candidates for chemotherapy or other systemic therapies |

| Service | Investigational |
|---|---|
| **Radioembolization** | **Radioembolization is considered investigational for all other hepatic metastases except as noted in the Medical Necessity section above.** |

| Service | Investigational |
|---|---|
| | **Radioembolization is considered investigational for all other indications not described in the Medical Necessity section above.** |

| Documentation Requirements |
|---|

**The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include office visit notes that contain the relevant history and physical supporting ANY of the following situations:**

- Individual with primary liver cancer that cannot be removed by surgery and limited to the liver (size of tumor(s) does not exceed total tumor size of 8 cm , and individual with good performance status)
- Treatment for hepatocellular carcinoma before a liver transplant
- Treatment of primary intrahepatic cholangiocarcinoma that cannot be removed by surgery
- Treatment of hepatic metastases from neuroendocrine tumors (carcinoid and noncarcinoid) with diffuse and symptomatic disease when systemic therapy has failed to control symptoms (symptoms related to excess hormone production)
- Treatment of hepatic metastases from breast, colorectal, or melanoma (ocular or cutaneous) that cannot be removed by surgery with the following characteristics:
    - That are progressive and unresectable in individual liver dominant disease

**AND**

    - That failed chemotherapy or are not candidates for chemotherapy or other systemic therapies

## Coding

The coding for radioembolization may depend on the medical specialty providing the therapy.

| Code | Description |
|---|---|
| **CPT** | |
| 37243 | Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction. |
| 75894 | Transcatheter therapy, embolization, any method, radiological supervision and interpretation |

| Code | Description |
|---|---|
| 79445 | Radiopharmaceutical therapy, by intra-arterial particulate administration |
| **HCPCS** | |
| C2616 | Brachytherapy source, nonstranded, yttrium-90, per source |
| S2095 | Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using ytrrium-90 microspheres |

**Note**: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

## Related Information

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 individuals 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.

### Definition of Terms

**Child-Pugh Score:** This score is used to assess the prognosis of chronic liver disease, usually cirrhosis.

**Eastern Cooperative Oncology Group (ECOG):** The ECOG performance status is used to assess an individual's disease progression and how the disease impacts the individual's activities of daily living (ADLs). **http://www.ecog.org/** (Accessed August 8, 2024)

## Evidence Review

## Description

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.

## Background

## Treatments for Hepatic and NeuroEndocrine Tumors

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 individuals with multiple diffuse lesions due to the low tolerance of the 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), particle and wave physics (microwave or laser ablation), or arterial embolization therapy including chemoembolization, bland embolization, or radioembolization.

## Radioembolization

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.

Currently, two commercial forms of Y90 microspheres are available: a glass sphere (TheraSphere) and a resin sphere (SIR-Spheres). Noncommercial forms are mostly used outside the US. 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 (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 US Food and Drug Administration (FDA) granted premarket approval of SIR-Spheres for use in combination with 5-floxuridine 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 individuals 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 (see **Regulatory Status** section).

## Summary of Evidence

For individuals who have unresectable hepatocellular carcinoma (HCC) who receive RE or RE with a liver transplant, the evidence includes primarily retrospective and prospective nonrandomized 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. Nonrandomized 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 drug-eluting bead (DEB)-TACE. Both trials reported similar outcomes for RE compared with alternatives. Evidence from nonrandomized studies has demonstrated that RE can permit successful liver transplantation in certain individuals. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable intrahepatic cholangiocarcinoma (ICC) who receive RE, the evidence includes a phase 2 study and 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. Due to high study heterogeneity, it is difficult to identify individuals that are most likely to benefit from treatment. A phase 2 study of RE with chemotherapy in the first-line setting reported a response rate of 39% and a disease control rate of 98%. The efficacy of RE in the neoadjuvant setting is being evaluated in an ongoing follow-up RCT. Another phase 2 study evaluating RE with or without subsequent chemotherapy in patients without prior treatment with chemotherapy or radiation found overall response rates of 25% and 16.7% in those who received RE with and without chemotherapy, respectively; the disease control rates were 75% and 58.3% amongst those who received RE with and without chemotherapy, respectively. However, at this time, the evidence is not yet sufficiently robust to draw definitive conclusions about treatment efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 individuals with neuroendocrine tumor-related symptoms or progression of the liver tumor. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable intrahepatic metastases from colorectal carcinoma (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. While studies of individuals with prior chemotherapy failure have methodologic problems and have not shown definitive superiority of RE compared with alternatives in terms of survival benefit, they tend to show greater tumor response and significantly delayed disease progression, particularly with combined use of RE and chemotherapy. For example, the Efficacy Evaluation of TheraSphere Following Failed First Line Chemotherapy in Metastatic Colorectal Cancer (EPOCH) RCT found significantly prolonged primary endpoints of progression free survival (PFS) (Hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.54 to 0.88) and hepatic PFS (HR, 0.59; 95% CI, 0.46 to 0.77) with combined RE and chemotherapy in individuals who had progressed on first-line chemotherapy. 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 (e.g., breast, melanoma, pancreatic) who receive RE, the evidence includes nonrandomized 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 that the technology results in an improvement in the net health outcome.

## Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in **Table 1**.

## Table 1. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| **Hepatocellular carcinoma** | | | |
| **Ongoing** | | | |
| **NCT06040099**[a] | Phase II Single-Arm Study of Durvalumab and Bevacizumab Following Transarterial Radioembolization Using Yttrium-90 Glass Microspheres (TheraSphere) in Unresectable Hepatocellular Carcinoma Amenable to Locoregional Therapy | 100 | Jul 2026 (recruiting) |
| **NCT06166576** | An Open-label, Prospective, Multi-center Clinical Trial to Evaluate the Efficacy and Safety of Ablative Radioembolization Using Yttrium-90 Glass Microspheres in Patients With Locally-advanced Hepatocellular Carcinoma | 30 | Nov 2027 (recruiting) |
| **NCT05953337**[a] | Radioembolization Oncology Trial Utilizing Transarterial Eye90 (ROUTE 90) for the Treatment of Hepatocellular Carcinoma (HCC) | 120 | Oct 2025 (recruiting) |
| **NCT04736121**[a] | A Prospective, Multicenter, Open-label Single Arm Study Evaluating the Safety & Efficacy of Selective Internal Radiation Therapy Using SIR-Spheres Y-90 Resin Microspheres on DoR & ORR in Unresectable Hepatocellular Carcinoma Patients (DOORwaY90) | 100 | Jun 2025 (recruiting) |
| **NCT04522544**[a] | A Phase II Study of Immunotherapy With Durvalumab (MEDI4736) and Tremelimumab in Combination With | 55 | Sep 2025 (recruiting) |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| | Either Y-90 SIRT or TACE for Intermediate Stage HCC With Pick-the-winner Design | | |
| NCT04069468[a] | A Prospective, Post Approval, Multiple Centre, Open-Label, Non-Interventional, Registry Study to Evaluate Effectiveness of TheraSphere in Clinical Practice in France (PROACTIF) | 500 | Jan 2025 (active) |
| NCT05377034[a] | A Multinational, Double-blind, Placebo-Controlled, Parallel Randomized Arms, Phase II Trial to Compare Safety and Efficacy of Selective Internal Radiation Therapy (Y-90 Resin Microspheres) Followed by Atezolizumab Plus Bevacizumab) Versus Selective Internal Radiation Therapy (SIRT-Y90) Followed by Placebo in Patients With Locally Advanced Hepatocellular Carcinoma (HCC) (STRATUM) | 176 | Oct 2026 (recruiting) |
| NCT05063565[a] | An Open-Label, Prospective, Multi-Center Clinical Trial to Evaluate the Efficacy and Safety of TheraSphere Followed by Durvalumab (Imfinzi) With Tremelimumab (Imjudo) for Hepatocellular Carcinoma (HCC) | 100 | June 2027 (recruiting) |
| **Unpublished** | | | |
| NCT04090645 | A Humanitarian Device Exemption Treatment Protocol of TheraSphere for Treatment of Unresectable Primary or Unresectable Secondary Liver Cancer | 187 | Apr 2021 (completed) |
| NCT01176604 | Protocol for Use of TheraSphere for Treatment of Unresectable Hepatocellular Carcinoma | 299 | Apr 2021 (completed) |
| NCT01556490[a] | A Phase III Clinical Trial of Intra-arterial TheraSphere in the Treatment of Patients With Unresectable Hepatocellular Carcinoma (HCC) (STOP-HCC) | 526 | Apr 2022 (completed) |
| NCT02072356 | A Humanitarian Device Exemption Treatment Protocol of TheraSphere For Treatment of Unresectable Hepatocellular Carcinoma | 290 | Jun 2021 (completed) |
| **Metastatic colorectal cancer** | | | |
| NCT05195710[a] | Preoperative Y-90 Radioembolization for Tumor Control and Future Liver Remnant Hypertrophy in Patients With Colorectal Liver Metastases | 50 | Mar 2024 (recruiting) |
| **Intrahepatic Cholangiocarcinoma** | | | |
| **Ongoing** | | | |
| NCT06375915 | Single Arm, Multicenter Phase II Study Investigating the Efficacy and Safety of a Novel Therapeutic Scheme in | 33 | Jan 2026 (recruiting) |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| | Patients With Unresectable CholAngiocarcinoma: RadioEmbolization in Combination With CisGem and Durvalumab (MEDI4736) | | |
| **Unpublished** | | | |
| NCT02807181[a] | SIRT Followed by CIS-GEM Chemotherapy Versus CIS-GEM Chemotherapy Alone as 1st Line Treatment of Patients With Unresectable Intrahepatic Cholangiocarcinoma (SIRCCA) | 89 | Oct 2022 (completed) |
| **Neuroendocrine Tumors** | | | |
| NCT04362436[a] | A Phase II Assessment of the Safety and Efficacy of TheraSphere Selective Internal Radiation Therapy (SIRT) in the Treatment of Metastatic (Liver) Neuroendocrine Tumours (NETs) (ArTisaN) | 24 | Sep 2024 (recruiting) |
| **Metastatic uveal melanoma** | | | |
| NCT02936388 | Transarterial Radioembolisation in Comparison to Transarterial Chemoembolisation in Uveal Melanoma Liver Metastasis (SirTac) | 108 | Dec 2022 (unknown status) |
| **Metastatic Breast Cancer** | | | |
| NCT06142344 | The Added Value of 166Ho Trans-arterial Radioembolization to Systemic Therapy in Liver Metastatic Breast Cancer Patients | 13 | Jan 2026 (recruiting) |

NCT: national clinical trial. [a] Denotes industry-sponsored or cosponsored trial.

## Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

## 2015 Input

In response to requests, input was received from three physician specialty societies (with five individual responses) and one academic medical center (with four individual responses), for a total of 9 respondents, while this policy was under review in 2015. There was consensus supporting the use of radioembolization (RE) for hepatic metastases from melanoma, particularly ocular melanoma, and breast cancer. There was also consensus supporting the use of RE for treatment of primary intrahepatic cholangiocarcinoma. There was less consensus on the use of RE for hepatic metastases from other specific tumor types, including pancreatic cancer. However, many reviewers supported the use of RE for treatment of other radiosensitive tumors metastatic to the liver with the liver-limited or liver-dominant disease for symptom palliation or prolongation of survival.

## 2010-2011 Input

In response to requests, input was received from two physician specialty societies (with five individual responses) and six academic medical centers, for a total of 11 respondents, while this policy was under review in 2010 and again in 2011. For the 2011 review, input was received from two physician specialty societies and three academic medical centers; all but one academic medical center had provided input in 2010. There was strong support for the use of RE in individuals with primary hepatocellular carcinoma, as a bridge to liver transplant in hepatocellular carcinoma, and in neuroendocrine tumors. There was also strong support for use of RE in individuals with liver metastases from colorectal cancers and support for its use in individuals with liver metastases from other cancers but with less consensus than for colorectal metastases. Those providing input were split as to whether RE should be used as monotherapy or in combination with other agents.

The support for the use of RE in individuals with chemotherapy-refractory colorectal metastases was primarily to prolong time to tumor progression and subsequent liver failure (a major cause of morbidity and mortality in this patient population), potentially prolonging survival. Additional support for the use of RE in this setting was for the palliation of symptoms from tumor growth and tumor bulk.

Support for the use of RE for liver metastases from tumors other than colorectal or neuroendocrine was generally limited to a number of specific tumor types, in particular, ocular melanoma, cholangiocarcinoma, breast, and pancreas.

## Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

## American College of Radiology et al

In 2021, the American College of Radiology issued a practice parameter jointly developed with the American Brachytherapy Society, the American College of Nuclear Medicine, the American Society for Radiation Oncology, the Society of Interventional Radiology, and the Society of Nuclear Medicine and Molecular Imaging addressing the use of RE for the treatment of liver malignancies with glass- or resin-based yttrium-90 microspheres.[100] The guidelines provided indications and contraindications for treatment as follows:

- "Indications for both agents include but are not limited to the following:
    - The presence of unresectable or inoperable primary or secondary liver malignancies (particularly colorectal cancer and neuroendocrine tumor metastases). The tumor burden should be liver dominant, not necessarily exclusive to the liver. Individuals should also have a performance status that will allow them to benefit from such therapy.
    - A life expectancy of at least 3 months."
- "Absolute contraindications include the following:
    - Inability to catheterize the hepatic artery
    - Fulminant liver failure
    - Initial mapping angiography and/or technetium-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy demonstrating nontarget deposition to the gastrointestinal organs that cannot be corrected by angiographic techniques.
    - Pretreatment hepatic arterial administration with technetium-99m MAA demonstrative of unfavorable (or unacceptable) shunt function between the liver and the pulmonary parenchyma. This shunt fraction must not be greater than acceptable limits specific to each brachytherapy device.

- Active hepatic infection
- Therapy during pregnancy may possibly be an option in extraordinary circumstances and with multidisciplinary consult and considerations."

- "Relative contraindications include the following:
  - Excessive tumor burden in the liver with great than 50-70% of the parenchyma replaced by tumor. In the setting of more extensive tumor burden, treatment can be considered if synthetic hepatic function is preserved.
  - Total bilirubin greater than 2 mg/dL (in the absence of obstructive cause), which indicates severe liver function impairment. Nonobstructive bilirubin elevations may indicate that liver metastases have caused liver impairment to the degree that risks outweigh benefits for this therapy. In contrast, individuals with hepatocellular carcinoma (HCC) and elevated bilirubin may be treated with radioembolization if a segmental or subsegmental infusion can be performed.
  - Prior radiation therapy to the liver or upper abdomen that included a significant volume of the liver (clinical judgment by the [authorized user] required).
  - Care must be employed when individuals are on systemic therapies that may potentiate or may alter the impact of radioembolization and should use caution when combining therapies."

## American Society of Clinical Oncology

The 2023 American Society of Clinical Oncology (ASCO) guidelines for the treatment of metastatic colorectal cancer (mCRC) makes the following relevant recommendation: [101]

- "SIRT [selective internal radiation therapy] is not routinely recommended for patients with mCRC and unilobar or bilobar metastases of the liver (Type: Evidence-based, harms outweigh benefits; Evidence quality: Low; Strength of recommendation: Weak)."

## National Comprehensive Cancer Network

### Primary Hepatocellular Carcinoma

The National Comprehensive Cancer Network (NCCN) guidelines (v.1.2024) on the treatment of hepatocellular 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. Individuals should be considered for locoregional therapy if they are not candidates for potential curative treatments (resection, transplantation, and for small lesions, ablative strategies). RE with yttrium-90 microspheres has an increased risk of radiation-induced liver disease in individuals with bilirubin levels greater than 2 mg/dL. Delivery of 205 Gy or more to the tumor may be associated with increased overall survival. A dose of greater than 400 Gy to 25% of the liver or less in patients with Child-Pugh A liver function is recommended. For anatomically limited disease, radiation segmentectomy with yttrium-90 or ablative dose stereotactic body radiation therapy should be considered. RE may be more appropriate in some individuals with advanced HCC, specifically individual with segmental or lobar portal vein, rather than main portal vein, thrombosis.[29]

### Metastatic Neuroendocrine Tumors

The NCCN guidelines (v.1.2023) on the treatment of neuroendocrine tumors recommend consideration of transarterial radioembolization (TARE) for lobar or segmental disease distribution and in patients with prior Whipple surgery or biliary tract instrumentation.[102] TARE is better tolerated than transarterial embolization/transarterial chemoembolization, but late radioembolization-induced chronic hepatotoxicity may occur in long-term survivors, and is particularly a concern among patients undergoing bilobar radioembolization.

### Metastatic Colon Cancer

The NCCN guidelines (v.3.2024) 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 individuals with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases." RE may also be considered "when hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume…" The guidelines also note that "further investigation is necessary to

identify the role of radioembolization at earlier stages of disease, particularly in patients with right-sided primary origin."[103]

### Metastatic Uveal Melanoma

The NCCN guidelines (v.1.2024) on the treatment of uveal melanoma state the following regarding RE: "Further study is required to determine the appropriate patients for and risk and benefits of this approach."[104]

## National Institute for Health and Care Excellence

### Primary Hepatobiliary Carcinoma

The July 2013 NICE interventional procedures guidance on selective internal radiation therapy for primary hepatocellular carcinoma states that the evidence for efficacy and safety are adequate for use with normal arrangements. However, "uncertainties remain about its comparative effectiveness, and clinicians are encouraged to enter eligible patients into trials comparing the procedure against other forms of treatment."[105]

In March 2021, a NICE technology appraisal guidance on sSIRTs for treating hepatocellular carcinoma was published, providing specific evidence-based recommendations for the use of SIR-Spheres (Sirtex), TheraSphere (Boston Scientific), and QuiremSpheres (Quirem Medical).[102] The guidance states that RE with SIR-Spheres or TheraSphere is recommended as an option for treating unresectable advanced hepatocellular carcinoma in adults only if "used for people with Child-Pugh grade A liver impairment when conventional transarterial therapies are inappropriate, and the company provides [the microspheres] according to the commercial arrangement." The guidance also stated that "clinical trial data for these SIRTs compared with other treatment options are limited. But, compared with sorafenib, SIRTs may have fewer and more manageable adverse effects, which can improve quality of life." The use of QuiremSpheres, imageable holmium-166 microspheres, was not recommended due to reduced clinical efficacy compared to sorafenib and higher cost. QuiremSpheres received its CE mark in April 2015 in Europe and is not commercially available in the US.

### Primary Intrahepatic Cholangiocarcinoma

The October 2018 NICE interventional procedures guidance on sSIRT for unresectable primary intrahepatic cholangiocarcinoma state that there are "well-recognized, serious but rare safety concerns. Evidence on its efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research."[106]

### Metastatic Colon Cancer

The March 2020 NICE interventional procedures guidance on SIRT for unresectable colorectal metastases in the liver states that "in people who cannot tolerate chemotherapy or have liver metastases that are refractory to chemotherapy, there is evidence of efficacy, but this is limited, particularly for important outcomes such as quality of life. Therefore, in these people, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research."[107]

## Medicare National Coverage

There is no national coverage determination.

## Regulatory Status

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

In 1999, TheraSphere (Boston Scientific; previously 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 individuals with unresectable hepatocellular carcinoma who can have placement of appropriately positioned hepatic arterial catheters (H980006).

On March 17, 2021, TheraSphere received approval through the premarket approval process for use as selective internal radiation therapy (SIRT) for local tumor control of solitary tumors (1-8 cm in diameter), in individuals with unresectable hepatocellular carcinoma, Child-Pugh Score A cirrhosis, well-compensated liver function, no macrovascular invasion, and good performance status (P200029).

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.

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## History

| Date | Comments |
|---|---|
| 03/30/04 | Add to Therapy Section - New Policy |
| 03/08/05 | Replace Policy - Policy reviewed; reference added; policy statement unchanged. |
| 03/14/06 | Replace Policy - Policy reviewed; reference added; policy statement unchanged. |
| 06/02/06 | Scope and Disclaimer Update - No other changes. |
| 11/14/06 | Replace Policy - Policy reviewed by Oncology Advisory panel and recommended for adoption on October 26, 2006. |
| 04/10/07 | Cross Reference Update - No other changes. |
| 06/15/07 | Cross Reference Update - No other changes. |
| 10/09/07 | Replace Policy - Policy updated with literature review through February 2007; policy statement unchanged. Additional humanitarian device exemption indication for glass spheres for primary hepatocellular cancer noted. Reference added. CPT coding updated. |
| 03/19/08 | Code Update - ICD-9 diagnosis code 197.7 added. |
| 11/11/08 | New PR Policy - Policy updated with literature search. Policy statement changed to medically necessary with bulleted criteria. This was changed to keep consistent with the TACE (8.01.505) policy statement. Reviewed and recommended by OAP on August 21, 2008. Policy status changed from BC to PR, replacing BC.8.01.43. |
| 08/11/09 | Replace Policy - Policy updated with literature search; no change to the policy statement. References added. Reviewed and recommended by OAP August 2009. |
| 12/14/10 | Replace Policy - Policy updated with literature search; no change to policy statement. NCCN 2010 reference added. Reviewed and recommended by OAP November 18, 2010. |
| 10/11/11 | Replace Policy – Policy updated with literature review; no change in policy statement. |
| 02/27/12 | Related Policies updated; 7.01.133 added. |
| 05/22/12 | Replace policy. Policy updated with literature review through February 2012; no change in policy statements. Physician specialty society input and references added. Clinical Trials and NCCN Guidelines updated. |
| 11/15/12 | Replace Policy. Minor edit for clarification of the acronym for RE and SIRT. Verified NCCN hyperlinks still active. Policy statement unchanged. Reviewed and recommended by OAP November 2012. |
| 05/28/13 | Replace policy. Policy updated with literature review. Policy reorganized. No change in policy statements. References added, removed, renumbered. ICD-10 codes added. |

| Date | Comments |
|---|---|
| 07/16/13 | Update Related Policies. Add 8.01.528. |
| 12/23/13 | Coding Update. CPT code 37204 discontinued effective 12/31/13. |
| 03/14/14 | Coding update. CPT code 37243, effective 1/1/14, added to the policy. |
| 03/27/14 | Coding update; CPT codes 37243 removed from policy. It does not apply to this policy, see 8.01.521. |
| 09/03/14 | Annual Review. Added a policy statement indicating all other indications not listed as medically necessary are investigational. Policy Guidelines added including Definition of Terms. Policy updated with literature review through June, 2014. Rationale section reformatted. References 15-16, 22-23, 32, 42-43, 48, 51 added. References 4-6 and 49-51 updated; others renumbered/removed. Policy statement added as noted. Coding update: CPT code 77776 added to the policy; ICD-9 and ICD-10 codes removed from policy – they are not utilized in adjudication of the policy. |
| 09/11/14 | Update Related Policies. Add 7.01.95. |
| 10/13/15 | Annual Review. Policy updated with literature review. Medically necessary indications were added for the treatment of hepatocellular carcinoma as a bridge to hepatic transplant. The indications for treatment of hepatic metastases from breast cancer or melanoma with liver dominant disease and intrahepatic cholangiocarcinoma were moved from medically necessary to investigational. These changes harmonize the medical necessity indications for this policy and 8.01.505- Transcatheter Arterial Chemoembolization (TACE) as a Treatment for Primary or Metastatic Liver Malignancies. References updated. |
| 07/01/16 | Annual Review, approved June 14, 2016. Prioritized annual review. Policy reformatted for clarity. Coverage added for symptomatic palliation of hepatic metastatic tumors. Criteria added for qualification for use as bridge to liver transplant in hepatocellular carcinomas. Discussion section clarified to support policy. Clinical trials section simplified. |
| 07/08/16 | Minor edit to investigational statement for clarity; intent is unchanged. |
| 10/01/16 | Interim Review, approved September 13, 2016. Policy updated with literature review through June 10, 2016; references 12-13, 47, and 49 added. Investigational statement added for previously untreated metastatic colorectal cancer. CPT codes 77776 and 77778 removed; deleted code as of 1/1/16 and reviewed by AIM, respectively. |
| 10/01/17 | Annual Review, approved September 5, 2017. No changes to policy statements. Policy updated with literature review through June 2017: references added 8-11, 15, 21, 31-32 and 56. |
| 03/01/18 | Coding update, removed CPT code 77399. |
| 10/01/18 | Annual Review, approved September 20, 2018. Policy updated with literature review through May 2018; references 16, 28, and 73 added. Policy statements unchanged. |

| Date | Comments |
|---|---|
| 11/01/19 | Annual Review, approved October 4, 2019. Policy updated with literature review through May 2019; references on NCCN updated. Policy statements unchanged. |
| 04/01/20 | Delete policy, approved March 10, 2020. This policy will be deleted effective July 2, 2020, and replaced with InterQual criteria for dates of service on or after July 2, 2020. |
| 06/10/20 | Interim Review, approved June 9, 2020, effective June 10, 2020. This policy is reinstated immediately and will no longer be deleted or replaced with InterQual criteria on July 2, 2020. |
| 08/01/2020 | Delete policy, approved July 14, 2020. This policy is replaced with 8.01.43. |
| 10/01/20 | Interim Review, approved September 17, 2020. Policy updated with literature review through May 2020; references added. Policy statements unchanged. |
| 05/18/21 | Update Related Policies. Corrected Renumbered Policy 8.01.505 to 8.01.11 |
| 10/01/21 | Annual Review, approved September 2, 2021. Policy updated with literature review through May 27, 2021; references added. Policy statements unchanged. |
| 09/01/22 | Annual Review, approved August 22, 2022. Policy updated with literature review through June 22, 2022; references added. NCCN and NICE guidelines updated. Policy statements unchanged. Added HCPCS code C2616. |
| 04/01/23 | Policy renumbered, approved March 14, 2023 from 8.01.43 to 8.01.521 Radioembolization for Primary and Metastatic Tumors of the Liver. Changed tumor size from 3 cm or larger to "size of tumor(s) does not exceed total tumor size of 8 cm" in the first policy bullet for medically necessary radioembolization treatment of primary hepatocellular carcinoma that is unresectable. Other minor edits made for clarification only, policy intent unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization where appropriate. |
| 10/01/23 | Annual Review, approved September 11, 2023. Policy updated with literature review through May 26, 2023; references added. Minor editorial refinements to policy statements; intent unchanged. |
| 10/01/24 | Annual Review, approved September 9, 2024. No changes to policy statements. |



**Scope**: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member

benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.