Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110
Original Effective Date: 02/23/2004
Current Effective Date: 05/10/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Microwave Tumor Ablation is addressed separately in medical policy 00569.

Note: Cryosurgical Ablation of Primary or Metastatic Liver Tumors is addressed separately in medical policy 00220.

Note: Radiofrequency Ablation of Primary or Metastatic Liver Tumors is addressed separately in medical policy 00182.

Note: Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies is addressed separately in medical policy 00227.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of radioembolization (RE) to treat primary hepatocellular carcinoma (HCC) that is unresectable and limited to the liver to be **eligible for coverage.**** (See Policy Guideline Section)

Based on review of available data, the Company may consider the use of radioembolization (RE) in primary hepatocellular carcinoma (HCC) as a bridge to liver transplantation to be **eligible for coverage.****

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Based on review of available data, the Company may consider radioembolization (RE) to treat primary intrahepatic cholangiocarcinoma (ICC) in patients with unresectable tumors to be **eligible for coverage.****

Based on review of available data, the Company may consider the use of radioembolization (RE) to treat hepatic metastases from neuroendocrine tumors (carcinoid and noncarcinoid) with diffuse and symptomatic disease when systemic therapy has failed to control symptoms to be **eligible for coverage.**** (See Policy Guideline Section)

Based on review of available data, the Company may consider the use of radioembolization (RE) to treat unresectable hepatic metastases from colorectal carcinoma (CRC), 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 to be **eligible for coverage.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers radioembolization for all other hepatic metastases except as noted above to be **investigational.***

Based on review of available data, the Company considers radioembolization (RE) for all other indications not described as above to be **investigational.***

Policy Guidelines

In general, radioembolization is used for unresectable hepatocellular carcinoma that is greater than 3 cm.

There is little information on the safety or efficacy of repeated radioembolization treatments or on the number of treatments that should be administered.

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Radioembolization should be reserved for patients with adequate functional status (Eastern Cooperative Oncology Group Performance Status 0-2), adequate liver function and reserve, Child-Pugh class A or B, and liver-dominant metastases.

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

Background/Overview

Treatments for Hepatic and Neuroendocrine Tumors

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 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, 2 commercial forms ofY90 microspheres are available: a glass sphere (TheraSphere) and a resin sphere (SIR-Spheres). Noncommercial forms are mostly used outside the U. S. While the commercial products use the same radioisotope (Y90) and have the same target dose (100 gray), they differ in microsphere size profile, base material (ie, resin vs glass), and size of commercially available doses. The physical characteristics of the active and inactive ingredients affect the flow of microspheres during injection, their retention at the tumor site, spread outside the therapeutic target region, and dosimetry calculations. The U.S. Food and Drug Administration 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 patients with hepatocellular carcinoma who have partial or branch portal vein thrombosis. For these reasons, results obtained with a product do not necessarily apply to another commercial (or non-commercial) products.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Currently, 2 forms ofY90 microspheres have been approved by the FDA.

In 1999, TheraSphere®‡ (manufactured by Nordion, under license by BTG International), a glass sphere system, was approved by the FDA through the humanitarian drug exemption process for radiotherapy or as a neoadjuvant treatment to surgery or transplantation in patients with unresectable hepatocellular carcinoma who can have placement of appropriately positioned hepatic arterial catheters (H980006).

In 2002, SIR-Spheres®‡ (Sirtex Medical), a resin sphere system, was approved by the FDA through the premarket approval process for the treatment of inoperable colorectal cancer metastatic to the liver (P990065).

FDA product code: NAW.

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Rationale/Source

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.

For individuals who have unresectable hepatocellular carcinoma who receive RE or RE with a liver transplant, the evidence includes primarily retrospective and prospective observational studies, with limited evidence from randomized controlled trials (RCTs). The relevant outcomes are overall survival (OS), functional outcomes, quality of life (QOL), and treatment-related morbidity. Observational studies have suggested that RE has high response rates compared with historical controls. Two small pilot RCTs have compared RE with alternative therapies for hepatocellular carcinoma, including transarterial chemoembolization and transarterial chemoembolization with drug-eluting beads. Both trials reported similar outcomes for RE compared with alternatives. Evidence from observational studies has demonstrated that RE can permit successful liver transplantation in certain patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have unresectable intrahepatic cholangiocarcinoma who receive RE, the evidence includes case series. The relevant outcomes are OS, functional outcomes, QOL, and treatment-related morbidity. Comparisons of these case series to case series of alternative treatments have suggested that RE for primary 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. However, the evidence is not yet sufficiently robust to draw definitive conclusions about treatment efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have unresectable neuroendocrine tumors who receive RE, the evidence includes an open-label phase 2 study, retrospective reviews, and case series, some of which have compared RE with other transarterial liver-directed therapies. The relevant outcomes are OS, functional outcomes, QOL, and treatment-related morbidity. This evidence has suggested that RE

provides outcomes similar to standard therapies and historical controls for patients with neuroendocrine tumor-related symptoms or progression of the liver tumor. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have unresectable intrahepatic metastases from colorectal cancer and prior treatment failure who receive RE, the evidence includes several small- to moderate-sized RCTs, prospective trials, and retrospective studies using a variety of comparators, as well as systematic reviews of these studies. The relevant outcomes are OS, functional outcomes, QOL, and treatment-related morbidity. RCTs of patients with prior treatment failure have methodologic problems, do not show definitive superiority of RE compared with alternatives but tend to show greater tumor response with RE. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have unresectable intrahepatic metastases from other cancers (eg, breast, melanoma, pancreatic) who receive RE, the evidence includes observational studies. The relevant outcomes are OS, functional outcomes, QOL, and treatment-related morbidity. These studies have shown significant tumor response; however, improvement in survival has not been demonstrated in controlled comparative studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input obtained in 2010, 2011, and 2015 has supported the use of RE for primary hepatocellular carcinoma, intrahepatic cholangiocarcinoma, hepatic metastases from neuroendocrine tumors, chemorefractory colorectal carcinoma, chemorefractory breast cancer, and chemorefractory melanoma, despite the lack of rigorous comparative clinical trials for many of the indications.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

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.

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2015 Input
In response to requests, input was received from 3 physician specialty societies (with 5 individual responses) and 1 academic medical center (with 4 individual responses), for a total of 9 respondents, while this policy was under review in 2015. There was consensus supporting the use of 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 2 physician specialty societies (with 5 individual responses) and 6 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 2 physician specialty societies and 3 academic medical centers; all but 1 academic medical center had provided input in 2010. There was strong support for the use of RE in patients 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 patients with liver metastases from colorectal cancers and support for its use in patients 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 patients 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

National Comprehensive Cancer Network

Primary Hepatobiliary Carcinoma
The NCCN guidelines (v.1.2020) on the treatment of hepatobiliary carcinoma indicate that the use of arterially directed therapies, including transarterial bland embolization, transarterial chemoembolization, and drug-eluting beads transarterial chemoembolization, and RE with yttrium-90 microspheres may be appropriate provided that the arterial blood supply can be isolated without excessive non-target treatment.

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

Metastatic Colon Cancer
The NCCN guidelines (v.3.2019) on the treatment of colon cancer provides a consensus recommendation that: "…arterial-directed catheter therapy, in particular yttrium-90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 1.

Table 1

NCT No.	Name	Planned Enrollment	Completion Date
Hepatocellular Carcinoma			
Ongoing			
NCT01135056	Phase III Multi-Centre Open-Label Randomized Controlled Trial of Selective Internal Radiation Therapy (SIRT) Versus Sorafenib in Locally Advanced Hepatocellular Carcinoma (SIRveNIB)	360	Jul 2018 (ongoing)
NCT01556490[a]	A Phase III Clinical Trial of Intra-arterial TheraSphere® in the Treatment of Patients With Unresectable Hepatocellular Carcinoma (HCC)	526	Sept 2019
Unpublished			
NCT01482442	A Prospective Randomized Open-labeled Trial Comparing RADIOEMBOLIZATION With Yttrium 90 Microspheres and Sorafenib in Patients With Advanced Hepatocellular Carcinoma	496	Apr 2016 (completed)
NCT00846131	A Single-Center Proof of Concept Pilot Study to Evaluate the Safety, Efficacy, and Tolerability of Sorafenib Combined With TheraSphere in Subjects With Hepatocellular Carcinoma Awaiting Liver Transplantation	24	Sep 2016 (completed)
NCT01381211	Transarterial RAdioembolization Versus ChemoEmbolization for the Treatment of HCC: A Multicenter Randomized Controlled Trial (TRACE Trial)	140	Dec 2016 (unknown)

NCT01556490[a]	A Phase III Clinical Trial of Intra-arterial TheraSphere® in the Treatment of Patients With Unresectable Hepatocellular Carcinoma (HCC)	529	Dec 2018 (Completed)
Metastatic colorectal cancer			
NCT01483027[a]	A Phase III Clinical Trial Evaluating TheraSphere® in Patients With Metastatic Colorectal Carcinoma of the Liver Who Have Failed First Line Chemotherapy	420	August 2020
Cholangiocarcinoma			
Ongoing			
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	June 2021
Unpublished			
NCT01912053	An Open-label, Multicenter, Phase II Trial, to Evaluate the Efficacy of Intra-hepatic Administration of Yttrium 90-labeled Microspheres (Therasphere®, Nordion) in Association With Intravenous Chemotherapy With Gemcitabine and Cisplatin for the Treatment of Intra-hepatic Cholangiocarcinoma, First Line	41	Nov 2017 (completed)
Metastatic uveal melanoma			
NCT02936388	Transarterial Radioembolisation in Comparison to Transarterial Chemoembolisation in Uveal Melanoma Liver Metastasis (SirTac)	108	Jan 2021

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 02/23/2004
Current Effective Date: 05/10/2021

01/31/2004	Medical Director review.
02/17/2004	Medical Policy Committee review.
02/23/2004	Managed Care Advisory Council approval.
02/01/2006	Medical Director review
02/15/2006	Medical Policy Committee review. Format revisions, Rationale/Source.
02/23/2006	Quality Care Advisory Council approval.
07/07/2006	Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
03/14/2007	Medical Director review.
03/21/2007	Medical Policy Committee approval. Coverage eligibility unchanged.
04/02/2009	Medical Director review.
04/15/2009	Medical Policy Committee approval. Added "(SIRT)" to title. Revised investigational statement from "Based on review of available data, the Company considers the use of internal radiation therapy for all indications including, but not limited to, the treatment of primary or metastatic tumors of the liver, to be investigational*" to "Based on review of available data, the Company considers selective internal radiation therapy using intra-arterial injection of radiolabeled microspheres to treat primary or metastatic liver tumors to be investigational.*" Coverage eligibility unchanged.
09/09/2010	Medical Policy Committee review.

Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110
Original Effective Date: 02/23/2004
Current Effective Date: 05/10/2021

09/15/2010	Medical Policy Implementation Committee approval. policy statement and title ("selective internal radiation therapy" changed to "radioembolization"). Policy statements changed to indicate that selective cases of hepatocellular carcinoma and metastatic neuroendocrine tumors may be considered medically necessary. Title changed to reflect current procedure name.
04/07/2011	Medical Policy Committee review.
04/13/2011	Medical Policy Implementation Committee approval. Added that "radioembolization to treat unresectable hepatic metastases from colorectal cancer that are both progressive and diffuse, in patients with liver-dominant disease who are refractory to chemotherapy or are not candidates for chemotherapy is eligible for coverage.
04/05/2012	Medical Policy Committee review.
04/18/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/11/2012	Medical Policy Committee review.
10/31/2012	Medical Policy Implementation Committee approval. Investigational statement for unresectable hepatic metastases from colorectal carcinoma removed since it is eligible for coverage.
10/03/2013	Medical Policy Committee review
10/16/2013	Medical Policy Implementation Committee approval. New investigational statement on intrahepatic cholangiocarcinoma added.
03/25/2014	Coding update due to codes added and deleted from policy
11/06/2014	Medical Policy Committee review
11/21/2014	Medical Policy Implementation Committee approval, Added "Based on review of available data, the Company considers radioembolization for all other indications not described as above to be investigational."
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015	Medical Policy Committee review
11/16/2015	Medical Policy Implementation Committee approval. Melanoma (ocular or cutaneous), or breast cancer added to eligibility statement for unresectable hepatic metastases.
11/03/2016	Medical Policy Committee review

Policy # 00110
Original Effective Date: 02/23/2004
Current Effective Date: 05/10/2021

11/16/2016	Medical Policy Implementation Committee approval. Medically necessary statements added for unresectable metastatic breast cancer and melanoma with liver-dominant disease and unresectable intrahepatic cholangiocarcinoma.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. No change to coverage.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. No change to coverage.
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/02/2020	Medical Policy Committee review
04/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/01/2021	Medical Policy Committee review
04/14/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 04/2022

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	37243, 75894, 77399, 77778, 79445
HCPCS	A9543, C2616, S2095
ICD-10 Diagnosis	C22.1, C22.9, C43.0-C43.9, C50.011-C50.929, C78.7, C79.81, D03.0-D03.9, D05.00- D05.92, D09.3, D09.8

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.