



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

**Policy #** 00110

**Original Effective Date:** 02/23/2004

**Current Effective Date:** 11/21/2018

*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.*

### **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**.

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**.

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**.

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**.

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**.

### **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 (RE) for all other hepatic metastases except as noted above to be **investigational**.\*

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

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.

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 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 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. Yttrium 90 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 is 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

Currently, 2 commercial forms of yttrium-90 microspheres are available: a glass sphere (TheraSphere) and a resin sphere (SIR-Spheres). Noncommercial forms are mostly used outside the United States. While the commercial products use the same radioisotope (yttrium 90) and have the same target dose (100 gray), they differ in microsphere size profile, base material (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 Food and Drug Administration (FDA) granted premarket approval of SIR-Spheres for use in combination with 5-fluorouridine 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 noncommercial) products.

### **FDA or Other Governmental Regulatory Approval**

#### **U.S. Food and Drug Administration (FDA)**

Currently 2 forms of yttrium-90 microspheres have been approved by the U.S. FDA.

In 1999, TheraSphere<sup>®†</sup> (manufactured by Nordion, Ontario, under license by BTG International), a glass sphere system, was approved by FDA through the humanitarian drug exemption process for radiation treatment or as a neoadjuvant 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<sup>®†</sup> (Sirtex Medical, Lake Forest, IL), a resin sphere system, was approved by FDA through the premarket approval process for the treatment of inoperable colorectal cancer metastatic to the liver.

FDA product code: NAW.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

### **Rationale/Source**

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

### **Radioembolization and/or liver transplant for unresectable hepatocellular carcinoma**

#### **Clinical Context and Test Purpose**

The purpose of radioembolization (RE) or radioembolization plus liver transplant in patients who have unresectable hepatocellular carcinoma (HCC) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does RE improve the net health outcome in individuals with unresectable HCC?

The following PICOTS were used to select literature to inform this review.

#### ***Patients***

The relevant population of interest is individuals with unresectable HCC who may or may not need a liver transplant. 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.

#### ***Interventions***

The treatment being considered is RE with or without a liver transplant.

#### ***Comparators***

The following practice is currently being used to make decisions about unresectable HCC: standard of care, often palliative. Results of 2 RCTs have shown a survival benefit for transarterial chemoembolization (TACE) therapy compared with supportive care in patients with unresectable HCC. One study randomized patients to TACE, transarterial embolization (TAE), or supportive care. One-year survival rates for TACE, TAE, and supportive care were 82%, 75%, and 63%, respectively; 2-year survival rates were 63%, 50%, and 27%, respectively. Targeted therapies have been investigated for HCC. For example, sorafenib was associated with improved overall survival (OS) in a randomized phase 3 trial evaluating 602 patients.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

### **Outcomes**

The general outcomes of interest are OS, functional outcomes, quality of life (QOL), and treatment-related morbidity.

### **Timing**

The time frame for outcomes measures varies from several months to 5 years.

### **Setting**

RE is delivered in a hospital setting having resources for management of radiopharmaceuticals.

## **RE for Unresectable HCC**

### **Systematic Reviews**

Tao et al (2017) reported on a network meta-analysis comparatively evaluating 9 minimally invasive surgeries for treatment of unresectable HCC. The interventions included were TACE, TACE plus sorafenib, sorafenib, TACE plus high-intensity focused ultrasound, TACE plus percutaneous ethanol injection, drug-eluting bead (DEB) plus TACE (DEB-TACE), yttrium-90 RE (90Y RE), TACE plus external-beam radiation therapy (EBRT), and ethanol ablation. The network included 17 studies with 2669 patients and 4 studies with 230 patients including 90Y RE. In a pairwise meta-analysis, patients treated with 90Y RE were more likely to achieve complete remission than those who received TACE (odds ratio [OR], 4.5; 95% confidence interval [CI], 1.3 to 15.1). However, in the network meta-analysis, there was no significant difference between the corresponding 8 treatments and TACE with respect to complete remission, partial response, stable disease, and objective response rate. The treatments were ranked for several outcomes using surface under the cumulative ranking curves. TACE plus EBRT had the highest surface under the cumulative ranking curves in complete remission (77%), partial response (89%), progressive disease (95%), and objective response rate (81%).

Ludwig et al (2017) conducted a meta-analysis of studies that indirectly compared DEB-TACE with 90Y RE for HCC. Fourteen studies (total N=2065 patients) comparing DEB-TACE or 90Y RE with conventional TACE for primary HCC treatment were included. The pooled estimate of median survival was 23 months for DEB-TACE and 15 months for RE. The estimated 1-year survival was significantly higher for DEB-TACE (79%) than for RE (55%; OR=0.57; 95% CI, 0.36 to 0.92; p=0.02). Survival did not differ statistically significantly at 2 or 3 years but did favor DEB-TACE. At 2 years, survival was 61% for DEB-TACE and 34% or RE (OR=0.65; 95% CI, 0.29 to 1.44; p=0.29) and at 3 years survival was 56% and 21% (OR=0.71; 95% CI, 0.21 to 2.55; p=0.62), respectively.

Two systematic reviews published in 2016 compared RE with TACE for the treatment of unresectable HCC. Lobo et al (2016) selected 5 retrospective observational studies (total N=533 patients). Survival at 1 year did not differ statistically between RE (42%) and TACE (46%; relative risk [RR], 0.93; 95% CI, 0.81 to 1.08; p=0.33). At 2 years, the survival rate was higher for RE (27% vs 18%; RR=1.36; 95% CI, 1.05 to 1.76;

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

$p=0.02$ ), but there was no statistically significant difference in survival rates at 3, 4, or 5 years. Postprocedural complications were also similar in the 2 groups. Facciorusso et al (2016) included 10 studies (total  $N=1557$  patients), two of which were RCTs. The OR for survival was not statistically significant at 1 year (OR=1.0; 95% CI, 0.8 to 1.3;  $p=0.93$ ) but favored RE in years 2 (OR=1.4; 95% CI, 1.1 to 1.90;  $p=0.01$ ) and 3 (OR=1.5; 1.0 to 2.1;  $p=0.04$ ).

Vente et al (2009) conducted a meta-analysis evaluating tumor response and survival in patients who received 90Y glass or resin microsphere RE for the treatment of primary HCC or metastases from colorectal cancer (CRC). (Refer to the Unresectable Metastatic CRC section for the data from the meta-analysis as pertains to that disease.) Selected studies were from 1986 through 2008 and presented tumor response (measured by computed tomography) and data on median survival times. To allow comparability of results for tumor response, the category of “any response” was introduced and included complete remission, partial response, and stable disease. Overall tumor response could only be assessed as any response because response categories were not uniformly defined in the analyzed studies. In 14 articles, clinical data were presented on tumor response and survival for 425 patients with HCC who had received 90Y RE. Treatment with resin microspheres (0.89) was associated with a significantly higher proportion of any response than glass microsphere treatment (0.78;  $p=0.02$ ). Median survival was reported in 7 studies, in which survival time was defined as survival from microsphere treatment or diagnosis or recurrence of HCC. Median survival from microsphere treatment varied between 7.1 months and 21.0 months, and median survival from diagnosis or recurrence ranged from 9.4 to 24.0 months.

### **Randomized Controlled Trials**

Kolligs et al (2015) reported on results for a small pilot RCT (the SIR-TACE study) comparing RE with TACE for the treatment of unresectable HCC. The trial included 28 subjects with unresectable HCC, preserved liver function, and an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 2 or less, with no vascular invasion or extrahepatic spread, who had 5 or fewer liver lesions or a single lesion of 10 cm or less. Patients were randomized to RE ( $n=13$ ) or TACE ( $n=15$ ). Over posttreatment follow-up, partial response rates were 13.3% for TACE and 30.8% for RE, with disease control rates (complete remission, stable disease, partial response) of 73.3% for TACE and 76.9% for RE. Median progression-free survival (PFS) was 3.6 months for TACE and 3.7 months for RE.

Pitton et al (2015) reported on results from a small RCT comparing RE with DEB-TACE for the treatment of unresectable HCC. The trial included 24 patients, with 12 randomized to each group. No deaths occurred within 30 days of the procedure. There were no statistically significant differences between groups in terms of in PFS (180 days for RE vs 216 days for DEB-TACE,  $p=0.619$ ) or OS (592 days for RE vs 788 days for DEB-TACE,  $p=0.927$ ).

### **Nonrandomized Comparative Studies**

Padia et al (2017) reported on a single-center, retrospective study (2010-2015) comparing segmental RE with segmental chemoembolization in 101 patients with localized, unresectable HCC not amenable to

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

ablation. Patients receiving chemoembolization had poorer ECOG Performance Status ratings and Child-Pugh class while those receiving RE had larger and more infiltrative tumors. Overall complete remission was 84% with RE and 58% with chemoembolization ( $p=0.001$ ). Median PFS was 564 days and 271 days ( $p=0.002$ ) and median OS was 1198 days and 1043 days ( $p=0.35$ ), respectively, for the RE group and the chemotherapy group.

Soydal et al (2016) retrospectively assessed outcomes for patients receiving RE and TACE for HCC. Each group included 40 patients. RE patients had a mean survival of 39 months vs 31 months for TACE patients ( $p=0.014$ ). There were no significant differences in complication or disease recurrence rates.

Oladeru (2016) retrospectively analyzed SEER registry data, comparing survival outcomes for patients with HCC receiving RE with EBRT. A total of 189 patients with unresectable HCC (77 receiving RE, 112 receiving EBRT) were treated between 2004 and 2011. Median OS for RE was 12 months and 14 months for EBRT. Median disease-specific survival was identical for both groups at 14 months. After adjustment for differences between patients, multivariable survival analysis showed no association between treatment and OS or disease-specific survival.

El Fouly et al (2015) reported on results of a nonrandomized study comparing RE with TACE for 86 patients with intermediate stage, nonresectable HCC. Sixty-three patients at a single institution were treated with TACE, while 53 patients at a second institution were treated with RE. Median OS for TACE (18 months) and RE (16.4 months) did not differ significantly between groups; similarly, the median time to progression did not differ significantly between groups (6.8 months for TACE vs 13.3 months for RE). TACE patients had more treatment sessions, lengthier hospital stays, and higher adverse event rates.

Gramenzi et al (2015) conducted a retrospective cohort study comparing RE with the kinase inhibitor sorafenib for intermediate- or advanced-stage HCC. Patients with HCC refractory to other therapies and no metastases or systemic chemotherapy were included, 74 of whom were treated with sorafenib and 63 with RE. Median OS between groups was similar (14.4 months for sorafenib-treated patients vs 13.2 months for RE-treated patients). After propensity-score matching of 32 subjects in each group, there were no significant differences in median OS or 1-, 2-, and 3-year survival rates between groups.

Carr et al (2010) reported on a consecutive series of patients with HCC seen at a single medical center and not candidates for surgical resection. Patients received conventional cisplatin-TACE between the years 1992 and 2000 ( $n=691$ ), Y90 microspheres between 2000 and 2005 ( $n=99$ ), or no treatment ( $n=142$ ). Median OS for the Y90 group was 11.5 months (95% CI, 8 to 16 months) and 8.5 months (95% CI, 8 to 10 months) for the TACE group ( $p<0.05$ ). Untreated patients had a median survival of 2 months. Although the authors detected a slight selection bias toward milder disease in the RE group, they concluded that Y90 and TACE appeared to be equivalent regional therapies for patients with unresectable, nonmetastatic HCC.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

### Section Summary: RE for Unresectable HCC

Systematic reviews, RCTs, and nonrandomized comparative studies have not demonstrated the superiority of RE over alternative active comparators. If the active comparators are effective treatments for HCC, then these results are consistent with some degree of efficacy for RE in the treatment of HCC. Limitations of the existing evidence include lack of formal noninferiority analysis, which would be helpful to establish whether RE is as effective as alternatives, and the small size of the available RCTs, which limits conclusions about the relative efficacy of RE vs alternatives. Nonetheless, in all studies, tumor response is observed, which may improve survival.

### RE as a Bridge to Liver Transplantation for Unresectable HCC

#### Systematic Reviews

Kulik et al (2018) published a systematic review of 18 comparative studies and 31 noncomparative studies that included patients with unresectable HCC who needed a liver transplant and received transplant alone or some type of bridging therapy as well (see Table 1). Of the 18 comparative studies, 2 studies (n=257 patients) reported on the incidence of dropout from transplantation wait-lists, and patients receiving bridging therapy. This group had reduced risk of dropout due to disease progression, compared with those receiving transplantation alone (RR=0.32) (see Table 2). Between-group differences were not statistically significant for mortality (5 comparative studies; n=531 patients) or recurrence rate (10 comparative studies; n=889 patients). Subgroup analysis was conducted for types of bridging therapy: for all-cause mortality after transplantation, the RR was 1.124 with TAE compared with transplantation alone (1 cohort). For disease recurrence, the RR for this bridging therapy type was 2.374 compared with transplantation alone. No RCTs were identified, and most of the selected studies had a high risk of bias on patient selection, adequate follow-up, and funding source when reported.

**Table 1. Characteristics of Systematic Reviews**

Study	Dates	Trials	Participants <sup>a</sup>	Design
Kulik et al (2018)	1996-2016	49	Unresectable hepatocellular carcinoma	<ul style="list-style-type: none"> <li>• 18 comparative</li> <li>• 31 noncomparative</li> </ul>

<sup>a</sup> Patients needed liver transplantation and received transplant alone or bridging therapy in addition to transplant.

**Table 2. Results of Systematic Reviews**

Study	Dropout From Wait-list	Mortality	Recurrence Rate	Subgroup Analysis by Therapy Type	Comments
Kulik et al (2018) <sup>16</sup>					
Comparative studies (N=18)	2 studies (n=257 patients)	5 studies (n=531 patients)	10 studies (n=889 patients)	<ul style="list-style-type: none"> <li>• All-cause mortality: TAE vs transplant</li> </ul>	No RCTs identified; many studies had
	Reduced risk of dropout in	Nonsignificant between-group	Nonsignificant between-group		

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.





## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

patients with bridging therapy vs transplant alone (RR=0.32; 95% CI, 0.06 to 1.85; $I^2=0\%$ )	difference	difference	alone, RR=1.124 (95% CI, 0.675 to 1.873)	high risk of bias for patient selection, adequate follow-up, and funding source
			• Recurrence: TAE vs transplant alone, RR=2.374 (95% CI, 0.609 to 9.252)	

CI: confidence interval; RR: relative risk; TAE: transarterial embolization.

### Randomized Controlled Trials

Salem et al (2016) reported on results of a phase 2 RCT comparing conventional TACE with TheraSphere RE (Y90) for treatment of unresectable, unablatable HCC. Twenty-four patients were assigned to Y90 and 21 patients to TACE; the ultimate end point of treatment for these patients was liver transplantation. The primary outcome was time to progression using intention-to-treat analysis. Median follow-up was 17 months. In the TACE group, there were 7 transplants at a median of 9 months (range, 3-17 months). In the Y90 group, there were 13 transplants at a median of 9 months (range, 4-15 months). Median time to progression exceeded 26 months in the Y90 group and 6.8 months in the TACE group (hazard ratio, 0.12; 95% CI, 0.03 to 0.56;  $p=0.007$ ). Median survival was 19 months with Y90 and 18 months in TACE ( $p=0.99$ ). Adverse events were similar between groups, with the exception of more diarrhea (21% vs 0%) and hypoalbuminemia (58% vs 4%) in the conventional TACE group. A limitation of the OS analysis was the censoring of the survival outcome at liver transplantation given that transplantation is related to the treatment effect.

Kulik et al (2014) reported on results of a pilot RCT of Y90 RE with or without sorafenib for patients who had HCC and were awaiting liver transplantation. The trial randomized 23 subjects; after accounting for losses due to self-withdrawal from the trial, failure to confirm HCC, and death, the modified intention-to-treat population included 10 subjects randomized to RE alone and 10 randomized to RE plus sorafenib. Overall, 17 of 20 patients underwent liver transplantation, with no difference in median time-to-transplant between groups. However, the addition of sorafenib was associated with increased peritransplant biliary complications and acute rejection.

### Nonrandomized Studies

In a retrospective review, Tohme et al (2013) reported on 20 consecutive HCC patients awaiting liver transplant who received RE as bridge therapy. When RE began, Milan criteria were met by 14 patients and sustained until transplantation. Of the 6 patients who did not meet Milan criteria initially, RE was able to downstage 2 patients to meet Milan criteria. After RE, the median time to liver transplant was 3.5 months. Complete or partial radiologic response to RE, assessed using modified Response Evaluation Criteria In Solid Tumors (RECIST), occurred in 9 patients. Additionally, on pathologic examination, 5 patients had no evidence of viable tumor whose disease met the Milan criteria.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

Ramanathan et al (2014) reported on various therapies, including RE, for 715 HCC patients of whom 231 were intended for transplant. In the intention-to-treat transplantation arm, 60.2% received a transplant. Survival rates posttransplant were 97.1% and 72.5% at 1 and 5 years, respectively. Tumor recurrence rates were 2.4%, 6.2%, and 11.6% at 1, 3, and 5 years, respectively.

Lewandowski et al (2009) compared the efficacy of RE with chemoembolization in downstaging 86 patients with HCC from stage T3 to T2 (potentially making these patients liver transplant candidates). Patients were treated with RE using Y90 microspheres (n=43) or TACE (n=43). Median tumor sizes were similar between treatment groups (5.7 cm for TACE vs 5.6 cm for RE). Partial response rates were 61% for RE and 37% for TACE, with downstaging from T3 to T2 in 58% of patients treated with RE vs 31% with TACE (p<0.05).

### **Section Summary: RE as a Bridge to Liver Transplantation for Unresectable HCC**

Studies have shown that successful liver transplant can be achieved in some patients who are initially treated with RE. Studies did not demonstrate the comparative efficacy of RE to alternatives for this indication.

### **RE for unresectable Intrahepatic Cholangiocarcinoma**

The evidence on the use of RE for intrahepatic cholangiocarcinoma (ICC) consists primarily of case series. The studies have demonstrated tumor response to RE. Tumor response may improve survival, but without direct comparison of survival with a control group, this improvement cannot be ascertained from case series.

### **Clinical Context and Test Purpose**

The purpose of RE in patients who have unresectable ICC is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does RE improve the net health outcome in individuals with unresectable ICC?

The following PICOTS were used to select literature to inform this review.

### **Patients**

The relevant population of interest is individuals with unresectable ICC. Cholangiocarcinomas are tumors that arise from the epithelium of the bile duct and are separated into intrahepatic and extrahepatic types. ICC appear in the hepatic parenchyma and are also known as peripheral cholangiocarcinomas.

### **Interventions**

The treatment being considered is RE.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

### **Comparators**

The following practice is currently being used to make decisions about unresectable ICC: standard of care, usually palliative. Resection is the only treatment with potentially curative effect, and 5-year survival rates have ranged from 20% to 43%. Patients with an unresectable disease may select among fluoropyrimidine- or gemcitabine-based chemotherapy, fluoropyrimidine chemoradiation, or best supportive care.

### **Outcomes**

The general outcomes of interest are OS, functional outcomes, QOL, and treatment-related morbidity.

### **Timing**

The time frame for outcomes measures varies from several months to 5 years.

### **Setting**

RE is delivered in a hospital setting with resources for management of radiopharmaceuticals.

### **Systematic Reviews**

Al-Adra et al (2015) reported on outcomes in a systematic review of studies on RE for ICC. Reviewers included 12 publications, seven of which were published in abstract form only. Of the peer-reviewed articles, three were described as prospective cohort studies, which are detailed below (Mouli et al [2013]; Hoffmann et al [2012]; Saxena et al [2010]; of note, the Hoffmann study was reported as retrospective). The overall weighted median survival was 15.5 months (range, 7-22.2 months), based on 11 studies. A weighted mean partial response was seen in 28% of patients and stable disease was seen in 54% at 3 months posttreatment.

Boehm et al (2015) conducted a systematic review comparing hepatic artery-based therapies, including hepatic arterial infusion (HAI), TACE, DEB-TACE, and Y90 RE, for unresectable ICC. Of 20 studies that met inclusion criteria, 5 evaluated Y90 RE. Median OS across studies was 22.8 months for HAI, 13.9 months for RE, 12.4 months for TACE, and 12.3 months for DEB-TACE. Complete remission or partial response occurred in 56.9% of patients treated with HAI compared with 27.4% of those treated with RE and 17.3% of those treated with TACE.

### **Case Series**

Chan et al (2017) retrospectively analyzed data from 10 patients from a prospectively collected database who were treated with resin- (n=6) or glass-based (n=4) RE for unresectable combined hepatocellular cholangiocarcinoma (see Table 3). No toxicities of grade 3 or greater were reported (see Table 4). Seven patients had elevated  $\alpha$ -fetoprotein and/or cancer antigen 19-9 levels before treatment: of these, 4 had one or more of the biomarkers decrease by 50% or more, and 2 patients had a decrease of 25% to 49%. According to RECIST version 1.1 criteria, all patients had stable disease; however, under the modified RECIST criteria, 6 patients had a partial response to RE. Median OS from the first RE was 10.2 months,

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

and median PFS from the same time point was 5.2 months. The macrovascular invasion was reported to be a significant prognostic factor of OS (p=0.005).

**Table 3. Summary of Retrospective Case Series Characteristics**

Study	Institution	Participants	Treatment Delivery
Chan et al (2017)	Prospectively collected database	Unresectable combined HCC-CC	<ul style="list-style-type: none"> <li>• 6 treated with resin-based RE</li> <li>• 4 treated with glass-based RE</li> </ul>

HCC-CC: hepatocellular cholangiocarcinoma; RE: radioembolization.

**Table 4. Summary of Retrospective Case Series Results**

Study	Median Survival, mo <sup>a</sup>	Toxicity	AFP and CA 19-9 Levels	Tumor Response (RECIST)
Chan et al (2017)	<ul style="list-style-type: none"> <li>• OS=10.2</li> <li>• PFS=5.2</li> </ul>	<ul style="list-style-type: none"> <li>• No toxicities grade ≥3</li> </ul>	<ul style="list-style-type: none"> <li>• 4 had decrease in AFP and/or CA 19-9 of ≥50%</li> <li>• 2 had decrease of 25%-49%</li> </ul>	<ul style="list-style-type: none"> <li>• RECIST v1.1: All patients had SD</li> <li>• mRECIST: 6 had PR</li> </ul>

AFP: α-fetoprotein; CA 19-9: cancer antigen 19-9; OS: overall survival; PFS: progression-free survival; SD: stable disease; mRECIST: modified RECIST; PR: partial response

<sup>a</sup> Measured from first radioembolization.

Jia et al (2017) retrospectively reviewed all 24 patients who underwent Y90 RE for unresectable and failed first-line chemotherapy for ICC at a single institution. Mean follow-up was 11 months (range, 3-36 months). Median OS from the time of diagnosis was 24 months (range, 18-30 months) and from the RE procedure was 9 months (range, 6-12 months). Survival rates at 6, 12, and 30 months were 70%, 33%, and 20%, respectively.

Mosconi et al (2016) retrospectively analyzed 23 consecutive patients with unresectable or recurrent ICC at a single institution. Overall median survival was 18 months (95% CI, 14 to 21 months). Survival was significantly longer in treatment-naive patients (52 months) than in those who received other treatments before RE (16 months; p=0.009).

Rayar et al (2015) reported on successful downstaging of unresectable ICCs after RE in 8 patients with initial unresectability due to the involvement of hepatic veins or portal veins of the future liver remnant. After RE, all patients underwent successful resection.

Mouli et al (2013) reported on 46 patients treated with RE for ICC using a retrospective review of prospectively collected data from a single institution. Survival varied by level of disease (multifocal, infiltrative, bilobar), and ranged from 5.7 to 15.6 months. Five patients achieved resectable status and underwent curative resection.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

A retrospective study by Hoffmann et al (2012) assessing RE with Y90 resin microspheres included 24 patients with nonresectable chemorefractory ICC and no extrahepatic disease. The mean age of the sample was 65.2 years. ECOG Performance Status score was 0 in 51.5%, 1 in 21.2%, and 2 in 27.3%. Previous therapy included chemotherapy in 78.8%, surgery in 36.4%, TACE in 9.1%, radiofrequency ablation in 5.1%, and EBRT in 3.0%. Tumor response was assessed by RECIST criteria. Complete remission was seen in 0%, partial response in 36.4%, stable disease in 51.5%, and progressive disease in 15.2%. Follow-up ranged from 3.1 to 44 months (median, 10 months). Median OS was 22 months and median time to progression was 9.8 months. Favorable subgroups with respect to survival included those with ECOG Performance Status score of 0, tumor burden as a percentage of liver volume of 25% or less, the response by cancer antigen 19-9 criterion, and RECIST partial response. The same subgroups, except those with a cancer antigen 19-9 response, had favorable time to progression results. Data were collected retrospectively and no toxicity results were reported.

A study by Haug et al (2011) evaluated prognostic factors of RE treatment in 26 consecutive patients with unresectable ICC who underwent RE with Y90 glass microspheres. All patients had a Karnofsky Performance Status of 60% or more. Mean age was 64.3 years, and 31% had extrahepatic disease. Prior treatments included chemotherapy in 65%, surgery in 28%, localized therapy in 20%, and none in 24%. Tumor response results according to RECIST criteria were: complete remission in 0%; partial response in 22%; stable disease in 65%; and progressive disease in 13%. Median OS was 51 weeks, and multivariate analysis found that a partial response from the quantitative interpretation of positron emission tomography was a significant independent predictor of survival. The authors found no cases of grade 3 toxicity in transaminases or bilirubin.

Saxena et al (2010) prospectively evaluated 25 patients with unresectable ICC who received RE with Y90 resin microspheres. Extrahepatic disease was present in 48% and mean age was 57 years. Prior treatments included surgery in 40%, chemotherapy in 72%, radiofrequency ablation in 6.1%, and EBRT in 3.0%. By RECIST tumor response criteria, complete remission was seen in 0%, partial response in 24%, stable disease in 48%, and progressive disease in 20%. Follow-up was collected between 0.4 months and 55 months (median, 8.1 months). In the entire group, median OS was 9.3 months. Among subgroups, longer survival duration was seen in patients with peripheral tumors and those with ECOG Performance Status score of 0. The proportion of patients with both grade 3 albumin toxicity and grade 3 bilirubin toxicity was 8%. Grade 3 alkaline phosphatase toxicity was observed in 4%. One (4%) patient experienced duodenal ulcer due to malperfusion of Y90 microspheres.

A study by Ibrahim et al (2008) reported on results for RE with Y90 glass microspheres among 24 patients with unresectable ICC. The group was 33% female and had a median age of 68 years. Extrahepatic disease was present in 33%. ECOG Performance Status scores were 0 in 42%, 1 in 50%, and 2 in 8%. Prior chemotherapy had been used in 29% of patients. Using World Health Organization tumor response criteria, complete remission was observed in 0%; partial response in 27%; stable disease in 68%; and progressive disease in 5%. Follow-up was collected over a median of 17.7 months and median OS was

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

14.9 months. Subgroups that had favorable survival results included those with ECOG Performance Status score of 0, no previous chemotherapy, and peripheral tumor. Grade 3 albumin toxicity was found in 17%, grade 3 bilirubin toxicity in 4%, and 1 (4%) patient developed a duodenal ulcer.

Rayar et al (2015) reported on successful downstaging of unresectable ICCs after RE in 8 patients with initial unresectability due to the involvement of hepatic veins or portal veins of the future liver remnant. After RE, all patients underwent successful resection.

### **Section Summary: Intrahepatic Cholangiocarcinoma**

The evidence for RE in ICC primarily consists of retrospective case reviews. Across studies, the median survival in patients treated with RE ranged from 6 to 24 months. There is little, direct comparative data available to demonstrate the effect on survival. Side effects are common but generally mild.

### **RE for unresectable neuroendocrine tumors**

#### **Clinical Context and Test Purpose**

The purpose of RE in patients who have unresectable neuroendocrine tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does RE improve the net health outcome in individuals with unresectable neuroendocrine tumors?

The following PICOTS were used to select literature to inform this review.

#### **Patients**

The relevant population of interest is individuals with unresectable neuroendocrine tumors. These 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 area) or pancreatic islet cells.

#### **Interventions**

The treatment being considered is RE.

#### **Comparators**

The following practice is currently being used to make decisions about unresectable neuroendocrine tumors: standard of care, usually palliative. Conventional therapy is generally considered to be palliative supportive care, to control, eradicate, or debulk hepatic metastases, often to palliate carcinoid syndrome or local pain from liver capsular stretching. Therapies for unresectable metastatic neuroendocrine tumors include medical (somatostatin analogues like octreotide), systemic chemotherapy, ablation (radiofrequency or cryotherapy), TAE or TACE, or radiotherapy. Although patients often achieve symptom relief with

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

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 revealed that: (1) modest response rates are of limited duration; (2) it is more effective for pancreatic neuroendocrine tumors than carcinoids; and (3) it is frequently associated with significant toxicity. Chemoembolization has shown response rates of nearly 80%, but the effect is of short duration, and a survival benefit has not been demonstrated.

### **Outcomes**

The general outcomes of interest are OS, functional outcomes, QOL, and treatment-related morbidity. Although considered indolent tumors at the time of diagnosis, up to 75% of patients experienced 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, because most patients have multiple diffuse lesions.

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).

### **Timing**

The time frame for outcomes measures varies from several months to 5 years.

### **Setting**

RE is delivered in a hospital setting with resources for management of radiopharmaceuticals.

### **Systematic Reviews**

Devcic et al (2014) conducted a meta-analysis of studies evaluating RE for liver-dominant metastatic neuroendocrine tumors. The analysis included 12 studies that provided RECIST data for hepatic metastatic neuroendocrine tumors treated with RE. For Y90 RE with resin microspheres only, objective radiographic response rates (complete remission or partial response by RECIST) ranged from 12% to 80%, with a random-effects weighted average of 50% (95% CI, 38% to 62%). Disease control rates (complete remission, partial response, stable disease) ranged from 62% to 100%, with a random-effects weighted average of 86% (95% CI, 78% to 92%).

### **Nonrandomized Comparative Studies**

Engelman et al (2014) retrospectively compared transarterial, liver-directed therapies, including RE, hepatic artery embolization (HAE), and hepatic artery chemoembolization (HACE), in 42 patients treated for metastatic neuroendocrine tumors. Treatment decisions were at the discretion of the referring physician and interventional radiologist, but the decision to proceed with therapy was typically based on the progression of symptoms nonresponsive to octreotide therapy or rapid progression of liver tumor burden on imaging. Seventeen patients had HACE, 13 had HAE, and 12 had RE. Among the 27 patients with symptoms related

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

to their liver metastases, there were no statistically significant differences in symptom improvement at 3 months after first liver-directed therapy across treatment modalities (6/13 for HACE; 4/8 for HAE; 5/6 for RE;  $p=0.265$ ). There were no differences between treatment modalities in radiographic response at 6 months postprocedure ( $p=0.134$ ), time to progression ( $p=0.968$ ), or OS ( $p=0.30$ ).

### Case Series

Rhee et al (2008) reported on the results of a multicenter, open-label, phase 2 study that assessed the safety and efficacy of RE, using glass or resin microspheres, in 42 patients with metastatic neuroendocrine liver disease who had failed prior treatment(s), including medical (eg, octreotide), surgical resection, bland or chemoembolization, and radiofrequency ablation or cryoablation. RECIST criteria were used to assess tumor response, which showed 92% of glass patients and 94% of resin patients had partial response or had stable disease at 6 months after treatment. Median survival was 22 months for glass and 28 months for resin.

Cao et al (2010) reported on outcomes for 58 patients with unresectable neuroendocrine liver metastases from 2 hospitals who were treated with RE from 2003 to 2008. Response was assessed with radiographic evidence before and after RE and measured using RECIST guidelines. Systemic chemotherapy was routinely given at a single institution. Mean patient age at the time of RE was 61 years (range, 29-84 years). Primary tumor site varied and included small bowel, pancreas, colon, thyroid, lung, and unknown. Thirty-one patients underwent surgical resection of their primary tumor, which was classified as low grade in 15, intermediate grade in 7, and high grade in 7. Forty-three percent of patients had extrahepatic metastatic disease at study entry. Median follow-up was 21 months (range, 1-61 months). Fifty-one patients were evaluable, and 6 achieved complete remission, 14 had a partial response, 14 had stable disease, and 17 experienced disease progression. OS rates at 1, 2, and 3 years were 86%, 58%, and 47%, respectively. Median survival was 36 months (range, 1-61 months). Prognostic factors for survival included the extent of tumor involvement of the liver, radiographic response to treatment, the presence of extrahepatic disease at the time of RE, histologic grade of the tumor, and whether patients responded to RE.

King et al (2008) reported on outcomes for patients treated in a single-institution prospective study. Thirty-four patients with unresectable neuroendocrine liver metastases were given radioactive microspheres (SIR-Spheres) and concomitant 7-day systemic infusion of fluorouracil (5-FU), between 2003 and 2005. Mean patient age was 61 years (range, 32-79 years). Mean follow-up was 35.2 months. Primary tumor sites varied and included bronchus ( $n=1$ ), thyroid ( $n=2$ ), gastrointestinal ( $n=15$ ), pancreas ( $n=8$ ), and unknown ( $n=8$ ). Subjective changes from baseline hormone symptoms were reported every 3 months. Twenty-four (71%) patients had, at baseline assessment, symptoms of carcinoid syndrome, including diarrhea, flushing, or rash. At 3 months, 18 (55%) of 33 patients reported improvements in symptoms, as did 16 (50%) of 32 at 6 months. Radiologic tumor response was observed in 50% of patients and included 6 (18%) complete remission and 11 (32%) partial response. Mean OS was 29.4 months.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.





# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

Kennedy et al (2008) retrospectively reviewed 148 patients from 10 institutions with unresectable hepatic metastases from neuroendocrine tumors. All patients had completed treatment of the primary tumor and metastatic disease and were not excluded based on prior therapy. Total number of resin microsphere treatments was 185, with retreatment in 22.3% of patients (19.6% received 2 treatments, 2.7% received 3 treatments). All patients were followed using imaging studies at regular intervals to assess tumor response (using either World Health Organization or RECIST criteria) until death, or they were censored if a different type of therapy was given after the microspheres. Median follow-up was 42 months. By imaging, response rates were stable disease in 22.7%; partial response in 60.5%; complete remission in 2.7%; and progressive disease in 4.9%. Hepatic and extrahepatic metastases contributed to death in most patients, with 7% lost to follow-up. Median survival was 70 months.

Additional case series in patients with treatment-refractory, unresectable neuroendocrine hepatic metastases have shown good tumor response and improvement in clinical symptoms with RE.

### **Section Summary: Unresectable Neuroendocrine Tumors**

The evidence for use of RE to treat unresectable neuroendocrine tumors primarily consists of retrospective case reviews. Objective response rates ranged from 12% to 80% and disease control rates ranged from 62% to 100% in a 2014 systematic review. In a small nonrandomized comparative study, RE, HAE, and HACE appeared similar in terms of radiographic response, time to progression, and OS, but the inference is limited by study designs and small sample sizes.

### **RE for unresectable intrahepatic metastases from cRC and prior treatment failure**

#### **Clinical Context and Test Purpose**

The purpose of RE in patients who have unresectable intrahepatic metastases from CRC and prior treatment failure is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does RE improve the net health outcome in individuals with unresectable intrahepatic metastases from CRC and prior treatment failure?

The following PICOTS were used to select literature to inform this review.

#### **Patients**

The relevant population of interest is individuals with unresectable intrahepatic metastases from CRC and prior treatment failure. Fifty to 60 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%. The emphasis of treating these patients with potentially curable disease is complete removal of all tumors with negative surgical margins. Most patients diagnosed with metastatic colorectal disease are initially classified as having

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

unresectable disease. In some with metastatic disease limited to the liver, preoperative chemotherapy is sometimes used to downstage the metastases from metastatic lesions to resectable lesions (conversion chemotherapy).

### **Interventions**

The treatment being considered is RE.

### **Comparators**

The following practice is currently being used to make decisions about unresectable intrahepatic metastases from CRC and prior treatment failure: standard of care, usually palliative. In patients with unresectable disease, the primary treatment goal is palliative, with a survival benefit shown in both second- and third-line systemic chemotherapy. 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. Palliative chemotherapy using combined systemic and HAI may increase disease-free intervals for patients with unresectable hepatic metastases from CRC.

### **Outcomes**

The general outcomes of interest are OS, functional outcomes, quality of life, and treatment-related morbidity.

### **Timing**

The time frame for outcomes measures varies from several months to 5 years.

### **Setting**

RE is delivered in a hospital setting with resources for management of radiopharmaceuticals.

### **Systematic Reviews**

In a systematic review, Saxena et al (2014) evaluated 20 experimental and observational studies on RE for chemoresistant, unresectable CRC liver metastasis (total N=979 patients). They included 2 RCTs (Gray et al [2001]; Hendlisz et al [2010]; described below), 5 non-RCTs or well-designed cohort studies, and 13 observational studies. After RE, the average reported complete remissions and partial response rates from 16 studies were 0% (range, 0%-6%) and 31% (range, 0%-73%), respectively. Nine months was the median time to intrahepatic progression (range, 6-16 months). In 11 studies reporting on OS, median survival time was 12 months (range, 8.3-3.6 months).

Rosenbaum et al (2013) evaluated 13 relevant studies in a systematic review on RE as monotherapy and 13 studies on RE combined with chemotherapy for chemoresistant, unresectable CRC liver metastasis. Complete remission, partial response, and stable disease rates ranged from 29% to 90% with RE only and from 59% to 100% for RE plus chemotherapy. At 12 months, survival rates ranged from 37% to 59% with RE only and from 43% to 74% for RE plus chemotherapy.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

A 2010 technology assessment from the California Technology Assessment Forum assessed 25 studies on the use for RE and inoperable metastatic CRC to the liver, including 2 RCTs (Gray et al [2001]; Van Hazel et al [2004]; described below), a small retrospective study comparing selective internal radiotherapy (SIRT) with chemoembolization (N=36), and 21 case series. The assessment concluded that the 3 comparative studies used different control interventions and that the nonrandomized study did not show any convincing improvements over chemoembolization. The reviewer found it feasible to deliver radiotherapy to liver metastases and achieve at least partial response in a substantial portion of patients with relatively few serious adverse events. He also found that the results of the 2 randomized studies were encouraging but not definitive because the trials were very small, response rates in the control groups were lower than expected, and control groups were not given what was then considered standard first-line chemotherapy for metastatic CRC. The assessment concluded that the use of SIRT for unresectable CRC did not meet any of the California Technology Assessment Forum criteria.

A Cochrane review by Townsend et al (2009) assessed the efficacy and toxicity of RE, alone or with systemic or regional hepatic artery chemotherapy, in the treatment of metastatic CRC liver metastases. Two trials met reviewers' inclusion criteria: Gray et al (2001) and van Hazel et al (2004). Reviewers concluded that there was a lack of evidence that SIRT improved survival or QOL in patients with metastatic CRC, whether given alone or with chemotherapy, and that there was a need for well-designed, adequately powered phase 3 trials assessing the effect of SIRT when used with contemporary combination chemotherapy regimens.

The meta-analysis by Vente et al (2009; previously described) included 19 studies (total N=792 patients) assessing metastatic CRC patients treated with Y90 RE. Included in the meta-analysis were 2 RCTs (Gray et al [2001], van Hazel et al [2004]). Two covariates were included in the meta-regression model: (1) whether an older generation of cytostatic agents (5-FU/LV [leucovorin or floxuridine]) or a newer generation (5-FU/LV plus oxaliplatin [FOLFOX] or 5-FU/LV plus irinotecan) was used, and (2) whether Y90 RE was given as salvage therapy or as first-line treatment with adjuvant chemotherapy. The specific cytostatic agent(s) used did not affect response ( $p=0.96$ ). Tumor response to Y90 RE was high, with any response rates of approximately 80% in a salvage setting, and more than 90% when used as a first-line neoadjuvant treatment to chemotherapy, regardless of the chemotherapy regimen used. Median survival after Y90 RE, irrespective of differences in determinants (microspheres type, chemotherapy protocol, salvage or first line), varied from 6.7 to 17.0 months.

### Randomized Controlled Trials

A phase 3 RCT by van Hazel et al (2016) compared modified FOLFOX chemotherapy and FOLFOX chemotherapy plus SIRT in 530 patients with previously untreated liver-dominant metastatic disease. Bevacizumab was permitted as additional treatment at the discretion of the treating physician. About 40% of patients had extrahepatic metastases at randomization and about 28% had metastases with more than 25% liver involvement. The primary end point was overall (any site) PFS. Secondary end points included liver-specific outcomes such as PFS in the liver, tumor response rate, and liver resection rate. The primary end

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

point of PFS at any site showed no difference between groups (10.6 months for RE vs 10.2 months for control; hazard ratio, 0.93;  $p=0.43$ ). Secondary end points of median PFS in the liver and objective response rate for RE in the liver vs controls were improved in the RE group (liver PFS, 20.5 months vs 12.6 months; liver response rate, 78.7% vs 68.8%), all respectively. OS outcomes were not available at the time of publication. The investigators have planned to analyze OS in combination with 2 other studies of chemotherapy with and without RE that have also not been completed. This combined preplanned analysis should provide important data on the efficacy of RE (in combination with current chemotherapy regimens) in first-line treatment of unresectable metastatic CRC.

The RCT by Gray et al (2001) randomized 74 patients with bilobar unresectable liver metastases to monthly HAI with 5-FU alone or to 5-FU plus a single infusion of Y90 microspheres. The investigators closed the trial after entering 74 patients ( $n=70$  eligible for randomization). The original goal was 95 patients. The smaller study population was adequate to detect increases in response rate (from 20% to 55%) and median disease time to progression (by 32% from 4.5 months), with 80% power and 95% confidence, but lacked sufficient statistical power to detect changes in survival. To monitor responses to therapy, investigators serially measured serum levels of carcinoembryonic antigen and estimated tumor cross-sectional area and volume from repeated computerized tomography scans read by physicians blinded to treatment assignment. For HAI plus RE vs HAI, they reported increased overall responses (complete remission plus partial response) measured by area (44% vs 18%  $p=0.01$ ) and volume (50% vs 24%,  $p=0.03$ ), or by serum carcinoembryonic antigen levels (72% vs 47%,  $p=0.004$ ), all respectively. They also reported increased time to progression detected by increased area (9.7 months vs 15.9 months;  $p=0.001$ ) or volume (7.6 months vs 12.0 months;  $p=0.04$ ), both respectively. However, there were no statistically significant differences between treatment arms in actuarial survival rates ( $p=0.18$ ) or in 11 QOL measures. Treatment-related complications (grades 3-4) included 23 events in each arm (primarily changes in liver function tests). Nevertheless, investigators concluded that a "single injection of SIR-Spheres plus HAI is substantially more effective" than the same HAI regimen delivered alone. Although the trial showed significantly longer time to progression with RE, several issues make the conclusion less certain. Accrual was halted early, leaving the study underpowered. Although the trial had an institutional review board oversight, the reporting suggested early closure was at the sole discretion of the principal investigator without independent review or prospectively designed data monitoring procedures and stopping rules. While in this trial, response rate and time to progression after SIRT plus HAI appeared superior to the same outcomes after HAI alone, results for the SIRT plus HAI group are within the range reported by other randomized trials of HAI in comparable patients. Results of this trial may reflect the use of a shorter-than-standard duration of HAI therapy and could be confounded by administration of nonprotocol chemotherapy before and after SIRT. The reported increases in response rates and time to progression improved neither duration of survival nor QOL.

A phase 2 RCT (2004) by the same research group assessed 21 patients with advanced colorectal liver metastases; a total of 11 patients received systemic chemotherapy (fluorouracil and leucovorin) plus RE, and 10 received systemic chemotherapy alone. Disease time to progression was greater in those receiving combination therapy (18.6 months vs 3.6 months, respectively;  $p<0.001$ ).

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

A phase 3 RCT by Hendlisz et al (2010), which assessed 46 patients, compared intravenous 5-FU plus RE (SIR-Spheres) with intravenous 5-FU alone in CRC metastatic to the liver and refractory to standard chemotherapy. The time to liver progression (the primary outcome) was significantly longer in the group receiving SIR-Spheres (2.1 months vs 5.5 months, respectively;  $p=0.003$ ). After progression, patients received further treatment, including 10 in the 5-FU alone arm who received RE. There was no difference in median survival (7.3 months vs 10.0 months, respectively;  $p=0.80$ ).

### **Nonrandomized Comparative Studies**

Seidensticker et al (2012) published a retrospective, matched-pair comparison of RE plus best supportive care with best supportive care alone for patients with chemorefractory, liver-dominant colorectal metastases ( $n=29$  in each group). Patients were matched on tumor burden, prior treatments, and additional clinical criteria. Results showed prolongation of survival in patients who received RE (median survival, 8.3 months vs. 3.5 months;  $p<0.001$ ; hazard ratio, 0.3; 95% CI, 0.16 to 0.55;  $p<0.001$ ). Adverse events were considered generally mild-to-moderate and manageable.

### **Section Summary: Unresectable Intrahepatic Metastatic CRC**

The evidence for use of RE to treat unresectable intrahepatic metastatic CRC includes systematic reviews, RCTs, and observational studies. RCTs reported mixed results for RE compared with alternatives in terms of time to progression or PFS; data were generally not available for OS. Radiofrequency ablation has been found inferior to resection in local recurrence rates and 5-year OS rates; further, it is generally reserved for patients with 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. Radiofrequency ablation is recommended for nonsurgical candidates with small metastases. The role of local (liver-directed) therapy (including RE, chemoembolization, and conformal radiotherapy) in debulking unresectable metastatic disease remains controversial.

### **RE for unresectable intrahepatic metastases from other cancers**

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.

### **Clinical Context and Test Purpose**

The purpose of RE in patients who have unresectable intrahepatic metastases from other cancers is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does RE improvement the net health outcome in individuals with unresectable intrahepatic metastases from other cancers?

The following PICOTS were used to select literature to inform this review.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

### **Patients**

The relevant population of interest is individuals with unresectable intrahepatic metastases from other cancers.

### **Interventions**

The treatment being considered is RE.

### **Comparators**

The following practice is currently being used to make decisions about other unresectable intrahepatic metastases: standard of care.

### **Outcomes**

The general outcomes of interest are OS, functional outcomes, QOL, and treatment-related morbidity.

### **Timing**

The time frame for outcomes measures varies from several months to 5 years.

### **Setting**

RE is delivered in a hospital setting with resources for management of radiopharmaceuticals.

### **Metastatic Intrahepatic Breast Cancer**

Most studies on the use of RE for metastatic breast cancer have evaluated the use of RE alone (ie, not in combination with chemotherapy) either between lines of chemotherapy or in patients refractory to standard of care chemotherapy.

### **Case Series**

Smits et al (2013) reviewed 6 studies on RE for metastatic breast cancer (total N=198 participants). Complete remission, partial response, and stable disease control rates at 2 to 4 months posttreatment varied from 78% to 96%. In 4 studies, the median survival ranged from 10.8 to 20.9 months. Ten patients had gastric ulceration, and 3 patients died due to treatment.

Tables 5 and 6 list the case series characteristics and outcomes. These tables combine the cases reported in the Smits systematic review as well as others reported since the publication of that review.

**Table 5. Summary of Key Case Series Characteristics**

Study	Institution	Participants	Treatment Delivery	Follow-Up
Pieper et al (2016)	Single center from 2006-2015	44 women with unresectable liver-dominant breast metastases who had failed 2+ lines of chemo	Yttrium-90 RE	121 d
Gordon et	Single center	75 women with stable extrahepatic disease	Yttrium-90 RE	

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

al (2014)		who had hepatic tumor progression after systemic chemo		
Saxena et al (2014)	Single center from 2006-2012	40 women with unresectable, chemo-resistant (at least 1 line of systemic chemo) breast cancer-related liver metastases	Yttrium-90 RE	11.2 mo
Cianni et al (2013)	Single center	52 women with chemotherapy-refractory breast cancer and inoperable liver metastases; chemo administered previously to all patients	Yttrium-90 RE	
Haug et al (2012)		58 women with chemo-refractory breast cancer and unresectable hepatic metastases	Yttrium-90 RE	3 mo
Jakobs et al (2008)		30 (29 women, 1 man) patients with whole-liver treatment for breast cancer metastases and had failed prior polychemo regimens	Yttrium-90 RE	4.2 mo
Bangash et al (2007)		27 women with progressive liver metastases from breast cancer while on polychemo	Yttrium-90 RE	90 d
Coldwell et al (2007)	3 hospitals	44 patients with hepatic metastases who failed 1st-, 2nd-, or 3rd-line treatment for primary breast tumor and not candidates for RFA, TACE, resection, IMRT, or SRT	Yttrium-90 RE	14 mo

chemo: chemotherapy; IMRT: intensity-modulated radiotherapy; RE: radioembolization; RFA: radiofrequency ablation; SRT: stereotactic radiotherapy; TACE: transarterial chemoembolization.

**Table 6. Summary of Key Case Series Results**

Study	Treatment	Median OS	Response, %				Toxicity
			CR	PR	SD	PD	
Pieper et al (2016)	Yttrium-90 RE	184 d					Grade 1: 1 <sup>a</sup> Grade 3: 1 <sup>b</sup>
Gordon et al (2014)	Yttrium-90 RE	6.6 mo					
Saxena et al (2014)	Yttrium-90 RE	13.6 mo	5% <sup>c</sup>	26% <sup>c</sup>	39% <sup>c</sup>	29% <sup>c</sup>	Grade 1-2: 40%
Cianni et al (2013)	Yttrium-90 RE	11.5 mo	0%	56%	35%	10%	
Haug et al (2012)	Yttrium-90 RE	47 wk	0%	26%	63%	12%	
Jakobs et al (2008)	Yttrium-90 RE	11.7 mo		61% <sup>d</sup>	35% <sup>d</sup>	4% <sup>d</sup>	1 death <sup>e</sup>
Bangash et al (2007)	Yttrium-90 RE	2.6-6.8 mo <sup>g</sup>	39% <sup>f</sup>	39% <sup>f</sup>	52% <sup>f</sup>	9% <sup>f</sup>	
Coldwell et al (2007)	Yttrium-90 RE	>14 mo		47% <sup>h</sup>			No radiation-related liver failures observed

CR: complete response; ORR: objective response rate; OS: overall survival; PD: progressive disease; PR: partial response; RE: radioembolization; SD: stable disease.

<sup>a</sup> Cholecystitis.

<sup>b</sup> Duodenal ulceration.

<sup>c</sup> For 38 women with ≥1 mo follow-up.

<sup>d</sup> For 23 patients with follow-up data, after median follow-up of 4 mo.

<sup>e</sup> Death due to treatment-related hepatic toxicity after median follow-up of 14.2 mo.

<sup>f</sup> After 90-d follow-up.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

<sup>g</sup> By Eastern Cooperative Oncology Group Performance Status.

<sup>h</sup> After 12-wk follow-up.

### **Metastatic Melanoma**

The evidence related to the use of RE for melanoma consists of relatively small observational studies, many of which focus on patients with uveal melanoma, for whom the liver is the most common site of metastatic disease.

### **Nonrandomized Comparative Studies**

Xing et al (2017) conducted a retrospective observational study comparing outcomes for patients who had unresectable melanoma (both uveal and cutaneous) liver metastases refractory with standard chemotherapy treated with Y90 RE (n=28) or best supportive care (n=30). The groups were similar at baseline in terms of Child-Pugh class, ECOG Performance Status scores, age, sex, and race. Patients treated with RE had larger tumors at baseline (mean, 7.28 cm) than those treated with best supportive care (mean, 4.19 cm; p=0.02). Median OS from diagnosis of melanoma liver metastases was longer in RE-treated subjects (19.9 months vs 4.8 months; p<0.000), as was median OS from diagnosis of the primary melanoma (119.9 months vs 26.1 months; p<0.001), respectively. Pre- and posttreatment imaging studies were available for 24 (85.7%) of 28 of those treated with RE. Of those, no patients had complete remission, 5 (17.9%) patients had a partial response, 9 (32.1%) patients had stable disease, and 10 (35.7%) patients had progressive disease. Two patients receiving RE had major (grade 5) clinical toxicities (ascites and hepatic encephalopathy and eventual death).

### **Case Series**

Eldredge-Hindy et al (2016) retrospectively evaluated outcomes for the use of Y90 RE in 71 patients with biopsy-confirmed uveal melanoma liver metastases. Median time from the diagnosis of liver metastases to RE was 9.8 months (95% CI, 7.4 to 12.2 months), and 82% of patients had received prior liver-directed therapies. Sixty-one (86%) patients had computed tomography or magnetic resonance imaging evaluation of treatment response at 3 months post-RE. Of those, 5 (8%) patients had a partial response, 32 (52%) patients had stable disease, and 24 (39%) patients had disease progression. Median OS was 12.3 months (range, 1.9-49.3 months).

Several smaller studies published from 2009 to 2013 have reported on the use of RE in patients with hepatic metastases from melanoma. Three included only patients with ocular melanoma, and the fourth included patients with ocular or cutaneous melanoma. Sample sizes ranged between 11 patients and 32 patients. Three studies excluded those with poor performance status. Median age was in the 50s for 3 studies and 61 in the fourth. One article did not describe any previous treatment, and another described it incompletely. Three studies reported tumor response data, by RECIST criteria. Among 32 patients in the study by Gonsalves et al (2011), 1 (3%) patient had complete remission, 1 (3%) had a partial response; 18 (56%) had stable disease; and 12 (38%) had progressive disease. In the study of 13 patients by Klingenstein et al (2013), none had complete remission; 8 (62%) had a partial response; 2 (15%) had stable

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.





# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

disease; and 3 (23%) had progressive disease. Nine of 11 patients in Kennedy et al (2009) provided response data: 1 had complete remission; 6 had a partial response; 1 had stable disease; and 1 had progressive disease. Median survival in Gonsalves, Klingenstein, and Kennedy were 10.0 months, 19 months, and not yet reached, respectively. Gonsalves reported on 4 (12.5%) patients with grade 3 or 4 liver toxicity. Klingenstein observed 1 patient with marked hepatomegaly. Kennedy described 1 patient with a grade 3 gastric ulcer. The fourth study (Piduru et al [2012]; N=12) did not include any toxicity data.

### Metastatic Pancreatic Cancer

Michl et al (2014) reported on a case series on RE for pancreatic cancer. A response was seen in 47%, with median local PFS in the liver of 3.4 months (range, 0.9-45.0 months). Median OS was 9.0 months (range, 0.9-53.0 months) and 1-year survival was 24%.

### Hepatic Sarcoma

Miller et al (2018) retrospectively reviewed 39 patients with metastatic (n=37) or primary (n=2) liver sarcoma in a multicenter study. All patients had received at least 1 course of chemotherapy before receiving resin-based (n=17) or glass-based (n=22) 90Y RE (see Table 7). Most toxicities observed (93%) were grade 1 or 2, and objective response rate (complete and partial responses) was 36% (see Table 8). Six months after treatment, 30 patients showed stable disease or response, and overall median OS was 30 months (95% CI, 12 to 43 months). The study was limited by its retrospective nature and by differences in patient selection and therapy techniques among the 4 centers represented. Also, the study might have been statistically underpowered.

**Table 7. Summary of Case Series Characteristics**

Study	Institution	Participants	Treatment Delivery	Follow-Up
Miller et al (2018)	4 centers	39 patients with metastatic (n=37) or primary (n=2) liver sarcoma	Previous chemotherapy prior to resin-based (n=17) or glass-based (n=22) yttrium-90 RE	6 mo

RE: radioembolization.

**Table 8. Summary of Case Series Results**

Study	Median OS (95% CI), mo	Toxicity	ORR, %	Tumor Response at 6-Month Follow-Up
Miller et al (2018)	30 (12 to 43)	93% of toxicities grade 1 or 2	36	30 patients had stable disease or response to treatment

CI: confidence interval; ORR: objective response rate; OS: overall survival.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

### **Section Summary: Unresectable Intrahepatic Metastases From Other Cancers**

The evidence for use of RE to treat metastatic breast cancer consists of case series including 27 to 75 patients, primarily patients who progressed while on chemotherapy. Median survival ranged from 3 to 21 months and partial response ranged from 25% to 60%.

The evidence bases for metastatic melanoma have demonstrated that RE has a significant tumor response; however, improvement in survival has not been demonstrated in controlled comparative studies and some serious adverse events.

The evidence bases for metastatic pancreatic cancer and hepatic sarcoma are currently insufficient to draw definitive conclusions on treatment efficacy.

### **Summary of Evidence**

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 RCTs. Relevant outcomes are overall survival, functional outcomes, quality of life, and treatment-related morbidity. Observational studies have suggested that RE has high response rates compared with historical controls. Two small pilot RCTs have compared RE with alternative therapies for 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. Relevant outcomes are overall survival, functional outcomes, quality of life, and treatment-related morbidity. Comparisons of these case series to case series of alternative treatments have suggested that RE for primary intrahepatic cholangiocarcinoma has response rates similar to those seen with standard chemotherapy. RE may play a role for patients with unresectable tumors that are chemorefractory or who are unable to tolerate systemic chemotherapy. 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. Relevant outcomes are overall survival, functional outcomes, quality of life, 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

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. Relevant outcomes are overall survival, functional outcomes, quality of life, and treatment-related morbidity. RCTs of patients with prior treatment failure have methodologic problems, do not show definitive superiority of RE compared 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. Relevant outcomes are overall survival, functional outcomes, quality of life, 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.

### References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Radioembolization for Primary and Metastatic Tumors of the Liver", 8.01.43, 7:2018.
2. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet*. May 18 2002;359(9319):1734-1739. PMID 12049862
3. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology*. May 2002;35(5):1164-1171. PMID 11981766
4. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Hepatobiliary Cancers. Version 2.2016. [http://www.nccn.org/professionals/physician\\_gls/pdf/hepatobiliary.pdf](http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf). Accessed July 18, 2016.
5. Tice J. Selective internal radiation therapy or radioembolization for inoperable liver metastases from colorectal cancer California Technology Assessment Forum 2010; [http://www.ctaf.org/sites/default/files/assessments/1150\\_file\\_SIRT\\_RE\\_final\\_W2.pdf](http://www.ctaf.org/sites/default/files/assessments/1150_file_SIRT_RE_final_W2.pdf). Accessed April, 2015.
6. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. Version 2.2016. [http://www.nccn.org/professionals/physician\\_gls/PDF/colon.pdf](http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf). Accessed July 18, 2016.
7. King J, Quinn R, Glenn DM, et al. Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. *Cancer*. Sep 1 2008;113(5):921-929. PMID 18618495
8. Kennedy AS, Salem R. Radioembolization (yttrium-90 microspheres) for primary and metastatic hepatic malignancies. *Cancer J*. Mar-Apr 2010;16(2):163-175. PMID 20404614
9. Vente MA, Wondergem M, van der Tweel I, et al. Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis. *Eur Radiol*. Apr 2009;19(4):951-959. PMID 18989675
10. Salem R, Thurston KG, Carr BI, et al. Yttrium-90 microspheres: radiation therapy for unresectable liver cancer. *J Vasc Interv Radiol*. Sep 2002;13(9 Pt 2):S223-229. PMID 12354840
11. Kolligs FT, Bilbao JI, Jakobs T, et al. Pilot randomized trial of selective internal radiation therapy vs. chemoembolization in unresectable hepatocellular carcinoma. *Liver Int*. Jun 2015;35(6):1715-1721. PMID 25443863
12. Pitton MB, Kloeckner R, Ruckes C, et al. Randomized comparison of selective internal radiotherapy (SIRT) versus drug-eluting bead transarterial chemoembolization (DEB-TACE) for the treatment of hepatocellular carcinoma. *Cardiovasc Intervent Radiol*. Apr 2015;38(2):352-360. PMID 25373796
13. Soydal C, Arslan MF, Kucuk ON, et al. Comparison of survival, safety, and efficacy after transarterial chemoembolization and radioembolization of Barcelona Clinic Liver Cancer stage B-C hepatocellular cancer patients. *Nucl Med Commun*. Jun 2016;37(6):646-649. PMID 26905317

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

14. Oladeru OT, Miccio JA, Yang J, et al. Conformal external beam radiation or selective internal radiation therapy—a comparison of treatment outcomes for hepatocellular carcinoma. *J Gastrointest Oncol.* Jun 2016;7(3):433-440. PMID 27284477
15. El Fouly A, Ertle J, El Dorry A, et al. In intermediate stage hepatocellular carcinoma: radioembolization with yttrium 90 or chemoembolization? *Liver Int.* Feb 2015;35(2):627-635. PMID 25040497
16. Gramenzi A, Golfieri R, Mosconi C, et al. Yttrium-90 radioembolization vs sorafenib for intermediate-locally advanced hepatocellular carcinoma: a cohort study with propensity score analysis. *Liver Int.* Mar 2015;35(3):1036-1047. PMID 24750853
17. Carr BI, Kondragunta V, Buch SC, et al. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. *Cancer.* Mar 1 2010;116(5):1305-1314. PMID 20066715
18. Kulik LM, Carr BI, Mulcahy MF, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. *Hepatology.* Jan 2008;47(1):71-81. PMID 18027884
19. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology.* Jan 2010;138(1):52-64. PMID 19766639
20. Kwok PC, Leung KC, Cheung MT, et al. Survival benefit of radioembolization for inoperable hepatocellular carcinoma using yttrium-90 microspheres. *J Gastroenterol Hepatol.* Nov 2014;29(11):1897-1904. PMID 24734957
21. Saxena A, Meteling B, Kapoor J, et al. Yttrium-90 radioembolization is a safe and effective treatment for unresectable hepatocellular carcinoma: A single centre experience of 45 consecutive patients. *Int J Surg.* Dec 2014;12(12):1403-1408. PMID 25091398
22. Kulik L, Vouche M, Koppe S, et al. Prospective randomized pilot study of Y90+/-sorafenib as bridge to transplantation in hepatocellular carcinoma. *J Hepatol.* Aug 2014;61(2):309-317. PMID 24681342
23. Tohme S, Sukato D, Chen HW, et al. Yttrium-90 radioembolization as a bridge to liver transplantation: a single-institution experience. *J Vasc Interv Radiol.* Nov 2013;24(11):1632-1638. PMID 24160821
24. Ramanathan R, Sharma A, Lee DD, et al. Multimodality therapy and liver transplantation for hepatocellular carcinoma: a 14-year prospective analysis of outcomes. *Transplantation.* Jul 15 2014;98(1):100-106. PMID 24503764
25. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. *Am J Transplant.* Aug 2009;9(8):1920-1928. PMID 19552767
26. Al-Adra DP, Gill RS, Axford SJ, et al. Treatment of unresectable intrahepatic cholangiocarcinoma with yttrium-90 radioembolization: A systematic review and pooled analysis. *Eur J Surg Oncol.* Jan 2015;41(1):120-127. PMID 25449754
27. Mouli S, Memon K, Baker T, et al. Yttrium-90 radioembolization for intrahepatic cholangiocarcinoma: safety, response, and survival analysis. *J Vasc Interv Radiol.* Aug 2013;24(8):1227-1234. PMID 23602420
28. Hoffmann RT, Paprottka PM, Schon A, et al. Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: factors associated with prolonged survival. *Cardiovasc Intervent Radiol.* Feb 2012;35(1):105-116. PMID 21431970
29. Saxena A, Bester L, Chua TC, et al. Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. *Ann Surg Oncol.* Feb 2010;17(2):484-491. PMID 19876691
30. Boehm LM, Jayakrishnan TT, Miura JT, et al. Comparative effectiveness of hepatic artery based therapies for unresectable intrahepatic cholangiocarcinoma. *J Surg Oncol.* Feb 2015;111(2):213-220. PMID 25176325
31. Haug AR, Heinemann V, Bruns CJ, et al. 18F-FDG PET independently predicts survival in patients with cholangiocellular carcinoma treated with 90Y microspheres. *Eur J Nucl Med Mol Imaging.* Jun 2011;38(6):1037-1045. PMID 21308371
32. Ibrahim SM, Mulcahy MF, Lewandowski RJ, et al. Treatment of unresectable cholangiocarcinoma using yttrium-90 microspheres: results from a pilot study. *Cancer.* Oct 15 2008;113(8):2119-2128. PMID 18759346
33. Rayar M, Sulpice L, Edeline J, et al. Intra-arterial yttrium-90 radioembolization combined with systemic chemotherapy is a promising method for downstaging unresectable huge intrahepatic cholangiocarcinoma to surgical treatment. *Ann Surg Oncol.* Sep 2015;22(9):3102-3108. PMID 25623598
34. Devcic Z, Rosenberg J, Braat AJ, et al. The efficacy of hepatic 90Y resin radioembolization for metastatic neuroendocrine tumors: a meta-analysis. *J Nucl Med.* Sep 2014;55(9):1404-1410. PMID 25012459
35. Engelman ES, Leon-Ferre R, Naraev BG, et al. Comparison of transarterial liver-directed therapies for low-grade metastatic neuroendocrine tumors in a single institution. *Pancreas.* Mar 2014;43(2):219-225. PMID 24518499
36. Rhee TK, Lewandowski RJ, Liu DM, et al. 90Y Radioembolization for metastatic neuroendocrine liver tumors: preliminary results from a multi-institutional experience. *Ann Surg.* Jun 2008;247(6):1029-1035. PMID 18520231

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

37. Cao CQ, Yan TD, Bester L, et al. Radioembolization with yttrium microspheres for neuroendocrine tumour liver metastases. *Br J Surg*. Apr 2010;97(4):537-543. PMID 20205229
38. Kennedy AS, Dezarn WA, McNeillie P, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients. *Am J Clin Oncol*. Jun 2008;31(3):271-279. PMID 18525307
39. Memon K, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for neuroendocrine liver metastases: safety, imaging, and long-term outcomes. *Int J Radiat Oncol Biol Phys*. Jul 1 2012;83(3):887-894. PMID 22137020
40. Paprottka PM, Hoffmann RT, Haug A, et al. Radioembolization of symptomatic, unresectable neuroendocrine hepatic metastases using yttrium-90 microspheres. *Cardiovasc Intervent Radiol*. Apr 2012;35(2):334-342. PMID 21847708
41. Peker A, Cicek O, Soydal C, et al. Radioembolization with yttrium-90 resin microspheres for neuroendocrine tumor liver metastases. *Diagn Interv Radiol*. Jan-Feb 2015;21(1):54-59. PMID 25430526
42. Saxena A, Bester L, Shan L, et al. A systematic review on the safety and efficacy of yttrium-90 radioembolization for unresectable, chemorefractory colorectal cancer liver metastases. *J Cancer Res Clin Oncol*. Apr 2014;140(4):537-547. PMID 24318568
43. Gray B, Van Hazel G, Hope M, et al. Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. *Ann Oncol*. Dec 2001;12(12):1711-1720. PMID 11843249
44. Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *J Clin Oncol*. Aug 10 2010;28(23):3687-3694. PMID 20567019
45. Rosenbaum CE, Verkooijen HM, Lam MG, et al. Radioembolization for treatment of salvage patients with colorectal cancer liver metastases: a systematic review. *J Nucl Med*. Nov 2013;54(11):1890-1895. PMID 24071510
46. Van Hazel G, Blackwell A, Anderson J, et al. Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer. *J Surg Oncol*. Nov 1 2004;88(2):78-85. PMID 15499601
47. Townsend A, Price T, Karapetis C. Selective internal radiation therapy for liver metastases from colorectal cancer. *Cochrane Database Syst Rev*. 2009(4):CD007045. PMID 19821394
48. van Hazel GA, Heinemann V, Sharma NK, et al. SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients With Metastatic Colorectal Cancer. *J Clin Oncol*. May 20 2016;34(15):1723-1731. PMID 26903575
49. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. *Cardiovasc Intervent Radiol*. Oct 2012;35(5):1066-1073. PMID 21800231
50. Hickey R, Lewandowski R, Salem R. Yttrium-90 radioembolization is a viable treatment option for unresectable, chemorefractory colorectal cancer liver metastases: further evidence in support of a new treatment paradigm. *Ann Surg Oncol*. Mar 2015;22(3):706-707. PMID 25358665
51. Mulcahy MF, Lewandowski RJ, Ibrahim SM, et al. Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. *Cancer*. May 1 2009;115(9):1849-1858. PMID 19267416
52. Saxena A, Meteling B, Kapoor J, et al. Is yttrium-90 radioembolization a viable treatment option for unresectable, chemorefractory colorectal cancer liver metastases? A large single-center experience of 302 patients. *Ann Surg Oncol*. Mar 2015;22(3):794-802. PMID 25323474
53. Lewandowski RJ, Memon K, Mulcahy MF, et al. Twelve-year experience of radioembolization for colorectal hepatic metastases in 214 patients: survival by era and chemotherapy. *Eur J Nucl Med Mol Imaging*. Oct 2014;41(10):1861-1869. PMID 24906565
54. Kennedy AS, Coldwell D, Nutting C, et al. Resin 90Y-microsphere brachytherapy for unresectable colorectal liver metastases: modern USA experience. *Int J Radiat Oncol Biol Phys*. Jun 1 2006;65(2):412-425. PMID 16690429
55. Kalva SP, Rana RS, Liu R, et al. Yttrium-90 Radioembolization as Salvage Therapy for Liver Metastases From Colorectal Cancer. *Am J Clin Oncol*. Nov 4 2014. PMID 25374143
56. Jakobs TF, Hoffmann RT, Dehm K, et al. Hepatic yttrium-90 radioembolization of chemotherapy-refractory colorectal cancer liver metastases. *J Vasc Interv Radiol*. Aug 2008;19(8):1187-1195. PMID 18656012
57. Smits ML, Prince JF, Rosenbaum CE, et al. Intra-arterial radioembolization of breast cancer liver metastases: a structured review. *Eur J Pharmacol*. Jun 5 2013;709(1-3):37-42. PMID 23545356

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

58. Gordon AC, Gradishar WJ, Kaklamani VG, et al. Yttrium-90 radioembolization stops progression of targeted breast cancer liver metastases after failed chemotherapy. *J Vasc Interv Radiol.* Oct 2014;25(10):1523-1532, 1532 e1521-1522. PMID 25156827
59. Saxena A, Kapoor J, Meteling B, et al. Yttrium-90 radioembolization for unresectable, chemoresistant breast cancer liver metastases: a large single-center experience of 40 patients. *Ann Surg Oncol.* Apr 2014;21(4):1296-1303. PMID 24337647
60. Cianni R, Pelle G, Notarianni E, et al. Radioembolization with (90)Y-labelled resin microspheres in the treatment of liver metastasis from breast cancer. *Eur Radiol.* Jan 2013;23(1):182-189. PMID 22836160
61. Haug AR, Tiega Donfack BP, Trumm C, et al. 18F-FDG PET/CT predicts survival after radioembolization of hepatic metastases from breast cancer. *J Nucl Med.* Mar 2012;53(3):371-377. PMID 22331219
62. Jakobs TF, Hoffmann RT, Fischer T, et al. Radioembolization in patients with hepatic metastases from breast cancer. *J Vasc Interv Radiol.* May 2008;19(5):683-690. PMID 18440456
63. Bangash AK, Atassi B, Kaklamani V, et al. 90Y radioembolization of metastatic breast cancer to the liver: toxicity, imaging response, survival. *J Vasc Interv Radiol.* May 2007;18(5):621-628. PMID 17494843
64. Coldwell DM, Kennedy AS, Nutting CW. Use of yttrium-90 microspheres in the treatment of unresectable hepatic metastases from breast cancer. *Int J Radiat Oncol Biol Phys.* Nov 1 2007;69(3):800-804. PMID 17524567
65. Xing M, Prajapati HJ, Dhanasekaran R, et al. Selective Internal Yttrium-90 Radioembolization Therapy (90Y-SIRT) Versus Best Supportive Care in Patients With Unresectable Metastatic Melanoma to the Liver Refractory to Systemic Therapy: Safety and Efficacy Cohort Study. *Am J Clin Oncol.* Aug 7 2014. PMID 25089529
66. Eldredge-Hindy H, Ohri N, Anne PR, et al. Yttrium-90 Microsphere Brachytherapy for Liver Metastases From Uveal Melanoma: Clinical Outcomes and the Predictive Value of Fluorodeoxyglucose Positron Emission Tomography. *Am J Clin Oncol.* Apr 2016;39(2):189-195. PMID 24441583
67. Gonsalves CF, Eschelmann DJ, Sullivan KL, et al. Radioembolization as salvage therapy for hepatic metastasis of uveal melanoma: a single-institution experience. *AJR Am J Roentgenol.* Feb 2011;196(2):468-473. PMID 21257902
68. Kennedy AS, Nutting C, Jakobs T, et al. A first report of radioembolization for hepatic metastases from ocular melanoma. *Cancer Invest.* Jul 2009;27(6):682-690. PMID 19219675
69. Klingenstein A, Haug AR, Zech CJ, et al. Radioembolization as locoregional therapy of hepatic metastases in uveal melanoma patients. *Cardiovasc Intervent Radiol.* Feb 2013;36(1):158-165. PMID 22526099
70. Piduru SM, Schuster DM, Barron BJ, et al. Prognostic value of 18f-fluorodeoxyglucose positron emission tomography-computed tomography in predicting survival in patients with unresectable metastatic melanoma to the liver undergoing yttrium-90 radioembolization. *J Vasc Interv Radiol.* Jul 2012;23(7):943-948. PMID 22609292
71. Michl M, Haug AR, Jakobs TF, et al. Radioembolization with yttrium-90 microspheres (SIRT) in Pancreatic cancer patients with liver metastases: efficacy, safety and prognostic factors. *Oncology.* 2014;86(1):24-32. PMID 24401529
72. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine Tumors. Version 2.2016. [http://www.nccn.org/professionals/physician\\_gls/PDF/neuroendocrine.pdf](http://www.nccn.org/professionals/physician_gls/PDF/neuroendocrine.pdf). Accessed July 18, 2016.
73. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2.2016. [http://www.nccn.org/professionals/physician\\_gls/PDF/breast.pdf](http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf). Accessed July 18, 2016.
74. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma. Version 3.2016. [http://www.nccn.org/professionals/physician\\_gls/PDF/melanoma.pdf](http://www.nccn.org/professionals/physician_gls/PDF/melanoma.pdf). Accessed July 18, 2016.
75. Kennedy A, Nag S, Salem R, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. *Int J Radiat Oncol Biol Phys.* May 1 2007;68(1):13-23. PMID 17448867
76. Tao R, Li X, Ran R, et al. A mixed analysis comparing nine minimally invasive surgeries for unresectable hepatocellular carcinoma patients. *Oncotarget.* Jan 17 2017;8(3):5460-5473. PMID 27705924
77. Ludwig JM, Zhang D, Xing M, et al. Meta-analysis: adjusted indirect comparison of drug-eluting bead transarterial chemoembolization versus 90Y-radioembolization for hepatocellular carcinoma. *Eur Radiol.* May 2017;27(5):2031-2041. PMID 27562480
78. Lobo L, Yakoub D, Picado O, et al. Unresectable hepatocellular carcinoma: radioembolization versus chemoembolization: a systematic review and meta-analysis. *Cardiovasc Intervent Radiol.* Nov 2016;39(11):1580-1588. PMID 27586657
79. Facciorusso A, Serviddio G, Muscatiello N. Transarterial radioembolization vs chemoembolization for hepatocarcinoma patients: A systematic review and meta-analysis. *World J Hepatol.* Jun 28 2016;8(18):770-778. PMID 27366304

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

80. Padia SA, Johnson GE, Horton KJ, et al. Segmental Yttrium-90 radioembolization versus segmental chemoembolization for localized hepatocellular carcinoma: results of a single-center, retrospective, propensity score-matched study. *J Vasc Interv Radiol.* Jun 2017;28(6):777-785 e771. PMID 28365172
81. Salem R, Gordon AC, Mouli S, et al. Y90 Radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology.* Dec 2016;151(6):1155-1163 e1152. PMID 27575820
82. Jia Z, Paz-Fumagalli R, Frey G, et al. Resin-based Yttrium-90 microspheres for unresectable and failed first-line chemotherapy intrahepatic cholangiocarcinoma: preliminary results. *J Cancer Res Clin Oncol.* Mar 2017;143(3):481-489. PMID 27826686
83. Mosconi C, Gramenzi A, Ascanio S, et al. Yttrium-90 radioembolization for unresectable/recurrent intrahepatic cholangiocarcinoma: a survival, efficacy and safety study. *Br J Cancer.* Jul 26 2016;115(3):297-302. PMID 27336601
84. Pieper CC, Meyer C, Wilhelm KE, et al. Yttrium-90 radioembolization of advanced, unresectable breast cancer liver metastases-a single-center experience. *J Vasc Interv Radiol.* Sep 2016;27(9):1305-1315. PMID 27461588
85. Kulik L, Heimbach JK, Zaiem F, et al. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis. *Hepatology.* Jan 2018;67(1):381-400. PMID 28859222
86. Chan LS, Sze DY, Poultsides GA, et al. Yttrium-90 radioembolization for unresectable combined hepatocellular-cholangiocarcinoma. *Cardiovasc Intervent Radiol.* Sep 2017;40(9):1383-1391. PMID 28432387

### Policy History

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

- |            |  |
|------------|--|
| 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.   |
| 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  |

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

	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
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.
Next Scheduled Review Date:	11/2019

### **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 2017 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.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.





# Louisiana

## Radioembolization for Primary and Metastatic Tumors of the Liver

Policy # 00110

Original Effective Date: 02/23/2004

Current Effective Date: 11/21/2018

*Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.*

*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. 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:** 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.