

Subject: Radioactive Yttrium-90 Microspheres for Treatment of Liver Cancer		Original Effective Date: 7/10/14
Guidance Number: MCG-181	Revision Date(s):	

PREFACE

This Medical Guidance is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the following website: <http://www.cms.hhs.gov/center/coverage.asp>.

FDA INDICATIONS

The use of Radioactive Yttrium-90 Microspheres for Treatment of Liver Cancer is a procedure and, therefore, not subject to FDA regulation. However any medical devices, drugs, biologics, or tests used as a part of this procedure may be subject to FDA regulation.

The FDA issued premarket approval (PMA) (P990065) for the SIR-Spheres (Sirtex Medical Ltd.) on March 5, 2002 as a Class III device under the Product Code NAW (Radionuclide Microsphere) in combination with floxuridine intrahepatic artery chemotherapy, for the treatment of unresectable metastatic liver tumors from primary colorectal cancer. Three supplemental approvals have been issued for manufacturing and labeling changes since the original approval, with the most recent (P990065 S006) on July 17, 2012. ¹

The FDA issued Humanitarian Device Exemption (HDE) (H980006) status for the TheraSphere (MDS Nordion Inc.) on December 10, 1999. TheraSphere is indicated 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. ²

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage guidance (MCG) document and provide the directive for all Medicare members. The directives from this MCG document may be followed if there are no available NCD or LCD documents available and outlined below.

A National Coverage Determination (NCD) for the use of Radioactive Yttrium-90 Microspheres for the treatment of liver cancer was not identified on the CMS website. ³

There are LCDs for Selective Internal Radiation Therapy (SIRT) for Primary and Secondary Hepatic Malignancy (90Y-Microsphere Hepatic Brachytherapy) and Radiopharmaceutical Agents. ³

INITIAL COVERAGE CRITERIA ⁴⁻¹¹

Radioactive Yttrium-90 Microspheres may be considered medically necessary and may be authorized when all of the following criteria are met: [ALL]

- A diagnosis of: [ONE]
 - Primary hepatocellular carcinoma or primary intrahepatic cholangiocarcinoma with: [ONE]
 - ◇ Unresectable tumor that is limited to the liver (Unresectable hepatocellular carcinoma is generally defined as tumors greater than 3 cm); or
 - ◇ A bridge to transplant in patients who meet criteria for liver transplantation ⁸ and [ONE]
 - No malignant portal vein thrombus; or
 - No extrahepatic disease involvement

OR

- Hepatic metastases with ONE of the following:
 - ◇ Diffuse symptomatic metastases from a neuroendocrine tumor (carcinoid or non-carcinoid);
 - ◇ Unresectable metastases from colorectal tumor
 - ◇ Liver dominant metastases

AND

- Systemic therapy has failed or individual is not a candidate for chemotherapy, surgical resection and/or transarterial chemoembolization (TACE); and
- One of the following: [ONE]
 - *ECOG performance score of: 0-2; or
 - **Child-Pugh score A or B; and
- A life expectancy of at least 3 months

**Note: Eastern Cooperative Oncology Group (ECOG, Zubrod, WHO) performance scale definition: ¹¹*

- 0 = Fully active; no performance restrictions
- 1 = Strenuous physical activity restricted; fully ambulatory and able to carry out light work
- 2 = Capable of all self-care but unable to carry out any work activities. Up and about >50 percent of waking hours
- 3 = Capable of only limited self-care; confined to bed or chair >50 percent of waking hours
- 4 = Completely disabled; cannot carry out any self-care; totally confined to bed or chair

***Note: The Child-Turcote-Pugh (CTP)¹¹ score determines short-term prognosis among groups of patients awaiting liver transplantation and has been widely adopted for risk-stratifying patients before transplantation.*

Child-Turcote-Pugh Score of Severity of Liver Disease			
Points	1	2	3
Encephalopathy	None	1 – 2	3 – 4

Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	< 2	2 – 3	> 3
For PBC/PSC, Bilirubin	< 4	4 – 10	> 10
Albumin (g/dL)	> 3.5	2.8 – 3.5	< 2.8
INR: International Normalized Ratio	< 1.7	1.7 – 2.3	> 2.3
PT = prothrombin time (seconds prolonged)	< 4	4 - 6	> 6

The individual scores are summed and then grouped as a classification:

< 7 = A

7-9 = B

> 9 = C (forecasts a survival of less than 12 months)

COVERAGE EXCLUSIONS⁴⁻¹¹

Absolute Contraindications include:

- Inability to catheterize the hepatic artery.
- Frank liver failure.
- Technetium-99m MAA hepatic arterial perfusion scintigraphy demonstrates significant reflux to the gastrointestinal organs that cannot be corrected by angiographic techniques such as embolization.

DESCRIPTION OF PROCEDURE

Microsphere

Radioactive Yttrium-90 microsphere administration is a nonsurgical procedure used to treat inoperable liver cancer. This procedure delivers targeted internal radiation therapy directly to the tumor. The radioactive microspheres are delivered by a high pressure infusion catheter that is inserted into the groin and threaded into the hepatic artery. The procedure takes 30 to 60 minutes to complete, and is usually performed on an outpatient basis. Patients are often discharged within 23 hours. The minimally invasive treatment can be used for primary and secondary liver cancer and may be used to downstage the cancer or to act as a bridging therapy so that resection, surgery, or transplantation may be done.

Hepatocellular Carcinoma

The incidence of hepatocellular carcinoma (HCC), or primary liver cancer is increasing due to the spread of hepatitis virus infection. In the majority of patients, HCC is associated with cirrhosis of the liver, and survival rates for HCC are poor. Patients with primary liver cancer are broadly classified into those with localized resectable, localized unresectable and advanced disease. Surgery is the only potentially curative treatment but only in patients with localized resectable disease, where the tumor is confined to a solitary mass in a portion of the liver that allows its complete surgical removal with a margin of normal liver, and in the absence of cirrhosis and chronic hepatitis. In patients with localized unresectable disease, although the cancer appears to be confined

to the liver, surgical resection of the entire tumor is not possible due to its location within the liver or the presence of concomitant medical conditions such as cirrhosis. While some of these patients may be candidates for liver transplantation, limited availability of donor livers remains a problem. For early-stage, unresectable HCC additional treatment options include percutaneous ablation with ethanol injection and radiofrequency ablation. More widespread disease is treated with transarterial embolization (TAE), or combined with the injection of chemotherapeutic agents called transarterial chemoembolization (TACE); both methods deprive the tumor of its blood supply by blocking or embolizing the hepatic artery.

GENERAL INFORMATION

Summary of Medical Evidence

There are no randomized controlled trials published in the peer reviewed medical literature for radioactive yttrium-90 microspheres in the treatment of liver cancer that compare this therapy with standard medical and/or surgical treatment of tumors in the liver. The overall body of evidence consists of controlled and comparison studies, meta-analysis and systematic reviews. Generally the findings indicate that this treatment may offer palliative management for unresectable liver cancer and as a bridging to liver transplantation.^{7 9 10 12}

A comparative effectiveness review (2013) of local therapies (i.e., ablation, embolization, and radiotherapy) for patients with unresectable HCC was conducted by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center for the Agency for Healthcare Research and Quality (AHRQ). The review was done to report on overall survival and quality of life outcomes and adverse events. Transplant candidates were excluded from this review. Three prospective case series and one retrospective case series with a total of 187 participants met inclusion criteria for review. There were no randomized controlled trials and no comparative trials that met inclusion criteria. Therefore, the strength of evidence was rated as insufficient to evaluate the outcomes of interest. One study reported a 1-year survival rate of 75%; three studies reported a median survival range of 11 to 15 months. Quality of life, local recurrence, and disease progression were not reported in any of the included studies. Adverse events were rare and no liver failure or hepatic abscess was reported. The authors recommended studies that compare various embolization techniques including radioembolization.⁷

Xie et al. (2012) performed a meta-analysis comparing the efficacy of transcatheter arterial chemoembolization (TACE) and microsphere embolization for treating unresectable hepatocellular carcinoma (HCC). Thirteen studies were included in the evaluation. A total of 597 patients were treated with microsphere embolization and 1,233 patients with chemoembolization. The data showed that microsphere embolization therapy was significantly better for longer overall survival, 1-year survival, longer time to progression and complete or partial response rate than that of chemoembolization treatment.¹²

Yang et al. (2012) systematically reviewed the clinical efficacy and safety of the use of hepatic arterial chemoembolization, bland embolization and radioembolization in the treatment of unresectable neuroendocrine tumor liver metastases (NETLM). Response to treatment, survival outcome and toxicity were examined in 37 studies that included 1575 patients. The authors concluded that these therapies are safe and effective in the

treatment of NETLM however, prospective clinical trials are needed to compare the efficacy and toxicity of these treatments.¹³

Lau et al (2011) systematically reviewed the role of selective internal irradiation (SIR) with yttrium-90 (90Y) microspheres for hepatocellular carcinoma (HCC). The evidence was limited to cohort studies and comparative studies with historical control. The results showed that 90Y microspheres are a safe and well-tolerated therapy for unresectable HCC (median survival range, 7 -21.6 months). 90Y microspheres have been reported to downstage unresectable HCC to allow for salvage treatments with curative intent, act as a bridging therapy before liver transplantation, and treat HCC with curative intent for patients who are not surgical candidates because of comorbidities. The authors concluded that 90Y microsphere is recommended as an option of palliative therapy for large or multifocal HCC without major portal vein invasion or extrahepatic spread. It can also be used for recurrent unresectable HCC, as a bridging therapy before liver transplantation, as a tumor downstaging treatment, and as a curative treatment for patients with associated comorbidities who are not candidates for surgery.¹⁴

Professional Organizations

American College of Radiology (ACR): In a joint guideline with the American Society for Radiation Oncology (ASTRO) and the Society of Interventional Radiology (SIR), ACR states that indications for radioembolization with microspheres include, but are not limited to:⁶

- The presence of unresectable and/or medically inoperable primary or secondary liver malignancies. The tumor burden should be liver dominant, not necessarily exclusive to the liver. Patients should also have a performance status that will allow them to benefit from such therapy, i.e., an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 or Karnofsky Performance Status (KPS) of 70 or more.
- A life expectancy of at least three months

The National Comprehensive Cancer Network (NCCN) clinical practice guideline for hepatobiliary cancers outline that all hepatocellular carcinomas, regardless of their location in the liver, may be amenable to embolization (chemoembolization, bland embolization, radioembolization) if the arterial blood supply to the tumor may be isolated. General patient selection criteria for embolization procedures include unresectable/inoperable disease with tumors not amenable to ablation therapy only, and the absence of large-volume extrahepatic disease. Patients with unresectable/inoperable disease, who are eligible to undergo embolization therapy and have tumor lesions > 5 centimeters (cm), should be considered for treatment using arterial embolic approaches. Those patients with lesions 3–5 cm can be considered for combination therapy with ablation and arterial embolization.⁸

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
37204	Transcatheter occlusion or embolization (eg, for tumor destruction, to achieve hemostasis, to occlude

	a vascular malformation), percutaneous, any method, non-central nervous system, non-head or neck
79445	Radiopharmaceutical therapy, by intra-arterial particulate administration

HCPCS	Description
C2616	Brachytherapy source, non-stranded, yttrium-90, per source
S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres

ICD-9	Description
155.0	Malignant neoplasm of liver, primary
155.2	Malignant neoplasm of liver, not specified as primary or secondary
197.7	Secondary malignant neoplasm of respiratory and digestive systems; liver, specified as secondary

ICD-10	Description
C22.0	Carcinoma malignant, hepatocellular
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct

RESOURCE REFERENCES

1. Food & Drug Administration (FDA) premarket approval (PMA) for the SIR-Spheres PMA number P990065. Accessed at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>.
2. Food & Drug Administration (FDA) HDE for TheraSphere. Accessed at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=H980006>.
3. Centers for Medicare & Medicaid Services (CMS). Medicare Coverage Database. Accessed at: <http://www.cms.gov/mcd/search.asp>.
4. Hayes Search & Summary. Radioactive Yttrium-90 Microspheres for Treatment of Unresectable Primary Liver Cancer. Winifred Hayes Inc. Lansdale, PA. April 15, 2014.
5. Hayes Search & Summary. Radioactive Yttrium-90 Microspheres for Treatment of Unresectable Primary Liver Cancer as a Bridge to Transplantation or Surgery. Winifred Hayes Inc. Lansdale, PA. April 17, 2014.
6. American College of Radiology (ACR), the American Society for Radiation Oncology (ASTRO), and the Society of Interventional Radiology (SIR). Practice guideline for radioembolization with microsphere brachytherapy device (rmbd) for treatment of liver malignancies. 2008. Amended 2009. Accessed at: <http://www.acr.org/~media/d8086059b5f541e9b64e55d68a71693b.pdf>
7. Belinson, S, Yang, Y, Chopra, R, Shankaran, V, Samson, D, Aronson, N. Local Therapies for Unresectable Primary Hepatocellular Carcinoma [Internet]. AHRQ Comparative Effectiveness Reviews. 2013 May. PMID: 23844445
8. National Comprehensive Cancer Network. NCCN Guidelines version 2.2014 updates. Hepatobiliary Cancer. Accessed at: <http://www.nccn.org>

9. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology*. 2010;138(1):52.
10. Kooby DA, Egnatashvili V, Srinivasan S, et al. Comparison of yttrium-90 radioembolization and transcatheter arterial chemoembolization for the treatment of unresectable hepatocellular carcinoma. *J Vasc Interv Radiol*. 2010;21(2):224.
11. UpToDate: Kurley SA, Stuart KE, et al. Nonsurgical therapies for localized hepatocellular carcinoma: Transarterial embolization, radiotherapy, and radioembolization. May 2014.
12. Xie F, Zang J, Guo X, et al. Comparison of transcatheter arterial chemoembolization and microsphere embolization for treatment of unresectable hepatocellular carcinoma: a meta-analysis. *J Cancer Res Clin Oncol*. 2012 Mar;138(3):455-62.
13. Yang TX, Chua TC, Morris DL. Radioembolization and chemoembolization for unresectable neuroendocrine liver metastases - a systematic review. *Surg Oncol*. 2012 Dec;21(4):299-308.
14. Lau W.Y., Lai E.C.H., Leung T.W.T. Current role of selective internal irradiation with yttrium-90 microspheres in the management of hepatocellular carcinoma: A systematic review. *International Journal of Radiation Oncology Biology Physics*. 81 (2) (pp 460-467), 2011.