Subject: Radioactive Yttrium-90 Microspheres for Treatment of Liver Cancer		Original Effective Date: 7/10/2014
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DISCLAIMER

This Molina Clinical Policy (MCP) 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 exclusion(s) 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 CMS website. 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 Clinical Policy (MCP) document and provide the directive for all Medicare members.[1]

DESCRIPTION OF PROCEDURE [33-37]

Microsphere

Radioactive Yttrium-90 microsphere, also known as selective internal radiation therapy (SIRT) or transarterial radioembolization (TARE), is a nonsurgical procedure used to treat inoperable liver cancer. There are currently 2 commercially available beta-emitting microsphere devices, in which yttrium-90 (90Y) is incorporated: 1 device with microspheres made of glass (TheraSphere; BTG International Ltd.) and the other with microspheres made of resin (SIR-Spheres). The radioactive microspheres are delivered by a high pressure infusion catheter that is inserted into the groin and threaded into the hepatic artery in order to deliver targeted internal radiation therapy directly to the tumor. The goal of the procedure is to irradiate and destroy the tumor(s) while sparing normal liver tissue. 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 radioembolization (TARE), 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.

RECOMMENDATION [2-3 4-30 31-32]

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 [32] 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:* [34]

- 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)[34] 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 EXCLUSIONS [2-3 31-32]

Absolute Contraindications include:

- Inability to catheterize the hepatic artery
- Prior radiation therapy involving the liver
- Technetium-99m MAA hepatic arterial perfusion scintigraphy demonstrates significant reflux to the gastrointestinal organs that cannot be corrected by angiographic techniques such as embolization
- Encephalopathy
- Biliary obstruction
- Child-Pugh C cirrhosis

SUMMARY OF MEDICAL EVIDENCE [4-30]

There is an abundance of published literature regarding clinical outcomes of SIRT and other locally ablative treatments for liver tumors. Current evidence presents favorable effects of SIRT on locoregional control of liver cancer, however most lack long-term follow-up data to document the duration of responses or survival after SIRT. Currently, only small randomized controlled trials have been published on the safety and efficacy of SIRT, while a growing body of lower level evidence has led to expert consensus support for a limited number of indications. A summary of the most applicable literature is presented below.

There is one randomized phase 2 clinical trial published in the peer reviewed medical literature for radioactive yttrium-90 microspheres in the treatment of liver cancer that compare the effects of cTACE and Y90 radioembolization in patients with HCC. Patients in the Y90 radioembolization group had significant longer median TTP (>26 months) than patients in the cTACE group (6.8 months).A significantly greater proportion of patients in the cTACE group developed diarrhea (21%) than in the Y90 group or hypoalbuminemia (58% in the cTACE group vs 4% in the Y90 group). Similar proportions of patients in each group had a response to therapy, marked by necrosis (74% in the cTACE group vs 87% in arterial chemoembolization (TACE) and microsphere embolization for treating unresectable hepatocellular carcinoma (HCC). Thirteen the Y90 group) (P=.433). Median survival time, censored to liver transplantation, was 17.7 months for the cTACE group (95% CI, 8.3 NC) vs 18.6 months for the Y90 group (95% CI, 7.4-32.5). This phase 2 study of patients with HCC of BCLC stages A or B, concluded that Y90 radioembolization to provide significantly longer TTP than cTACE. Y90 radioembolization provides better tumor control and could reduce dropout from transplant waitlists. [21]

Lobo et al. (2016) conducted a systematic review and meta-analysis to compare TACE and TARE that included a total of 553 patients with unresectable HCC. 284 underwent TACE and 269 underwent TARE. Median ages were 63 and 64 years for TACE and TARE, respectively. Meta-analysis showed no statistically significant difference in survival for up to 4 years between the two groups. TACE required at least one day of hospital stay compared to TARE which was mostly an outpatient procedure. TACE had more post-treatment pain than TARE but less subjective fatigue. There was no difference between the two groups in the incidence of post-treatment nausea, vomiting, fever, or other complications. In addition, there was no difference in partial or complete response rates between the two groups. The authors concluded that TARE appears to be a safe alternative treatment to TACE with comparable complication profile and survival rates. [17]

Ludwig et al. (2016) performed a meta-analysis comparing conventional (c)TACE versus (90)Y-radioembolization or DEB-TACE for HCC treatment. Analysis revealed a 1-year overall survival benefit for DEB-TACE over (90)Y-radioembolization (79 % vs. 54.8 %), but not for the 2-year (61 % vs. 34 %) and 3-year survival (56.4 % vs. 20.9 %). There was significant heterogeneity in the 2- and 3-year survival analyses. The pooled median overall survival was longer for DEB-TACE (22.6 vs. 14.7 months). There was no significant difference in tumour response rate. The meta analysis concluded that DEB-TACE and (90)Y-radioembolization are efficacious treatments for patients suffering from HCC. DEB-TACE demonstrated survival benefit at 1-year compared to (90)Y-radioembolization but direct comparison is warranted for further evaluation. [18]

Oladeru et al (2016) compared the outcomes of overall and disease specific survival (DSS) using selective internal radiotherapy (SIRT) versus stereotactic body radiotherapy (SBRT) to treat hepatocellular carcinoma (HCC). A total of 189 patients with unresectable HCC were identified and used for statistical analysis, with 112 receiving SBRT and 77 receiving SIRT. Overall and disease-specific survival was compared using multivariable cox proportional hazard models. After adjusting for confounding factors (age at diagnosis, gender, race, grade, stage, AFP level and type of surgery), there were no significant difference in overall survival (OS) [hazard ratio (HR), 0.72; 95% confidence interval (CI), 0.49-1.07; P=0.1077] and DSS (HR, 0.70; 95% CI, 0.46-1.05; P=0.0880) for SIRT compared to SBRT. However, patients with elevated AFP level were associated with higher death risk (P=0.0459) and disease specific death risk (P=0.0233) than those with AFP within normal limits in both treatment groups. The authors concluded the findings suggest both treatment approaches result in similar outcomes in overall and disease-specific survival benefit. Future prospective randomized trials are needed to better evaluate and compare the two radiation modalities, as well as other non-operative therapies used in the treatment of HCC. [19]

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. [4]

Xie et al. (2012) performed a meta-analysis comparing the efficacy of transcatheter 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. [26]

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. [27]

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 [31- 33]

American College of Radiology (ACR) and the Society of Interventional Radiology (SIR): The ACR and SIR developed practice parameters (2014) for radioembolization (also referred to as selective internal radiation therapy [SIRT], transarterial radioembolization [TARE], and brachytherapy) with microsphere brachytherapy devices for the treatment of liver malignancies. According to the parameters, treatment goals of radioembolization can be palliative, curative, or serve as a bridge to transplantation. The ultimate goal is to achieve intrahepatic tumor control. In all cases, indications warranting the use of radioembolization include patients with unresectable or inoperable primary or secondary liver malignancies. Eligible patients should have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a Karnofsky Performance Status (KPS) $\geq$ 70, and a life expectancy $\geq$ 3 months. The parameters recommend an interdisciplinary team for evaluation and management of eligible patients. Team members' disciplines should include interventional radiology, radiation oncology, nuclear medicine, medical physics, radiation safety, hepatology, gastroenterology, medical oncology, and surgical oncology. The guidelines provide specific qualifications and responsibilities of each member of the interdisciplinary team as well as details of the radioembolization procedure and post procedure care. [31]

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. Bridge therapy to decrease tumor progression prior to liver transplant is also recommended. [32]

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
37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction
75854	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
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-10	Description: [For dates of service on or after 10/01/2015]
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

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Review/Revision History:

7/10/14: Policy created
12/16/15 & 6/15/16: Policy reviewed, no changes
5/9/2017: The policy was reviewed and the clinical criteria section did not change. The following sections were updated: Exclusions, Summary of medical evidence, professional guidelines and references.
7/10/18 & 6/19/19: Policy reviewed, no changes to criteria. Updated references.