Molina Clinical Policy
Radioembolization for Primary and Metastatic Tumors of the Liver: Policy No. 181

Last Approval: 8/9/2023
Next Review Due By: August 2024

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. 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 (e.g., 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 MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Hepatocellular carcinoma (HCC), or primary liver cancer, is becoming more prevalent due to the spread of hepatitis virus infection (Schwartz & Carithers 2023). HCC is usually associated with cirrhosis of the liver, and the prognosis for HCC is poor (Abdalla et al. 2022). Patients with primary liver cancer are categorized as having localized resectable, localized unresectable, or advanced disease. Surgical excision is the preferred treatment for liver tumors; however, many liver tumors are inoperable due to the placement of the tumor within the liver or the presence of concurrent medical conditions such as cirrhosis (Curley et al. 2022). While some of these patients may be candidates for liver transplantation, the restricted availability of donor livers remains a barrier (Tsoulfas et al. 2022). Additional therapy options for nonresectable HCC in the early stage include percutaneous ablation with ethanol injection and radiofrequency ablation (Abdalla et al. 2022).

Radioembolization, a type of nuclear medicine therapy used to treat primary or metastatic hepatic malignancies, is a transcatheter intra-arterial therapy utilizing yttrium 90 (Y-90) (Curley et al. 2022; Tsoulfas et al. 2022). Radioembolization, selective internal radiation therapy (SIRT), intra-arterial radiation therapy, or trans-arterial radioembolization (TARE) are all locoregional therapies that have the goal of deterring tumor progression in patients that are awaiting liver transplantation (Hayes 2022). During therapy, an interventional radiologist uses x-ray fluoroscopy to guide a catheter percutaneously via a patient's femoral artery to the correct hepatic artery. A vial containing Y-90 microspheres is infused into the body through a catheter connection. The microspheres are impregnated with Y-90 and become permanently lodged. The microspheres are selectively delivered through the hepatic vasculature to the target tumor(s). The procedure is performed on an outpatient basis and takes 30 to 60 minutes to complete. Patients are usually discharged within 23 hours. Radioembolization has been proposed as a treatment for a variety of primary and metastatic liver tumors and has been utilized to downstage the cancer or as a bridge therapy prior to resection, surgery, or transplantation (Tsoulfas et al. 2022).

Regulatory Status *(Intended for informative purposes; coverage is not contingent solely on the basis of FDA approval)*

Food and Drug Administration (FDA): There are two types of FDA approved Y-90 microspheres: SIR-Spheres® and TheraSphere®. The use of Y-90 microspheres to treat primary, unresectable liver cancer is a procedure and is exempt from FDA oversight. However, the FDA may have regulations governing any medical devices, medications, biologics, or diagnostics utilized as part of this procedure. Additional information is available by searching the FDA premarket and device approval databases with product code: NAW.

Two forms of Y-90 microspheres have received FDA approval:

1. **SIR-Spheres®** (Sirtex Medical) are Y-90 microspheres made of resin. SIR-Spheres microspheres are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intrahepatic artery floxuridine chemotherapy. FDA premarket approval was granted on March 5, 2002 (FDA 2002).
2. **TheraSphere®** (BTG) are Y-90 microspheres made of glass.
    - TheraSphere received approval in 1999 as a neoadjuvant treatment to surgery or transplantation in patients with unresectable HCC who can have placement of appropriately positioned hepatic arterial

catheters through the humanitarian drug exemption (HDE) process for radiotherapy (FDA 1999). In 2006, this HDE was expanded to include patients with HCC who have partial or branch portal vein thrombosis (FDA 2006).

- TheraSphere received approval through the PMA process on March 17, 2021, for use as SIRT for local tumor control of solitary tumors (1-8 cm in diameter), in patients with unresectable HCC, Child-Pugh Score A cirrhosis, well-compensated liver function, no macrovascular invasion, and good performance status (FDA 2021).

The U.S Nuclear Regulatory Commission also regulates the usage of TheraSphere® and SIR-Spheres® by issuing licenses for their application (NRC 2019).

RELATED POLICIES

Radiofrequency Ablation of Primary or Metastatic Liver Tumors: Policy No. 391
Liver Transplantation (Adult and Pediatric): Policy No. 114
Pre-Transplant Evaluation: Policy No. 323

COVERAGE POLICY

Radioembolization (i.e., TheraSphere®, SIR-Spheres®) **may be considered medically necessary** and may be authorized when **ALL** of the following criteria are met:

1. A diagnosis of **ONE** of the following:
   a. Primary HCC **or** primary intrahepatic cholangiocarcinoma with:
      - Unresectable tumor that is limited to the liver (Unresectable HCC is generally defined as tumors greater than 3 cm); **OR**
      - A bridge to transplant in Members meeting criteria for liver transplantation and **ONE** of the following:
        i. No malignant portal vein thrombus; **OR**
        ii. No extrahepatic disease involvement

   OR

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

AND

2. Systemic therapy has failed, or member is not a candidate for chemotherapy, surgical resection and/or transarterial chemoembolization (TACE); **AND**

3. **ONE** of the following:
   a. ECOG performance score of 0-2;* **OR**
   b. Child-Pugh score A or B.**

AND

4. A life expectancy of at least 3 months.

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

- 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-Turcotte-Pugh score determines short-term prognosis among groups of patients awaiting liver transplantation and has

been widely adopted for risk-stratifying patients before transplantation.

Child-Turcotte-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)

Limitations and Exclusions

Absolute contraindications to Y-90 radioembolization 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;
- ECOG > 2 (poor performance status);
- Child-Pugh C cirrhosis (severely compromised liver function);
- Impaired liver function causing hyperbilirubinemia (may be a relative or absolute contraindication depending on the disease burden, hepatic distribution requiring treatment and treatment goals)

There is limited data on the safety and efficacy of repeated radioembolization treatments, as well as the optimal number of treatments.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

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. There is a growing body of literature to suggest that radioembolization might be an effective treatment option for patients with liver-limited, unresectable disease though additional randomized controlled trials (RCTs) are needed to determine the relative risks and benefits of TARE with Y-90 microspheres in patients with unresectable HCC and long-term impact on liver function (NCCN 2023). A summary of applicable literature is presented below.

Zeng et al. (2023) completed a systematic review and meta-analysis to compare the efficacy and safety of SIRT, sorafenib, and a combination therapy of SIRT and sorafenib (SIRT+sorafenib). The analysis included 9 studies (6 retrospective and 3 RCTs) with a total of 1954 patients. The outcomes measured included overall survival (OS), progression free survival (PFS), and adverse events (AEs). For OS, the retrospective studies showed SIRT to be superior to sorafenib alone and SIRT+sorafenib (HR 0.60, 95% CI 0.42–0.87; $I^2 = 56\%$) while the RCTs showed no significant difference between any of the groups (HR 0.92, 95% CI 0.79–1.08; $I^2 = 0\%$). The overall comparison including the retrospective studies and RCTs showed a statistically significant difference in OS between SIRT and

sorafenib (HR 0.73, 95% CI 0.56–0.94; p = 0.01). PFS was only included in 3 studies but showed no significant difference between any of the groups (HR 0.87, 95% CI 0.62–1.22). In terms of AEs, sorafenib alone was found to lead to a higher incidence rate of grade 3 or higher AEs when compared to SIRT alone. The most common AEs when comparing SIRT alone and sorafenib alone were weight loss (SIRT=0.60%, sorafenib=1.83%), diarrhea (SIRT=1.33%, sorafenib=5.95%), and rash or desquamation (SIRT=0.47%, sorafenib=3.15%). The most common AEs when comparing SIRT+sorafenib and sorafenib alone were fatigue (SIRT+sorafenib=1.92%, sorafenib=7.21%), rash or desquamation (SIRT+sorafenib=0.93%, sorafenib=3.15%), and liver dysfunction (SIRT+sorafenib=0.47%, sorafenib=6.51%). Researchers noted that SIRT+sorafenib did not raise the risk of grade 3 or higher AEs but potentially introduced more AEs than either SIRT or sorafenib alone. Researchers also noted that SIRT alone was superior to SIRT+sorafenib and sorafenib alone.

Lemieux et al. (2021) completed a systematic review and meta-analysis with the goal of assessing the efficacy and safety of Y-90 TARE to the standard of care in non-surgical HCC patients. Standard of care was based on Barcelona Clinic Liver Cancer (BCLC) staging. The meta-analysis included 8 RCTs with a total of 1439 patients. The primary outcome measured was OS. Secondary outcomes measured included the time to radiological progression (defined by PFS and time to progression at any site), disease control rate (defined as the sum of complete response, partial response, and stable disease), the incidence of severe or significant AEs, and the incidence of gastrointestinal ulcers of any severity. The patient population was noted to be mostly male (n=86%) with 59% having advanced HCC, 35.5% having intermediate HCC, and 5.5% having early HCC. Y-90 TARE was performed using resin microspheres in 5 RCTs and glass microspheres in 3 RCTs. The OS was reported in all trials. However, 2 trials only reported median survival rates or survival rates at 6- and 12-months and were not included in the analysis. There was no significant difference noted in OS between Y-90 TARE and the standard of care. PFS was reported in 4 trials and the time to progression was reported in 5 trials. The overall time to radiological progression (combined PFS and time to progression) showed no differences between Y-90 TARE and standard of care. However, it was noted that Y-90 TARE had a significantly longer time to progression in the glass microsphere subgroup. The disease control rate was reported in 5 RCTs and showed no significant difference between interventions. AEs were reported by all studies and analysis showed Y-90 TARE was associated with significantly lower rates of grade 3 or higher AEs when compared to the standard of care. No significant differences were noted in the rates of gastrointestinal ulcers.

Abdel-Rahman and Elsayed (2020) conducted a systematic review and meta-analysis on 6 RCTs (n = 1,340) to determine the benefits and harms of Y-90 microsphere radioembolization in comparison with placebo, no intervention, or other available interventions in patients with advanced liver cancer. The major outcomes that were measured were the overall median survival rate, the quality of life, and the occurrence of significant AEs. Cancer-related mortality, progression time, and tumor response were examined as secondary outcomes. Individuals with advanced HCC were evaluated in an RCT between radioembolization with sorafenib and sorafenib alone. Radioembolization combined with sorafenib may be associated with greater incidence of non-serious adverse events than sorafenib alone, according to evidence of very low certainty discovered by the authors. The median OS in the sorafenib group was 11.4 months and in the radioembolization plus sorafenib group it was 12.1 months. Two RCTs compared radioembolization to sorafenib in patients with locally advanced HCC and unresectable tumors. The radioembolization group had a one-year mortality rate of 62%, whereas the sorafenib group had a mortality rate of 60%. Radioembolization was associated with equivalent rates of OS and disease control when compared to sorafenib alone, according to the findings of the authors. With radioembolization, the risk of non-serious AEs was reduced. Three RCTs compared radioembolization to chemoembolization in patients with HCC in the intermediate stage. Survival rates at one year were 70% for both groups. Radioembolization and chemoembolization share a comparable risk of significant AEs, according to evidence of low certainty found by the authors.

National and Specialty Organizations

The **National Comprehensive Cancer Network (NCCN)** clinical practice guideline for hepatocellular carcinoma (V1.2023) states:

> Bridge therapy is used to decrease tumor progression and the dropout rate from the liver transplantation waiting list. It is considered for patients who meet the transplant criteria. … A number of studies have investigated the role of locoregional therapies as a bridge to liver transplantation in patients on a waiting list. These studies included RFA, transarterial embolization (TAE), chemoembolization, TACE, TACE with drug-eluting beads (DEB-TACE), TARE with Y-90 microspheres, conformal radiation therapy (CRT) and sorafenib as “bridge” therapies.

Limitations of these studies include size and heterogeneity of the study populations; however, the NCCN CPG states, "Nevertheless, the use of bridge therapy in this setting is increasing, and it is administered at most NCCN Member Institutions, especially in areas where there are long wait times for a transplant."

The NCCN clinical practice guidelines for HCC (V1.2023) states the following with Category 2A recommendations in the Principles of Locoregional Therapy- Arterially Directed Therapies section:

- Locoregional therapy should be considered in patients who are not candidates for surgical curative treatments, or as a part of a strategy to bridge patients for other curative therapies.
- Lesions 3 to 5 cm may be treated to prolong survival using arterially directed therapies, or with combination of an arterially directed therapy and ablation as long as tumor location is accessible for ablation.
- All tumors irrespective of location may be amenable to arterially directed therapies provided that the arterial blood supply to the tumor maybe isolated without excessive non-target treatment.
- Unresectable/inoperable lesions > 5cm should be considered for treatment using arterially directed or systemic therapy.
- Arterially directed therapies include TAE, chemoembolization (TACE, and DEB-TACE) and radioembolization (RE) with Y-90 microspheres.
- All arterially directed therapies are relatively contraindicated in patients with bilirubin >3 mg/dL unless segmental injections can be performed. RE with Y-90 microspheres has an increased risk of radiation-induced liver disease in patients with bilirubin over 2 mg/dL.
- Arterially directed therapies in highly selected patients have been shown to be safe in the presence of limited tumor invasion of the portal vein.
- The treating physician may choose the angiographic endpoint of embolization.

The **European Society for Medical Oncology (ESMO)** published updated guidelines in 2022 for the management of HCC (Ducreux et al. 2022). The guidelines state the following:

- Bridging treatments are typically used if the expected waiting time for a liver transplant is > 6 months. Bridging treatments consist of TACE, DEB-TACE, TARE, and radiofrequency or microwave ablation.
- Radiofrequency or microwave ablation is typically used for patients with a BCLC score of 0 due to ablation being equivalent to surgery in terms of survival.
- TACE and DEB-TACE is the standard treatment for intermediate BCLC cases (tumor > 3cm and multinodular [≥ 4 nodules]) with an ECOG performance status of 0 or Child-Pugh score of A and without vascular invasion, extrahepatic disease, or portal thrombosis.
- TARE can be utilized in place of TACE if TACE is not available. However, evidence suggests TARE is associated with a longer time to progression compared to TACE.
- Combination treatments of sorafenib and TACE have not shown overall survival advantages when compared to either treatment alone.
- Stereotactic body radiotherapy (SBRT) has been shown to have similar outcomes to radiofrequency ablation. It has been suggested that SBRT may be useful for the treatment of tumors that are difficult to reach using radiofrequency ablation. However, SBRT is currently not widely utilized.

The **American College of Radiology (ACR), American Brachytherapy Society (ABS), American College of Nuclear Medicine (ACNM), American Society for Radiation Oncology (ASTRO), Society of Interventional Radiology (SIR), and Society of Nuclear Medicine and Molecular Imaging (SNMMI)** have published joint practice guidelines for radioembolization (also known as SIRT, TARE, and brachytherapy) with microsphere brachytherapy devices for the treatment of liver cancers. According to the parameters, radioembolization therapy aims can be palliative, curative, or a bridge to transplantation. The ultimate objective is intrahepatic tumor suppression. Patients with unresectable or inoperable primary or secondary liver cancers are the only indications for the use of radioembolization. Patients who qualify must have an ECOG performance level of 0 or 1, a Karnofsky Performance Status 70, and a survival expectancy of less than three months. For evaluation and management of eligible patients, the guidelines propose a multidisciplinary team. The disciplines of team members should include of interventional radiology, radiation oncology, nuclear medicine, medical physics, radiation safety, hepatology, gastrointestinal, medical oncology, and surgical oncology. The rules specify the qualifications and responsibilities of each multidisciplinary team member, as well as the radioembolization method and post-operation care (ACR 2019).

The **European Association for the Study of the Liver (EASL)** guideline authors reviewed evidence regarding the

use of Y-90microspheres in patients with BCLC stage A for bridging to transplantation, in patients with BCLC-B in comparison to TACE, and in patients with BCLC-C in comparison to sorafenib. Based on moderate evidence, they found that while the results imply a good safety profile and local tumor management, the data do not prove an overall survival benefit when compared to TACE or sorafenib. The authors emphasized that the subset of patients who benefit from TARE needs to be determined, and that the use of TARE, either alone or in combination with systemic therapy, should not be used until a multidisciplinary board has deliberated. However, they did not provide a clear recommendation for the use of TARE for bridging to transplantation or de-escalation (EASL 2018).

The **National Institute for Health and Care Excellence (NICE)** asserts that TheraSphere could be used to treat patients with operable and inoperable HCC as an alternative or adjunct to 1 of several options currently available (including liver resection, transplantation, local ablation, chemoembolization and transcatheter therapies, and systemic therapies), depending on multiple factors such as the patient's general health and tumor stage. The evidence from 11 studies reported in the briefing is of mixed quality and demonstrates that patients treated with TheraSphere do not have significantly longer overall life periods than those treated with standard TACE with lipiodol (NICE 2016).

SUPPLEMENTAL INFORMATION

TARE is a technique that involves delivering high-dose beta radiation internally to the tumor-associated capillary bed while preserving normal liver tissue. 334,376 TARE is administered through catheter of microspheres (glass or resin microspheres) embedded with Y-90, a beta radiation emitter (NCCN 2023).

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology) Codes

CPT	Description
37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural road mapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction
75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
79445	Radiopharmaceutical therapy, by intra-arterial particulate administration

HCPCS (Healthcare Common Procedure Coding System) Codes

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
Q3001	Radioelements for brachytherapy, any type, each

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

08/09/2023 Policy reviewed, no changes to coverage criteria. Overview, Summary of Medical Evidence, and References sections updated. Added code Q3001 and replaced code 75854 with 75894. Grammatical edits to Disclaimer section and Documentation Requirements disclaimer.

08/10/2022 Policy reviewed and updated. Title updated to 'Radioembolization for Primary and Metastatic Tumors of the Liver' (previously Radioactive Microspheres for Liver Cancer.' Clarifications to coverage criteria with no change in intent. Added 'Related Policies' section. Updated references. IRO review 06/27/22 by practicing board certified diagnostic radiologist.

08/11/2021	Policy reviewed, no changes, updated references.
06/17/2020	Policy reviewed, no changes, updated references.
06/19/2019	Policy reviewed, no changes, updated references.
07/10/2018	Policy reviewed, no changes, updated references.
05/09/2017	Policy reviewed, no changes. Sections updated: Exclusions, Summary of Medical Evidence, references.
06/15/2016	Policy reviewed, no changes.
12/16/2015	Policy reviewed, no changes.
07/10/2014	New policy.

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