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

Last Approval: 8/10/2022
Next Review Due By: August 2023

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. HCC is usually associated with cirrhosis of the liver, and the prognosis for HCC are poor. Patients with primary liver cancer are categorized as having localized resectable, localized unresectable and advanced disease. Surgical excision is the preferred treatment for liver tumors. Many liver tumors, however, are inoperable due to the placement of the tumor within the liver or the presence of concurrent medical conditions such as cirrhosis. While some of these patients may be candidates for liver transplantation, the restricted availability of donor livers remains a barrier. Percutaneous ablation with ethanol injection and radiofrequency ablation are additional therapy options for nonresectable HCC in the early stage.

Radioembolization, a type of nuclear medicine therapy used to treat primary or metastatic hepatic malignancies, is a transcatheter intra-arterial therapy utilizing yttrium 90 (90Y). Radioembolization, selective internal radiation therapy (SIRT), intra-arterial radiation therapy, or trans-arterial radioembolization (TARE) are all various names for the same clinical procedure. 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 90Y microspheres is infused into the body through a catheter connection. The microspheres, impregnated with 90Y become permanently lodged, are selectively delivered through the hepatic vasculature to the target tumor(s), in which tumors greater than 0.5 cm rely on the hepatic artery for blood flow while the normal liver is predominantly perfused via the portal vein. 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.

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 90Y microspheres FDA approved, SIR-Spheres® and TheraSphere® . The use of 90Y microspheres to treat primary, unresectable liver cancer is a procedure and, as such, 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. FDA product code: NAW.

Two forms of Y90 microspheres have received FDA approval:

1. **SIR-Spheres®** (Sirtex Medical) are 90Y 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 (P990065) on March 5, 2002.
2. **TheraSphere®** (BTG) are microspheres of glass 90Y.
    - TheraSphere received approval 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 (H980006) 1999. In 2007, this HDE was expanded to include patients with HCC who have partial or branch portal vein thrombosis.
    - TheraSphere received approval through the PMA process 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 (P200029). March 17, 2021.

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

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 hepatocellular carcinoma **or** primary intrahepatic cholangiocarcinoma with:
      - 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 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-Turcote-Pugh (CTP) 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)

Limitations and Exclusions

Absolute contraindications to Y90 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 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, a-f). RCTs have shown that Y-90 is not superior to sorafenib for treating advanced HCC (Chow et al. 2018; Vilgrain et al. 2018) In both trials, overall survival rates were not significantly different between the two treatment groups (NCCN 2022). A summary of applicable literature is presented below.

Abdel-Rahman and Elsayed (2020) conducted a systematic review and meta-analysis on 6 randomized controlled trials (RCTs) (n = 1,340) to determine the benefits and harms of 90Y 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 adverse events. Cancer-related mortality, progression time, and tumor response were examined as secondary outcomes. Individuals with advanced HCC were evaluated in a randomized controlled trial 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 overall survival in the sorafenib group was 11.4 months and in the radioembolization plus sorafenib group it was 12.1 months. Two randomized controlled trials 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 overall survival and disease control when compared to sorafenib alone, according to the findings of the authors. With radioembolization, the risk of non-serious adverse events was reduced. Three randomized controlled trials 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 adverse events, according to evidence of low certainty found by the authors.

Kallini et al. (2017) compared the safety profiles of TheraSphere® (glass) and SIRSpheres® (resin) Y90 microspheres for the treatment of HCC in a systematic review. Baseline characteristics and adverse events involving the gastrointestinal, hepatobiliary, and respiratory systems were collected from all grades. The study included 31 observational studies. More patients treated with resin microspheres reported gastric ulcers, hepatic encephalopathy, cholecystitis, hepatic failure, and pleural effusion in all grades of adverse events. Patients receiving resin microspheres experienced an increase in hepatobiliary adverse events of grade 3 or higher. Glass microspheres had a similar safety profile to resin microspheres in events related to post-embolization syndrome. Glass microsphere treatment resulted in more ascites and nausea of grade 3 or higher. Based on a review of the published literature, the authors concluded that glass microspheres have a safer profile with fewer gastrointestinal and pulmonary adverse events in the treatment of HCC than resin microspheres. There is no head-to-head data comparing these two FDA-approved microspheres described for patients receiving TARE with intent to downstage or bridge to transplantation.

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.

Curley et al. 2021 noted in a review titled “Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates not eligible for local thermal ablation,” radioembolization using intra-arterial injection of 90Y-labeled glass or resin microspheres induces extensive tumor necrosis while maintaining an acceptable safety profile. However, no studies have shown an effect on survival, and there is no consensus on when and if this therapy should be chosen over TACE for the treatment of unresectable HCC (Curley et al. 2021). In the setting of an HCC complicated by a malignant main or lobar branch portal vein thrombus, radioembolization may be preferred over TACE. Newer techniques for superselective radioembolization, such as segmental radioembolization (also known as radiation segmentectomy), may provide high rates of local control with less radiation-induced liver disease where available and for appropriately selected patients. A multidisciplinary team must evaluate the candidate for radioembolization. Benefits over other forms of nonsurgical locoregional therapy include low toxicity, the ability to treat patients with significant tumor burden (often in a single setting rather than multiple sessions, as with classic TACE), and relatively limited side effects. However, the treatment’s utility is limited by its high cost and certain anatomical constraints (e.g., radioactive material passing through to the lung in some patients with shunting).

According to a Health Technology Assessment report, ‘Comparative Effectiveness Review Of Radioactive Yttrium-90 Microspheres For Treatment Of Primary Unresectable Liver Cancer’ (2021), TARE with 90Y is a locoregional therapy that has demonstrated promising outcomes in retrospective comparative studies. For intermediate-stage unresectable primary HCC, 90Y radioembolization had equivalent efficacy in terms of survival outcomes and maybe superior efficacy in tumor response and better patient tolerance than TACE. Overall, the amount of evidence supporting this comparison was low. The evidence is of insufficient quality and quantity to form conclusions on the comparative efficacy and safety of TARE and doxorubicin-loaded drug-eluting bead–based TACE. Two randomized controlled trials (RCTs) and three retrospective studies now compare TARE to sorafenib as first- or second-line therapy for individuals with primary HCC. TARE did not enhance overall survival or tumor progression when compared to sorafenib; however, some data

suggests that tumor response may be better when compared to sorafenib, and TARE was typically more well tolerated by patients than sorafenib. Overall, the evidence level for comparing sorafenib to TARE was low. There is insufficient evidence to determine which type of bead, TheraSphere or SIR-Sphere, offers superior results; nevertheless, there is some evidence that TheraSphere beads may have greater tolerance than resin-based SIR-Sphere beads.

National and Specialty Organizations

The **American College of Radiology (ACR) and the Society of Interventional Radiology (SIR)** have published practice guidelines for radioembolization (also known as selective internal radiation therapy [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 Eastern Cooperative Oncology Group 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/SIR).

The **National Comprehensive Cancer Network (NCCN)** clinical practice guideline in Oncology for hepatocellular carcinoma (V5.2021) 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), transarterial radioembolization (TARE) with yttrium-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 CPG for HCC (V5.2021) 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 transarterial bland embolization (TAE) chemoembolization (transarterial chemoembolization [TACE] and TACE with drug-eluting beads [DEB-TACE]) and radioembolization (RE) with yttrium-90 microspheres.
- All arterially directed therapies are relatively contraindicated in patients with bilirubin >3 mg/dL unless segmental injections can be performed. RE with yttrium-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 angiographic endpoint of embolization may be chosen by the treating physician.

The **European Association for the Study of the Liver (EASL)** guideline authors reviewed evidence regarding the use of yttrium-90 (90Y) microspheres in patients with Barcelona Clinic Liver Cancer (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, chemoembolisation 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, 2022).

CODING & BILLING INFORMATION

CPT Codes

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 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

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 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

8/10/2022	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.
8/11/2021	Policy reviewed, no changes, updated references.
6/17/2020	Policy reviewed, no changes, updated references.

6/19/2019	Policy reviewed, no changes, updated references.
7/10/2018	Policy reviewed, no changes, updated references.
5/9/2017	Policy reviewed, no changes. Sections updated: Exclusions, Summary of Medical Evidence, references.
6/15/2016	Policy reviewed, no changes.
12/16/2015	Policy reviewed, no changes.
7/10/2014	New policy.

REFERENCES

Government Agencies

1. Centers for Medicare and Medicaid Services (CMS). Medicare coverage database (search: yttrium, microsphere, radioembolization). Available from CMS. Accessed June 2022. NCD not identified for radioactive 90Y microspheres for treatment of primary unresectable liver cancer.
2. National Cancer Institute (NCI). Adult primary liver cancer treatment (PDQ®). Available from NCI. Published 2021. Accessed June 2022.
3. United States Food and Drug Administration (FDA). Premarket approval (PMA) for the SIR-Spheres (PMA no. P99006). Available from FDA. Accessed June 2022.
4. United States Food and Drug Administration (FDA). Humanitarian device exemption (HDE): TheraSphere. Available from FDA. Accessed June 2022.

Peer Reviewed Publications

1. Belinson S, Yang Y, Chopra R, et al. Local Therapies for Unresectable Primary Hepatocellular Carcinoma. Agency for Healthcare Research and Quality (US), Rockville (MD); 2013. PMID: 23844445.
2. Chow PKH, Gandhi M, Tan SB, et al. SIRveNIB: Selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. J Clin Oncol 2018;36:1913-1921. PMID: 29498924 DOI: 10.1200/JCO.2017.76.0892
3. Lobo L, Yakoub D, Picado O, et al. Unresectable hepatocellular carcinoma: radioembolization versus chemoembolization: a systematic review and meta-analysis. Cardiovasc Intervent Radiol. 2016 Nov;39(11):1580-1588. Doi: 10.1007/s00270-016-1426-y.
4. Salem R, Gordon AC, Mouli S, et al. Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. Gastroenterology. 2016 Aug 26. Pii: S0016-5085(16)34971-X. doi: 10.1053/j.gastro.2016.08.029.
5. Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label 7adioembol controlled phase 3 trial. Lancet Oncol. 2017 Dec;18(12):1624-1636. Doi: 10.1016/S1470-2045(17)30683-6. Epub 2017 Oct 26. PMID: 29107679.

National and Specialty Organizations

1. American College of Radiology (ACR). ACR-SIR Practice Parameter for Radioembolization with Microsphere Brachytherapy Device (RMBD) for Treatment of Liver Malignancies. Available from ACR. Published 2014. Updated 2019. Accessed June 2021.
2. American College of Radiology (ACR), the American Brachytherapy Society (ABS), the American College of Nuclear Medicine (ACNM), the American Society for Radiation Oncology (ASTRO), the Society of Interventional Radiology (SIR), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI). ACR–ABS–ACNM–ASTRO–SIR–SNMMI practice parameter for selective internal radiation therapy (Sirt) or radioembolization for treatment of liver malignancies. Brachytherapy. May-Jun 2021;20(3):497-511. doi: 10.1016/j.brachy.2021.01.006. Available from ACR. Published 2019.
3. European Association for the Study of the Liver (EASL). EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182-236.
4. National Comprehensive Cancer Network (NCCN). Hepatobiliary cancer guideline. http://www.nccn.org. Accessed June 2021. Registration and login required.

Other Evidence Based Reviews and Publications

1. Curley SA, Stuart KE, et al. Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates not eligible for local thermal ablation. Available from UpToDate. Updated Nov 29, 2021. Accessed June 2022. Registration and login required.
2. Hayes. Health technology assessment: Radioactive yttrium-90 microspheres for the treatment of primary unresectable liver cancer for downstaging or as a bridge to transplantation or surgery. Published September 11, 2019. Updated January 5, 2021. Accessed June 2022. Available from Hayes. Registration and login required.
3. Hayes. Health technology assessment: Radioactive yttrium-90 microspheres for treatment of secondary liver cancer. Available from Hayes. Published March 31, 2015. Updated April 29, 2019. Archived April 30, 2020. Accessed June 2022. Registration and login required.
4. Hayes. Health technology assessment: Comparative effectiveness review of radioactive yttrium-90 microspheres for treatment of primary unresectable liver cancer. Available from Hayes. Published June 2019. Updated Jul 19, 2021. Accessed June 2022. Registration and login required.

Other Peer Reviewed and National Organization Publications (used in the development of this policy)

1. NCCN Guidelines Hepatobiliary Cancers v.1.2022 cites the following studies:
   - Kulik LM, Carr BI, Mulcahy MF, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology 2008;47:71-81. Available here.
   - Mazzaferro V, Sposito C, Bhoori S, et al. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. Hepatology 2013;57:1826-1837. Available here.
   - 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):52-64.

- Sangro B, Carpanese L, Cianni R, et al.; European Network on Radioembolization with Yttrium-90 Resin Microspheres (ENRY). Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology. 2011; 54(3):868-878.
- Vouche M, Habib A, Ward TJ, et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: multicenter radiology-pathology correlation and survival of radiation segmentectomy. Hepatology. 2014; 60(1):192-201.
- Woodall CE, Scoggins CR, Ellis SF, et al. Is selective internal radioembolization safe and effective for patients with inoperable hepatocellular carcinoma and venous thrombosis? J Am Coll Surg 2009;208:375-382. Available here.

APPENDIX

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*