

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria

Therasphere and SIR Sphere for Unresectable Hepatocellular Carcinoma

- SIRT (Selective Internal Radiation Therapy)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	11/01/2023 Noridian retired Treatment with Yttrium-90 Microspheres (A52950) . These services still need to meet medical necessity as outlined in the LCA and will require review. LCAs are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an article. Most LCAs are not retired because they are incorrect. Therefore, continue to use LCA A52950 for determining medical necessity.

For Non-Medicare Members

- I. The use of Yttrium-90 (90Y) microsphere radioembolization (SIR-Spheres® or TheraSphere®) is medically necessary if **ONE** of the following is met:
 - A. Unresectable metastatic liver tumors from primary colorectal cancer (CRC)
 - B. Unresectable liver-only or liver-dominant metastases from neuroendocrine tumors (NET) (e.g. carcinoid, islet cell tumor/pancreatic endocrine tumor) and **ALL** of the following:
 1. The disease is diffuse* and symptomatic (*For this medical policy, the term “diffuse” disease is defined as tumor tissue spread throughout the affected organ (e.g., diffuse liver disease))
 2. Only in persons who have failed systemic therapy with octreotide to control carcinoid syndrome (e.g., debilitating flushing, wheezing and diarrhea)
 - C. Unresectable primary hepatocellular carcinoma (HCC)
- II. Yttrium-90 (90Y) microsphere radioembolization is not covered for any other indication because its clinical utility has not been established.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, and the third most common cause of cancer-related mortality. It is responsible for more than half a million deaths across the globe each year. Treatment options for patients diagnosed with hepatocellular carcinoma (HCC) are limited. Less than 15% are candidates for surgical resection at presentation, and the use of external beam radiation is limited due to the intolerance of normal liver parenchyma to tumoricidal radiation doses (the dose required to destroy solid tumors (>70 Gy) is much higher than the liver tolerance dose of 35 Gy). In addition, systematic chemotherapy was found to have little impact on survival and negative impact on the health-related quality of life due to the toxicity to other organs and systems. These limitations have led to the emergence of local and regional treatments such as radiofrequency ablation, local administration of cytostatic drugs like hepatic arterial infusion and isolated hepatic infusion, or intrarterial embolization techniques such as transarterial chemo-embolization and selective intrarterial radioembolization therapy (Steel 2003, Salem 2004, Ibrahim 2008, Bult 2009, Riaz 2009).

Yttrium-90 (90Y) intra-arterial radiotherapy also known as radioembolization, is an emerging technique for the treatment of patients with unresectable primary or metastatic liver tumors. It is a minimally invasive catheter-based therapy that delivers internal radiation via the arterial vessels that feed the tumor. The technology takes advantage of the dual blood supply of the liver as the normal hepatic tissue obtains more than 70% of its blood supply through the portal vein, while intrahepatic malignancies derive their blood supply almost entirely from the hepatic artery i.e. arterial rather than portal circulation. The concept of intra-arterial radioembolization was first explored by injecting yttrium-90 containing microspheres in the hepatic artery of rabbits with liver tumor. The first clinical trial on selected patients was conducted in the mid 1980s, but was discontinued due to the several patient deaths of myelosuppressions due to leaching (leakage) of the microspheres (Vente 2009).

In an attempt to overcome the problem of leaching, yttrium containing solid glass microspheres were developed (TheraSphere®, MDS Nordion, Ottawa, Ontario, Canada). These consist of microscopic glass beads 20-30 µ in diameter embedded with the radionuclide yttrium-90. The glass microspheres are delivered into the liver tumor through a catheter placed into the hepatic artery and subsequently get lodged in the microvasculature surrounding the tumor. Their size causes them to be trapped in the tumor capillary bed where they deliver very high irradiation doses to the tumors while sparing the surrounding liver parenchyma. Once inside the liver neither the medical personnel nor the family members can be irradiated. The microspheres are not biodegradable; they have a half-life of 64.1 hours (2.67 days) and emit pure beta-radiation with a mean tissue penetration of 2.5 mm and a maximum of 1 cm. The therapy is given as an outpatient interventional radiology procedure, and lasts from 30 to 40 minutes (Carr 2004, Ibrahim 2008, Bult 2009).

Another 90Y product available for clinical use is SIR-Spheres® (SIRTeX Medical Ltd., Sydney, Australia). These consist of biodegradable resin-based microspheres containing Yttrium-90 (90Y) and have an average size of 35 µ in diameter. Upon administration of the spheres in vivo, they are permanently implanted. Similar to TheraSphere, SIR-Spheres emit pure β-radiation with a half life of 2.67 days. Both types of microspheres have shown to preferentially localize to abnormally vascularized liver tumors, where they exert intense localized radiation, while limiting radiation exposure to the uninvolved hepatic parenchyma (Ibrahim 2008, Bult 2009).

Radioembolization is not without complications; it may lead to post-radioembolization syndrome which includes fatigue, nausea, vomiting, anorexia, fever, abdominal pain and cachexia. More serious adverse events include radiation induced liver toxicity, vascular injury when introducing the catheter, radiation pneumonitis from microspheres shunting around the liver and into the lungs, and gastrointestinal tract ulceration. Absolute contraindications for the use of 90Y microspheres include pretreatment with 99mTc macroaggregated albumin scan demonstrating significant hepatopulmonary shunts, and inability to prevent deposition of the microspheres to the gastrointestinal tract with modern catheter techniques (Ibrahim 2008, Riaz 2009).

TheraSphere (MDS Nordion, Ottawa, Canada) was approved by the FDA in 1999 under the Humanitarian Device Exemption Guidelines for the treatment of unresectable hepatocellular carcinoma.

SIR-Spheres® (SIRTeX Medical Ltd., Sydney, Australia) received FDA premarket approved in 2002 for the treatment of colorectal cancer metastasized in the liver with adjuvant floxuridine administered via the hepatic artery.

Medical Technology Assessment Committee (MTAC)

Therasphere in the Treatment of Unresectable Hepatocellular Carcinoma

04/10/2002: MTAC REVIEW

Evidence Conclusion: There is insufficient published evidence to determine the effectiveness of Therasphere for the treatment of unresectable hepatocellular carcinoma (HCC). Many of the empirical studies were done with animals. Only small case series (four studies, each with $n < 20$) with human populations were available.

Articles: The search yielded 24 articles, many of which dealt with technical aspects of the procedure. There were no randomized controlled trials or meta-analyses. There were several case series, all with small sample sizes ($n < 20$). None of the empirical articles were considered of sufficient quality to be evaluated.

The use of Therasphere in the treatment of unresectable hepatocellular carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

06/05/2006: MTAC REVIEW

Therasphere in the Treatment of Unresectable Hepatocellular Carcinoma

Evidence Conclusion: The empirical studies published before the previous MTAC review of the TheraSphere in 2002, were very small case series with less than 20 patients. For this review the literature search identified a small comparative non-controlled trial and few additional relatively larger series, many of which were published by the same group of investigators. In the comparative trial 28 patients received either TheraSphere therapy or Cisplatin. The patients were not randomized to the treatment groups, the study was unblinded, and the authors did not discuss how the patients were selected for each of the two therapies. The trial was not powered to detect significant differences between the study groups, had a short follow-up duration, and the 6-months data were available for only 50% of the patients. Its results indicate that patients treated with 90-Yttrium microspheres reported significantly higher scores on physical, functional, and social well-being vs. those treated with cisplatin. There was no significant difference in survival between the two groups according to Kaplan Meier curves.

The other case series reviewed was relatively small, had no control or comparison group, included a heterogeneous group of patients with different comorbidities, and the therapy received was not uniform for all patients. Its results indicate that 47% of the patients and 51% of the lesions had a greater than 50% reduction in size. The median survival was 20.8 months among non-high risk patients, and 11.1 month for those at high risk. In conclusion, the evidence published after the previous review is still insufficient to determine the effectiveness and safety of TheraSphere for the treatment of unresectable hepatocellular carcinoma (HCC).

Articles: The search yielded 27 articles, many of which dealt with technical aspects of the procedure. No randomized controlled trials or meta-analyses were identified. There was a small non-randomized cohort study that compared TheraSphere treatment with Cisplatin, as well as several small prospective and retrospective case series with sizes ranging from 15 to less than 90 patients. The study with a comparison group, as well as a prospective case series with no patient overlap with the comparative trial, and clinically important outcomes, were selected for critical appraisal. Steel J, Baum A, and Carr B. Quality of life in patients diagnosed with primary hepatocellular carcinoma: hepatic arterial infusion of cisplatin versus 90-Yttrium microspheres (TheraSphere)® *Psycho-Oncology* 2004;13;73-79. See [Evidence Table](#). Salem R, Lewandowski RJ, Atassi B, et al. Treatment of unresectable hepatocellular carcinoma with use of 90Y microspheres (TheraSphere): safety, tumor response, and survival *J Vasc Interv Radiol*. 2005;16:1627-1639 See [Evidence Table](#).

The use of Therasphere in the treatment of unresectable hepatocellular carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

07/06/2010: MTAC REVIEW

Therasphere in the Treatment of Unresectable Hepatocellular Carcinoma

Evidence Conclusion: There is insufficient published evidence to determine efficacy and toxicity of TheraSphere in the treatment of unresectable liver cancer when given alone or in combination with systemic or regional chemotherapy. There is insufficient published evidence to determine the efficacy and toxicity of Sir-Spheres in the treatment of liver metastases from colorectal cancer when given alone or in combination with systemic or regional chemotherapy.

Larger RCTs are randomizing patients to first line chemotherapy with or without ⁹⁰Y microsphere radioembolization are currently underway and may provide more evidence on the benefits of adding radioembolization therapy to first line chemotherapy.

Articles: The literature search yielded around 200 articles; many were review articles or publications that dealt with technical aspects of the procedure. There was one meta-analysis of studies (Vente 2009) on patients with primary or secondary liver malignancies treated with ⁹⁰Y glass or resin microspheres, and another Cochrane review (Townsend 2009) of RCTs on radioembolization for liver metastases from colorectal cancer. Vente meta-analysis pooled the data from case series but presented a summary result for each of the RCTs separately. The Cochrane review also presented the results of the same 2 trials separately. The search also identified two phase-2 randomized trials conducted by the same research group in Australia that compared Sir-Spheres plus

chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary colorectal cancer. The first published RCT (Gray 2001) compared Sir-Spheres with regional chemotherapy vs. regional chemotherapy alone in 74 patients, and the second (Van Hazel 2004) compared Sir-Spheres combined with systemic chemotherapy vs. systemic chemotherapy alone in 21 patients. The two trials were included in both meta-analyses. The search did not reveal any randomized controlled trials on TheraSphere.

The majority of other published studies were prospective or retrospective case series including patients with HCC or hepatic metastatic colorectal cancer (mCRC). A small number of case series reported on patient with liver metastases secondary to neuroendocrine or breast cancers. The following meta-analysis and the larger RCT were selected for critical appraisal: Vente MAD, Wondergem M, van den Bosch MAAJ, et al. Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis. *Europ Radiol* 2009;19:951-959. See [Evidence Table](#). Gray B, Van Hazel G, Burton M, et al. Randomized trial of SIR-Spheres® plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. *Ann Oncol* 2001;12:1711-1720. See [Evidence Table](#).

The use of Therasphere in the treatment of unresectable hepatocellular carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

The use of SIRsphere in the treatment of unresectable hepatocellular carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

02/13/2012: MTAC REVIEW

Therasphere in the Treatment of Unresectable Hepatocellular Carcinoma

Evidence Conclusion: The best evidence published to date, after the last 2010 MTAC review, consisted of one small phase III randomized controlled trial on radioembolization using SIR-Spheres in patients with liver metastatic colorectal cancer, and two comparative efficacy analyses conducted to compare of the safety and efficacy of yttrium 90 (⁹⁰Y) radioembolization in patients with unresectable hepatocellular carcinoma. In all published series and studies the radioembolization were performed by highly trained professionals in specialized centers.

TheraSphere: Salem and colleagues (2011) recently published a comparative analysis of the outcomes of two relatively large cohorts of patients (total N= 463) with unresectable HCC who were treated in a single center with either transarterial chemotherapy (TACE) or radioembolization using ⁹⁰Y microspheres (TheraSphere). The study was not a randomized trial, nor designed to determine equivalence between the two therapies. The authors indicated that treatment response and survival were calculated from first treatment, and follow-up duration was longer for TACE. They also explained that patients undergoing TACE were younger and more likely to receive it as a bridge to transplantation. The overall results of the analysis showed longer time to progression with radioembolization using ⁹⁰Y microspheres. There was no significant difference between the two therapies in time to response or survival. The study was not designed as an equivalence study, and lack of significant difference does not indicate that the two therapies are equivalent. An analysis performed by the authors showed that a randomized trial with 1000 patients would be required to establish equivalence in survival. There were no statistically significant differences in major toxicities between the two therapies. Patients treated with chemoembolization were more likely to experience abdominal pain and higher hepatic transaminase elevation. Lance et al's (2011) comparative analysis only included 73 patients treated with either chemoembolization or radioembolization with glass or resin ⁹⁰Y microspheres. The results did not show survival advantage with radioembolization but found higher rates of hospitalization in the chemoembolization group due to the postembolization syndrome.

Sir-Sphere: Hendlisch and colleagues' (2010), RCT compared the efficacy and safety of intravenous fluorouracil (FU) given alone or with of intra-arterial ⁹⁰Y-resin microspheres (SirSpheres) in 46 patients with liver-limited metastatic colorectal cancer (mCRC) who failed other chemotherapies. The trial was randomized, controlled, and multicenter. However, it was conducted among a highly selected group of patients; it was not blinded and allowed patients in the FU alone group who had documented progression to cross-over to the radioembolization plus FU group at the investigators' discretion. As a result, 70% of those in the FU alone group also received radioembolization, which is significant source of bias, but the authors performed an intention to treat analysis (ITT), ie. analyzed the patients in the groups they were randomized to. The overall results of the study indicate that radioembolization with yttrium 90 resin microspheres in addition to intravenous fluorouracil significantly improved the response to therapy and time to liver progression compared to FU alone among the selected patients included in the trial. Radioembolization was not associated with more toxicity than chemoembolization. The effect on survival was not statistically significant, which could be attributed to the small sample size, especially with the high cross-over that could have improved the outcomes in the FU only group.

Articles: The literature search for studies published after the last review revealed one Phase III trial that compared IV fluorouracil infusion alone or with radioembolization with SIR-Spheres for a specific indication, two

retrospective comparative analyses that compared radioembolization with TheraSphere vs. transcatheter chemoembolization, and a number of retrospective and prospective single center case series with different population sizes. The largest case series and the larger comparative analyses were published by the same group of authors (Salem et al. 2010, 2011) and had a potential population overlap. The comparative analysis, as well as the Phase III trial, were selected for critical appraisal. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology*. 2011;140:497-507. See [Evidence Table](#). Hendlitz A, den Eynde M V, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *J Clin Oncol*. 2010;28:3687-3694. See [Evidence Table](#).

The use of Therasphere in the treatment of unresectable hepatocellular carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

The use of SIRsphere in the treatment of unresectable hepatocellular carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
C2616	Brachytherapy source, nonstranded, yttrium-90, per source
Q3001	Radioelements for brachytherapy, any type, each
S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres *S codes not covered by Medicare
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
75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
With diagnosis codes	
C22.0	Liver cell carcinoma
C22.1	Intrahepatic bile duct carcinoma
C22.3	Angiosarcoma of liver
C22.4	Other sarcomas of liver
C22.7	Other specified carcinomas of liver
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the [Pre-authorization Code Check](#).**

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Date Created	Date Reviewed	Date Last Revised
04/10/2002	07/16/2010 ^{MDCRPC} , 05/03/2011 ^{MDCRPC} , 03/06/2012 ^{MDCRPC} , 04/03/2012 ^{MDCRPC} , 02/05/2013 ^{MDCRPC} , 12/03/2013 ^{MPC} , 10/07/2014 ^{MPC} , 08/04/2015 ^{MPC} , 06/07/2016 ^{MPC} , 04/04/2017 ^{MPC} , 02/06/2018 ^{MPC} , 01/08/2019 ^{MPC} , 01/07/2020 ^{MPC} , 01/05/2021 ^{MPC} , 01/04/2022 ^{MPC} , 01/10/2023 ^{MPC} , 05/07/2024 ^{MPC} , 04/01/2025 ^{MPC}	11/13/2023

^{MDCRPC} Medical Director Clinical Review and Policy Committee

^{MPC} Medical Policy Committee

Revision History	Description
02/28/2018	Added Noridian coverage article
02/16/2022	Updated applicable codes
11/13/2023	Updated Coverage Article Link (A52950), which has been retired.