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Subject: Selective Internal Radiation Therapy

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Selective internal radiation therapy (SIRT) also referred to as intrahepatic radioembolization is the intra-arterial delivery of small beads (microspheres) impregnated with yttrium-90 via the hepatic artery. SIRT is performed by threading a catheter from the groin into the hepatic artery. Radioactive isotopes containing yttrium-90 are delivered to the liver tumor through a catheter placed into the hepatic artery emitting localized radiation therapy. This therapy is proposed as a treatment for both primary and metastatic liver tumors.

The Food and Drug Administration (FDA) has approved two commercial forms of 90Y microspheres; TheraSphere® (MDS Nordion) and SIR-Spheres® (Sirtex Medical). TheraSphere® are glass microspheres, indicated for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters. TheraSphere® was approved by the FDA under Humanitarian Device Exemption. SIR-Spheres® are resin microspheres, indicated for the treatment of unresectable metastatic liver tumors from primary colorectal with adjuvant intra-hepatic artery chemotherapy (IHAC) of Floxuridine (FUDR).

Summary and Analysis of Evidence: Gabr et al (2021) reported long-term outcomes of liver transplantation (LT) for patients with hepatocellular carcinoma (HCC) who were bridged/downstaged by Y90. Patients undergoing LT following Y90 between 2004 and 2018 were included, with staging by United Network for Organ Sharing (UNOS) tumor-node-metastasis criteria at baseline pre-Y90 and pre-LT. Post-Y90 toxicities were recorded. Histopathological data of HCC at explant were recorded. Long-term outcomes, including overall survival (OS), recurrence-free survival (RFS), disease-specific mortality (DSM), and time-to-recurrence, were reported. Time-to-endpoint analyses were estimated using Kaplan-

Meier. Univariate and multivariate analyses were performed using a log-rank test and Cox proportional-hazards model, respectively. During the 15-year period, 207 patients underwent LT after Y90. OS from LT was 12.5 years, with a median time to LT of 7.5 months [interquartile range, 4.4-10.3]. A total of 169 patients were bridged, whereas 38 were downstaged to LT. Respectively, 94 (45%), 60 (29%), and 53 (26%) patients showed complete, extensive, and partial tumor necrosis on histopathology. Three-year, 5-year, and 10-year OS rates were 84%, 77%, and 60%, respectively. Twenty-four patients developed recurrence, with a median RFS of 120 (95% confidence interval, 69-150) months. DSM at 3, 5, and 10 years was 6%, 11%, and 16%, respectively. There were no differences in OS/RFS for patients who were bridged or downstaged. RFS was higher in patients with complete/extensive versus partial tumor necrosis ($P < 0.0001$). For patients with UNOS T2 treated during the study period, 5.2% dropped out because of disease progression. The authors conclude that Y90 is an effective treatment for HCC in the setting of bridging/downstaging to LT. Patients who achieved extensive or complete necrosis had better RFS, supporting the practice of neoadjuvant treatment before LT.

Liu et al (2022) conducted a meta-analysis to assess the efficacy of yttrium-90 selective internal radiation therapy (SIRT) in treating patients with breast cancer with hepatic metastasis. A total of 24 studies from 14 institutions were included in the present meta-analysis. On the basis of the data from 412 patients, post-embolization MST was 9.8 [95% confidence interval (CI): 9.0-11.6] months. Patients with additional extrahepatic metastasis had a poorer survival rate compared with those with localized hepatic metastasis only (MST: 5.3 vs. 15 months, $p < 0.0001$). Patients with <25% liver tumor burden exhibited more promising survival than those with >25% (MST: 10.5 vs. 6.8 months, $p < 0.0139$). On the basis of RECIST, mRECIST, and PERCIST criteria, tumor response rate was 36% (95% CI: 26%-47%), 49% (95% CI: 34%-65%), and 47% (95% CI: 17%-78%), respectively, whereas tumor control rate was 85% (95% CI: 76%-93%), 73% (95% CI: 59%-85%), and 97% (95% CI: 91%-100%), respectively. The authors concluded that SIRT is feasible and effective in treating patients with breast cancer with liver metastasis. Patients with lower hepatic tumor burden and without extrahepatic metastasis demonstrated more survival benefit. Future randomized controlled trials are warranted.

Gonsalves et al (2011) assessed the safety and efficacy of radioembolization in the management of hepatic metastasis of uveal melanoma after failure of immunoembolization or chemoembolization. From January 2007 through April 2009, 32 patients underwent radioembolization therapy for hepatic metastasis of uveal melanoma. Pretreatment tumor burdens were divided into three categories: less than 25% (n = 25), 25-50% (n = 5), and greater than 50% (n = 2). Toxicity, extrahepatic disease, and hepatic tumor response were assessed 1 month and then every 3 months after treatment. Best radiographic response of hepatic metastasis was determined with the Response Evaluation Criteria in Solid Tumors criteria. Overall survival and progression-free survival of hepatic metastasis were estimated by Kaplan-Meier analysis. Differences in survival between subgroups were evaluated by log-rank test in univariate analysis. The clinical follow-up period ranged from 1.0 to 29.0 months (median, 10.0 months). The median overall survival was 10.0 months, and the progression-free survival of hepatic metastasis, 4.7 months. Twenty-two patients died 1.0-29.0 months (median, 5.8 months) after treatment owing to progression of liver disease (n = 13), extrahepatic disease (n = 4), or both (n = 5). Patients who had a pretreatment tumor burden less than 25% had longer median overall survival (10.5 vs 3.9 months, $p = 0.0003$) and progression-free survival (6.4 vs 3.0 months, $p = 0.03$) than patients who had a pretreatment tumor burden of 25% or greater. Patients who had a complete response (n = 1), partial response (n = 1), or stable disease (n = 18) had longer median overall survival (14.7 vs 4.9 months, $p = 0.0006$) and progression-free survival of hepatic metastasis (7.9 vs 3.1 months, $p < 0.0001$) than patients with tumor progression (n = 12). Self-limiting grade 1-2 systemic toxicity included tiredness (n = 9), indigestion (n = 2), and abdominal discomfort (n = 5). Grade 3-4 hepatic toxicity was attributed to tumor progression. The authors concluded that radioembolization is safe and effective salvage therapy for limited metastasis of uveal melanoma.

Devicie et al (2014) evaluate the efficacy of (90)Y resin radioembolization is an emerging treatment in patients with liver-dominant metastatic neuroendocrine tumors (mNETs). One hundred fifty-six studies were screened; 12 were selected, totaling 435 procedures for response assessment. Funnel plots showed no evidence of publication bias (P = 0.841). Critical appraisal revealed a median of 75% of desired criteria included in selected studies. Very high between-study heterogeneity ruled out a fixed-effects model. The random-effects weighted average objective response rate (complete and partial responses, CR and PR, respectively) was 50% (95% confidence interval, 38%-62%), and weighted average disease control rate (CR, PR, and stable disease) was 86% (95% confidence interval, 78%-92%). The percentage of patients with pancreatic mNET was marginally associated with poorer response (P = 0.030), accounting for approximately 23% of the heterogeneity among studies. The percentage of CR and PR correlated with median survival (R = 0.85; P = 0.008). The authors concluded that meta-analysis confirms radioembolization to be an effective treatment option for patients with hepatic mNET. The pooled data demonstrated a high response rate and improved survival for patients responding to therapy.

POSITION STATEMENT:

Selective internal radiation therapy (SIRT) with an FDA approved microsphere **meets the definition of medical necessity** for the following:

- Unresectable metastatic liver tumors from primary colorectal cancer (CRC); **OR**
- Unresectable primary hepatocellular carcinoma (HCC); **OR**
- In primary hepatocellular carcinoma as a bridge to liver transplantation; **OR**
- To treat hepatic metastases from neuroendocrine tumors (carcinoid and noncarcinoid) with diffuse and symptomatic disease when systemic therapy (e.g., chemotherapy) has failed to control symptoms**; OR**
- To treat primary intrahepatic cholangiocarcinoma in members with unresectable tumors**; OR**
- To treat unresectable hepatic metastases from liver predominant melanoma (ocular or cutaneous) that is both progressive and diffuse, in members who are refractory to chemotherapy or are not candidates for chemotherapy or other systemic therapies**; OR**
- To treat unresectable hepatic metastases from liver predominant breast cancer that is both progressive and diffuse, in members who are refractory to chemotherapy or are not candidates for chemotherapy or other systemic therapies.

Selective internal radiation therapy is considered **experimental or investigational** for all other indications, due to insufficient evidence to support conclusions regarding the effect of selective internal radiation therapy on health outcomes.

BILLING/CODING INFORMATION:

HCPCS Code:

S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres

ICD-10 Diagnosis Codes That Support Medical Necessity:

C18.0 – C18.9	Malignant neoplasm of colon
C22.0	Liver cell carcinoma

C22.2	Hepatoblastoma
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
C7B.02	Secondary carcinoid tumors of liver
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct

LOINC Codes:

The following information may be required documentation to support medical necessity: physician history and physical, physician progress notes, plan of treatment and reason for selective internal radiation therapy.

Documentation Table	LOINC Codes	LOINC Time Frame Modifier Code	LOINC Time Frame Modifier Codes Narrative
Physician history and physical	28626-0	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim
Attending physician progress note	18741-9	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim
Plan of treatment	18776-5	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

DEFINITIONS:

Humanitarian Device Exemption (HDE) a Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. An approved HDE authorizes marketing of the HUD. An HUD may only be used in facilities that have established a local institutional review board (IRB) to

supervise clinical testing of the HUD and after the IRB has approved the use of the device to treat or diagnose the specific disease (FDA , 2010).

RELATED GUIDELINES:

Brachytherapy-Oncologic Applications, 04-777260-20

OTHER:

Other names used to report selective internal radiation therapy:

Intra-arterial brachytherapy
Radioembolization (RE)
Selective Internal Radiation (SIRT)
Transarterial embolization (TARE)

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 08/22/24.

GUIDELINE UPDATE INFORMATION:

11/15/10	New Medical Coverage Guideline.

10/01/11	Revision; formatting changes.
12/15/11	Updated position statement; add “In primary hepatocellular carcinoma as a bridge to liver transplantation”, “To treat hepatic metastases from neuroendocrine tumors (carcinoid and noncarcinoid) with diffuse and symptomatic disease when systemic therapy (e.g., chemotherapy) has failed to control symptoms”. Revised experimental or investigational statement; remove “including but not limited to when used as a bridge to transplantation”. Added ICD-9 diagnosis code 209.72 and ICD-10 diagnosis code C7b.02 and C78.7. Updated references.
09/15/12	Scheduled review; position statements maintained and references updated.
05/15/14	Scheduled review; position statements maintained and references updated.
09/15/15	Annual review; added position statement for primary intrahepatic cholangiocarcinoma, unresectable hepatic metastases from liver predominant melanoma (ocular or cutaneous) and unresectable hepatic metastases from liver predominant breast cancer. Added ICD-9 code 197.7. Updated references.
10/01/15	Revision; updated ICD9 and ICD10 coding section.
11/01/15	Revision: ICD-9 Codes deleted.
11/15/16	Revision; no change to position statement. Updated references.
11/15/17	Review; no change to position statement. Updated references.
08/15/19	Review; no change to position statement. Updated references.
09/15/21	Review; no change to position statement. Updated references.
09/15/23	Review; no change to position statement. Updated references.
09/15/24	Review; no change to position statement. Updated references.