

Transarterial Radioembolization (TARE)/ Selective Internal Radiation Therapy (SIRT) for the Treatment of Malignant Cancers of the Liver

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[Instructions for Use](#)

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Related Medical Management Guideline
None

Coverage Rationale

Transarterial Radioembolization (TARE)/selective internal radiation therapy (SIRT) using yttrium-90 microspheres is proven and medically necessary for the following indications in individuals with an [Eastern Cooperative Oncology Group \(ECOG\) Performance Status](#) of 0, 1, or 2:

- Primary hepatocellular carcinoma (HCC) that is unresectable and limited to the liver
- Primary hepatocellular carcinoma as a bridge to liver transplantation
- Unresectable liver metastases from neuroendocrine tumors when systemic therapy has failed to control symptoms
- Unresectable liver metastases from colorectal carcinoma in individuals with [Limited Extra-Hepatic Disease](#) who are [Refractory](#) to or relapsed following systemic chemotherapy
- Unresectable intrahepatic cholangiocarcinoma

Transarterial Radioembolization (TARE)/selective internal radiation therapy (SIRT) using yttrium-90 microspheres is unproven and not medically necessary for all other indications due to insufficient evidence of efficacy.

Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the protocol titled [Medical Records Documentation Used for Reviews](#).

Definitions

Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status: A standard criteria for measuring how the disease impacts a person's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (e.g., walking, working, etc.).

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Limited Extra-Hepatic Disease: Metastases limited to lung with < 5 nodules with ≤ 1 cm diameter or a single nodule ≤ 1.7 cm diameter and/or a single area of lymph node involvement < 2 cm diameter. (Wasan., et al 2017)

Refractory: Cancer that does not respond to treatment. The cancer may be resistant at the beginning of treatment, or it may become resistant during treatment. Also called resistant cancer. (NCI, 2021)

Transarterial Radioembolization (TARE): A potent intra-arterial therapy that uses radioactive microspheres impregnated with yttrium 90. Also called radioembolization and selective internal radiation therapy. (Choi, 2022)

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this guideline does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	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
75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
79445	Radiopharmaceutical therapy, by intra-arterial particulate administration

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

Description of Services

The preferred treatment for liver tumors is surgical excision. However, many liver tumors are inoperable because they are located too close to blood vessels or other critical structures or are too advanced, thus making surgery potentially unsafe and inadvisable. For inoperable liver tumors, physicians may recommend palliative treatments to reduce pain and improve quality of life.

Transarterial Radioembolization (TARE) is a form of brachytherapy also referred to as Selective Internal Radiation Therapy (SIRT) in which yttrium-90 isotopes are delivered to a tumor directly through the hepatic arteries to deliver high radiation doses with relative sparing of adjacent normal liver. (King et al., 2020)

Liver Metastases From Colorectal Cancer

In 2022, Emmons and associates explored the survival and toxicities after transarterial radioembolization (TARE) for metastatic colorectal cancer (mCRC) through a prospective, multicenter, observational registry. The study participants were those who received TARE using resin microspheres for treating liver-dominant mCRC as a first, second, or third line of therapy or beyond from 42 centers. The outcomes measured were overall survival (OS), progression-free survival (PFS), and toxicity outcomes through the Kaplan-Meier analysis. Enrolled were 498 participants, who received TARE being utilized as first-line therapy for 74 of the 498 participants, 180 using the second line, and 188 participants utilizing third-line treatment or beyond. The study results demonstrated that the median OS of the entire cohort was 15.0 months (95% CI: 13.3, 16.9). The median OS by line of therapy was 13.9 months for first-line treatment, 17.4 months for second-line therapy, and 12.5 months for third-line therapy ($x^2 = 9.7$; $P = .002$). Whole-group PFS was 7.4 months (95% CI: 6.4, 9.5). The median PFS by the line of therapy was 7.9 months for first line therapy, 10.0 months for second-line treatment, and 5.9 months for third-line therapy ($x^2 = 8.3$; $P = .004$). TARE-attributable grade 3 or 4 hepatic toxicities were 8.4% for bilirubin (29 of 347 participants) and 3.7% for albumin (13 of 347). Grade 3 and higher toxicities were more significant with third-line therapy for bilirubin ($P = .01$) and albumin ($P = .008$). The authors concluded that the median OS after TARE with Y-90 microspheres for liver-dominant mCRC was 15 months. The longest OS achieved was part of second-line therapy; grade 3 or greater hepatic function toxicity rates were less than 10%. The study is limited due to the lack of randomization and open-label treatment, the screening failures were not tracked, there was less than 100% data entry due to the observational structure of the study, and some of the cohorts received previous hepatic interventions.

A ECRI Clinical Evidence Assessment report on TARE for treating metastases to the liver focused on TARE's safety and effectiveness for treating unresectable metastatic liver tumors and how they compare with those of other treatment modalities. The report included 3 systematic reviews (SR) and 3 meta-analyses that pooled evidence from randomized controlled trials (RCT), melanoma (1 SR), breast cancer (1 SR), and neuroendocrine tumors (2 SRs). For individuals with chemorefractory colorectal cancer (CRC) metastasis who received TARE as third-line therapy, TARE (⁹⁰Y) improved OS compared with best supportive care. For individuals with CRC metastasis, adding TARE to first-line treatment did not improve survival. OS was higher with transarterial chemoembolization (TACE) than with TARE for individuals with neuroendocrine tumor metastasis, based on evidence from 1 SR. The SR included only 6 retrospective cohort studies at high risk of selection bias. For individuals with melanoma and breast cancer metastasis there was a lack of comparative outcomes for OS prevented analysis of TARE's safety and effectiveness. One guideline recommended TARE with chemotherapy in all second-line or later treatment settings for CRC metastasis, and 2 guidelines stated TARE should be considered as a treatment option as a second-line or later treatment for CRC metastasis. (ECRI, 2021a)

Mulcahy et al. (2021) conducted a randomized, open-label, international, multicenter phase 3 trial regarding radioembolization (RE) with chemotherapy for colorectal liver metastases. The study evaluates the impact of transarterial Yttrium-90 RE in combination with second line systemic chemotherapy for colorectal liver metastases (CLM). Between May 2012 and August 2020 four hundred twenty-eight participants from 95 centers in North America, Asia, and Europe were randomly assigned either to chemotherapy with or without TARE. Out of the 215 individuals assigned to the TARE group; 187 received TARE, 16 received only chemotherapy, and 12 with no treatment. The control group consisted of 213 participants; 191 received second line chemotherapy and 22 received no therapy. The median time to TARE was 25 days from the time of assignment, with median overall follow up at 36 and 42.3 months. The median (OS) was 14.0 and 14.4 months for the TARE and chemotherapy groups, respectively. The objective response rate (ORR) was 34% and 21.1% for TARE and chemotherapy groups respectively. Disease control rate (DCR) were 79.5% and 72.8% for the TARE and chemotherapy groups respectively. A benefit in PFS of TARE was seen for those with no detectable extrahepatic lesions, and those with extrahepatic benign lesions. The study concludes adding TARE for systemic therapy for second line CLM leads to longer PFS and hPFS.

A systematic review was conducted including 4 randomized trials and 8 clinical cohort series (Baltatzis & Siriwardena 2019, included in the 2021a ECRI report). The study population was comprised of 120 individuals undergoing liver resection after chemotherapy and selective internal radiation therapy (SIRT). The conversion rate to hepatectomy in previously unresectable participants was 13.6%. The interval from SIRT to surgery ranged from 39 days to 9 months. The longest survivor was reported at 96 months after hepatectomy. There were 4 (3.3%) deaths after hepatectomy for individuals treated by chemotherapy and SIRT. The authors concluded that the study showed that 13.6% of individuals with initially inoperable disease underwent resection with low procedure-related mortality. (Authors Cosimelli et al. 2010, Hendlisz et al. 2010, and Maleux et al. 2016, which were previously discussed in this policy, are included in this review.)

Jakobs et al. (2017) performed a study with the aim of providing further evidence for the efficacy/safety of RE using yttrium-90 resin microspheres for unresectable chemorefractory liver metastases from colorectal cancer (mCRC). They followed 104 consecutively individuals treated with RE until death. OS was calculated from the day of the first RE procedure. Response was defined by changes in tumor volume as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 and/or a ≥ 30 % reduction in serum carcinoembryonic antigen (CEA) at 3 months. Survival was 23 months for individuals who had a complete response to prior chemotherapy and 13 months for individuals with a partial response or stable disease. The authors concluded that RE can achieve meaningful survival for individuals with chemorefractory liver-predominant mCRC and is generally well tolerated.

Kalva et al. (2017) conducted a retrospective study to report safety and survival outcomes of Yttrium-90 (Y-90) radioembolization (RE) when used as salvage therapy for chemotherapy-resistant liver mCRC. Forty-five participants with hepatic mCRC underwent Y-90 RE after failure of systemic chemotherapy. Y-90 RE was technically successful in all. Twenty-three individuals had no toxicities, 6 people had grade 3 toxicities, and no one had grade 4 toxicity. Two participants died within 30 days of treatment from renal failure unrelated to the procedure. One individual had partial response, 34 had stable disease, and 6 had progressive disease. PET response was seen in 46% of those with 2 individuals (4%) demonstrating complete and 22 (42%) demonstrating partial metabolic response. The median survival was 186 days. Those who had response on PET following Y-90 therapy had a median OS of 317 days whereas participants with no response on PET had a median OS of 163 days. The authors concluded that Y-90 RE as a salvage therapy for chemotherapy-resistant hepatic metastases from colon cancer was safe and resulted in disease stability.

The FOXFIRE, SIRFLOX, and FOXFIRE-global randomized studies evaluated the efficacy of combining first-line chemotherapy with SIRT using yttrium-90 resin microspheres for individuals with mCRC with liver metastases (Wasan et al., 2017, included in the 2021a ECRI report). The studies were designed for combined analysis of OS. Chemotherapy-naïve individuals with mCRC with liver metastases not suitable for curative resection or ablation were randomly assigned (1:1) to either oxaliplatin-based chemotherapy FOLFOX (N = 549) or FOLFOX plus single treatment SIRT concurrent with cycle 1 or 2 of chemotherapy (N = 554). Median follow-up was 43.3 months. There were 411 deaths in the FOLFOX alone group and 433 deaths in the FOLFOX plus SIRT group. The median survival time in the FOLFOX plus SIRT group was 22.6 months compared with 23.3 months in the FOLFOX alone group. Serious adverse events (AEs) of any grade occurred in 244 individuals receiving FOLFOX alone and 274 receiving FOLFOX plus SIRT. The authors concluded that the OS was not significantly different between groups (HR, 1.04; 95% CI 0.90 to 1.19). They recommended further studies to study the role of SIRT in carefully selected populations and as a consolidation therapy after chemotherapy.

The mCRC liver metastases outcomes after radioembolization (MORE) study was a retrospective analysis of 606 individuals with unresectable CLM treated with RE using 90Y-labeled resin microspheres. The first analysis of this study was completed with a last follow-up of 77.7 months. The authors, Kennedy et al. (2017) provide an updated survival analysis, with the last follow-up of 125 months. All those with a diagnosis of mCRC who had received at least 1 RE treatment and 1 follow-up visit were included in the analysis. Data were collected at baseline, on the day of the first 90Y-RE treatment (day 0), and at all subsequent visits or until death. Dates of death were obtained for 574 out of a total of 606 individuals, and OS data analyzed. Updated median OS was 10.0 months at a median follow-up of 9.5 months versus the originally reported median OS of 9.6 months at a follow-up of 8.6 months in the first MORE analysis. Individuals received a median (range) of 2 lines of chemotherapy. Baseline characteristics and factors significantly associated with survival are consistent with those reported in the first safety analysis of the MORE study. These factors include poor Eastern Cooperative Oncology Group (ECOG) performance status, markers of advanced disease such as increased extent of tumor-to-target liver involvement, poor baseline liver function, pre-treatment anemia, lung shunt fraction, and number of lines of prior chemotherapy. The authors concluded that long-term follow-up confirms that 90Y-RE treatment offers favorable survival benefits for individuals with unresectable mCRC.

Van Hazel et al. (2016) evaluated SIRFLOX, a randomized, multicenter trial designed to assess the efficacy and safety of adding SIRT using yttrium-90 resin microspheres to standard fluorouracil, leucovorin, and oxaliplatin (FOLFOX)-based chemotherapy for individuals with previously untreated mCRC. Chemotherapy-naïve individuals with liver metastases were randomly assigned to receive either modified FOLFOX (mFOLFOX6; control) or mFOLFOX6 plus SIRT (SIRT) plus or minus bevacizumab. The primary end point was PFS at any site. Median PFS at any site was 10.2 v 10.7 months in control versus SIRT. Median PFS in the liver was 12.6 v 20.5 months in control versus SIRT. ORRs at any site were similar (68.1% v 76.4% in control v SIRT). ORR in the liver was improved with the addition of SIRT (68.8% v 78.7% in control v SIRT). Grade ≥ 3 AEs, including recognized SIRT-related effects, were reported in 73.4% and 85.4% of participants in control versus SIRT. The authors concluded that the addition of SIRT to FOLFOX-based first-line chemotherapy for individuals with liver-dominant or liver-only mCRC did not improve PFS at any site but significantly delayed disease progression in the liver.

Clinical Practice Guidelines

American Society of Clinical Oncology (ASCO)

In the 2023 ASCO guidelines for treating metastatic colorectal cancer (mCRC), the society gives the following recommendation: SIRT is not routinely recommended for individuals with mCRC and unilobar or bilobar metastases of the liver (Type: Evidence-based, harms outweigh benefits; Evidence quality: Low; Strength of recommendation: Weak). (Morris et al., 2023)

National Comprehensive Cancer Network (NCCN)

NCCN clinical practice guidelines for colon and rectal cancers state Yttrium-90 microsphere selective internal radiation are an option in highly selected individuals with chemotherapy-resistant/refractory disease and with predominant hepatic metastases. Additionally, when hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches using preoperative portal vein embolization, staged liver resection, or yttrium-90 RE can be considered. The use of arterial-directed therapies in highly selected individuals is a category 2A recommendation category of Evidence and Consensus based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. (NCCN, Colon, v4.2023; NCCN, Rectal, v6.2023)

National Institute for Health and Care Excellence (NICE)

NICE states that SIRT is a potentially beneficial treatment for individuals with non-resectable colorectal metastases in the liver. In people who cannot tolerate chemotherapy or have liver metastases that are refractory to chemotherapy, there is evidence of efficacy, but this is limited, particularly for important outcomes such as quality of life. In people who can have chemotherapy, evidence on OS and quality of life is inadequate in quality. This procedure should only be done by clinicians with specific training in SIRT. Further research should report details of patient selection, whether the primary colorectal tumor arose in the left or right side of the colon, extrahepatic disease, and tumor-to-liver volume. Outcomes should include survival and quality of life. (NICE, 2020)

Liver Metastases From Neuroendocrine Tumors

In an International, multicenter, retrospective study, Schaarschmidt and colleagues (2022) analyzed the use of Y-90 for individuals with neuroendocrine neoplasms (NEN) with hepatic metastases and the potential role of Y-90 in a multimodal treatment concept. Pre-Y-90 treatment, 297 angiographic evaluations for individuals with NEN took place and were analyzed. Outcomes measured were tumor response using RECIST 1.1, and survival data, with the OS between different groups being compared using the Kaplan-Meier curves and log-rank test. The study results showed that after 90Y RE, the DCR according to RECIST 1.1 was 83.5% after three months and 50.9% after 12 mo. OS in the entire population was 38.9 ±33.0 mo. High tumor grade ($P < 0.006$) and high tumor burden ($P = 0.001$) were associated with a significant decrease in OS. The presence of extrahepatic metastases ($P = 0.335$) and the type of metastatic vascularization pattern ($P = 0.460$) had no influence on OS. Those who received 90Y RE as second-line therapy had a slightly longer but not statistically significant OS than individuals who had 90Y RE in a salvage setting (44.8 vs. 30.6 months $P = 0.078$). Hepatic and global PFS after 90Y RE significantly decreased for pretreated individuals, compared to individuals with second-line therapy ($P = 0.011$ and $P = 0.010$, respectively). The authors concluded that Y-90 RE could be an essential alternative to peptide receptor radionuclide therapy and second-line treatment for individuals with progressive, liver-dominant disease pretreated with somatostatin analogs. Limitations of the study include its retrospective nature and differences in procedural technique. A prospective study would support the author's conclusions.

A retrospective, multi-institutional review of literature comparison of individuals with unresectable neuroendocrine liver metastases (NELM) undergoing TACE ($N = 197$) versus TARE with yttrium-90 (y-90) ($N = 51$) was conducted by Egger et al. (2020). The individuals were CT scanned every six months along with tumor marker and clinical examinations. Median follow-up for the entire cohort was 34 months. There were no differences in overall morbidity (TARE 13.7% vs TACE 22.6%, $p = 0.17$), grade III/IV complication (5.9% vs 9.2%, $p = 0.58$), or 90-day mortality. There was no difference in median OS (OS, 35.9 months vs 50.1 months, $p = 0.3$) or progression-free survival (PFS, 15.9 months vs 19.9 months, $p = 0.37$). The authors concluded both TACE and TARE with y-90 are safe and effective methods for unresectable NELM. TARE is associated with a shorter hospital stay, less liver toxicity and fewer complications.

A retrospective case series (Frilling 2019, included in the 2021a ECRI report) was performed consisting of individuals treated with SIR-Spheres. Results were included in a systematic review and meta-analysis of published results with glass or resin microspheres. ORR was defined as complete or partial response. DCR was defined as complete/partial response or stable disease. Twenty-four people were identified. ORR and DCR in the institutional series was 14/24 and 21/24 at 3 months. OS and progression-free survival at 3-years was 77.6% and 50.4%, respectively. There were no grade 3/4 toxicities post-procedure. A fixed-effects pooled estimate of ORR of 51% (95% CI: 47%-54%) was identified from meta-

analysis of 27 studies. The fixed-effects weighted average DCR was 88% (95% CI: 85%-90%, 27 studies). The authors concluded that the current data demonstrated evidence of the clinical effectiveness and safety of RE for NETLM. Prospective randomized studies to compare RE with other liver directed treatment modalities are needed.

Cramer et al. (2016) conducted a prospective longitudinal study to determine the effect of Y RE therapy on health-related quality of life (HRQOL) in individuals with neuroendocrine tumor liver metastases (NETLM). Baseline Short-Form 36 HRQOL scores were evaluated for significant change at 1, 3-, 6-, 12-, and 24-months following Y RE. OS times were calculated from first Y using the Kaplan-Meier method and analyzed using the log-rank test. Thirty participants were enrolled in the study. At 6- and 12-month follow-up, mean mental health and social functioning domain scores were significantly higher than baseline. The remainder of domains showed no significant difference at 6 or 12 months. Those with baseline Mental Component Summary (MCS) over 50.0 had significantly longer mean survival than those under 50.0 (37.50 vs. 18.19 months). People with baseline Physical Component Summary (PCS) over 50.0 had no significant difference in survival compared to those under 50.0 (38.09 vs. 30.69 months). The authors concluded that individuals with NETLM treated with Y have sustained HRQOL for up to 24 months following treatment. Temporary increases in mental health and social functioning at medium-term follow-up were observed.

A retrospective study was conducted by Barbier et al. (2016) to evaluate the safety and efficacy of SIRT for individuals with unresectable liver metastases from NETLMs. In 40 people, 54 evaluable SIRT procedures were performed: 33 to the right liver lobe, 13 to the left lobe, and 8 to both lobes. Late follow-up imaging (mean 20 months) was performed after 44 of the treatments. Tumor response was evaluated according to the modified RECIST on CT or MR images. Medical records were reviewed. Objective tumor response and DCRs were 54% and 94%, respectively, at the early follow-up examination (mean 3 months) and 34% and 57%, respectively at the late follow-up examination. Mean OS from the first SIRT was 34.8 months and survival rates at 1, 2, 3 and 5 years were 76%, 59%, 52% and 35% respectively. Adverse effects were generally mild and easily manageable, except in one individual who died from radiation-induced liver failure. The authors concluded that SIRT with (90)Y-labelled resin microspheres is a safe and effective treatment for progressive NETLM. The study is limited by its retrospective observations and small sample size.

Peker et al. (2015) conducted a retrospective study (N = 30) that evaluated the effectiveness and safety of RE with yttrium-90 (90Y) microspheres in cases with unresectable NETLMs between April 2008 and June 2013. The primary neuroendocrine tumor site was the pancreas in seven individuals (23%), small bowel in six (20%), large bowel/rectum in five (17%), bronchus in two (7%), and unknown in 10 individuals (33%) The mean follow-up was 23.0 ±19.4 months and the median OS was 39 months. Imaging follow-up at three-month intervals demonstrated partial response in 43%, complete remission in 3%, stable disease in 37%, and progressive disease in 17% of the individuals. Before treatment, estimated liver involvement was 37% in 11 individuals, 27% in eight, 30% in nine and 76%–100% in two individuals. The authors concluded that the study demonstrates the effectiveness and safety of RE for treating unresectable NETLMs.

A systematic review and meta-analysis of published literature was conducted by Devcic et al. (2014) to evaluate the efficacy of (90)Y resin RE for individuals with liver-dominant metastatic neuroendocrine tumors (mNETs). Of the 12 studies included, 6 were retrospective, 3 were prospective, 1 was prospectively collected but retrospectively reviewed, and 2 did not specify. The total number of procedures with response data was 435, in 414 individuals. The pooled data demonstrated a weighted ORR of 50%, DCR of 86%, and improved OS for individuals responding to therapy. The authors concluded that ⁹⁰Y resin RE is an effective treatment option for those with liver-dominant mNETs.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN clinical practice guidelines for neuroendocrine and adrenal tumors principles of liver-directed therapy for tumor metastases includes hepatic arterial embolization, including bland transarterial embolization, chemoembolization and RE. Additionally, that TARE is better tolerated than transarterial embolization (TAE)/TACE, but late radioembolization-induced chronic hepatotoxicity (RECHT) may occur in long-term survivors and is particularly a concern among individuals undergoing bilobar RE. The recommendation is for hepatic regional therapy (arterial embolization, chemoembolization, or RE for unresectable liver metastases (category 2B). Liver-directed therapies may be considered for individuals with progressive liver-predominant metastatic disease, to reduce tumor bulk and relieve symptoms of hormone hypersecretion; options include hepatic regional therapies including bland hepatic arterial embolization, RE, and chemoembolization. (NCCN, Neuroendocrine and Adrenal Tumors, V1.2023)

Primary Hepatocellular Carcinoma (HCC)

In 2022, Chow and associates investigated the comparison between radiofrequency ablation (RFA) to radiation therapy (RT) for TACE to Y90 for treating HCC through a systematic review and network meta-analysis of survival data. Using a

multivariate network meta-analysis, the authors extracted survival data from Kaplan-Meier survival curves and meta-analyzed. The exploration acquired a total of 5549 individuals comprised in 24 RCTs or propensity score matched (PSM) observational studies. The results demonstrated that while 1-year OS was more excellent for Y90 than TACE (RR 0.85, 95% CI: 0.72–0.99), all other 1-year OS comparisons across the four modalities produced comparable OS, and there were no differences across any modalities in 2-year and 3-year OS. TACE had a fair PFS advantage relative to RFA (RR 0.81, 95% CI: 0.68–0.95) and RT (RR 0.65, 95% CI: 0.51–0.83) at two years. The authors concluded that all modalities resulted in a similar OS. (Author Salem et al. 2016, previously discussed in this policy, is included in this review.)

Dhondt and colleagues (2022) conducted a single-center, prospective, randomized control trial (TRACE); yttrium-90 glass TARE was compared with doxorubicin-eluting beads TACE (DEB-TACE) for individuals with intermediate-stage HCC extended to Eastern Cooperative Oncology Group performance status 1 and early-stage HCC individuals who are not eligible for surgery or the ablation. The outcomes measured were the time to progression (TTP) (TTP overall; Kaplan-Meier analysis) in the intention-to-treat (ITT) and per protocol (PP). The participants were randomized to either the TARE arm (N = 38) or the DEB-TACE arm (N = 34). The results of the trial showed a median TTP overall was 17.1 months in the TARE arm and 9.5 months for the DEB-TACE arm (ITT: HR 0.36; 95% CI: 0.18, 0.70; P = 0.002) (PP: 32 and 34 participants respectively: HR 0.29; 0.14, 0.60; P < 0.001). Median OS was 30.2 months after TARE and 15.6 months after DEB-TACE (ITT: HR 0.48; 0.28, 0.82; P = 0.006). Severe AE grade \geq 3 [13 of 33 (39%) as opposed to 19 of 36 (53%) after TARE and DEB-TACE in that order, P = 0.47] and 30-day mortality [0 of 33 (0%) opposed to 3 of 36 (8%), P = 0.24] were comparable in the safety populations. In the interim, the HR for the primary endpoint TTP < 0.39 indicates the study's halt. The authors concluded that Yttrium-90 RE provides better tumor control and survival than the drug-eluting chemoembolization beads in specific individuals with early and intermediate HCC.

A ECRI report evaluated TARE in comparison to other treatment modalities through SRs and reported outcomes for individuals with unresectable primary liver tumors at different disease stages. The studies assessed consisted of 2 SR on TARE vs TACE, 1 SR regarding RT vs. TARE, 2 SRs and 1 RCT on sorafenib vs. TARE, studies on TARE alone included 1 SR and 1 SR on people with HCC, portal vein tumor thrombosis (PVT), and intrahepatic cholangiocarcinoma (ICC) and treatment with TARE. Findings include no difference in AEs between TARE and cTACE as well as TARE and DEB-TACE. In comparing TARE and Sorafenib for intermediate-locally advanced HCC the authors reported OS rate did not differ between treatment options. TARE vs. Sorafenib for individuals with Intermediate-locally advanced and advanced HCC serious AEs occurred more often in the sorafenib group vs. the TARE group. For those with advanced HCC the authors reported serious AEs occurred more often with SIRT and sorafenib than with sorafenib alone. When comparing TARE vs 3-dimensional conformal radiotherapy vs stereotactic body radiotherapy the stated 1-year survival rate did not vary statistically between people with HCC and PVT treated with TARE, 3-dimensional conformal radiotherapy, or stereotactic body radiotherapy. Lastly, in comparing TARE for individuals with HCC and PVT a median OS of 9.7 months after TARE in all people with HCC with PVT was reported. Limitations include differences in population, lack of generalization across studies or people, high risk for bias due to heterogeneity in population, small size, and retrospective design. The authors conclude TARE for individuals with HCC will improve OS rates compared to conventional TACE. (ECRI, 2021b)

ECRI evaluated TheraSphere (Boston Scientific Corp.) for treating HCC through a clinical evidence assessment. The assessment focused on the safety and effectiveness of TheraSphere compared to other treatments, such as TACE. The report summarizes the evidence as somewhat favorable, concluding that TARE with TheraSphere is safe and increases time to disease progression when compared to standard care for individuals with unresectable HCC. Further pointing out that the therapy improves liver transplant prospects, however, does not improve OS. Larger multicenter RCTs that compare TheraSphere with other treatments would help confirm the therapy's safety and effectiveness. (ECRI, 2021c)

In a 2021 systematic review and meta-analysis conducted by Lemieux and associates (included in the 2021c ECRI report), the investigation of RCTs comparing Y90-TARE to the standard of care in non-surgical HCC individuals yielded 1,604 citations. The outcomes measured were OS, progression-free survival, TTP, DCR, grade \leq 3 AE, and rates of gastrointestinal ulcers. For the analysis, hazard, and risk ratios were utilized. The exploration results demonstrated no improvement in OS when Yttrium-90 TARE was compared to standard treatments [HR 0.99 (95% CI 0.81–1.21), 6 studies, $I^2 = 77.6\%$]. Nevertheless, Yttrium-90 TARE correlated with fewer grade \leq 3 AE [RR 0.64 (95% CI 0.45–0.92), 7 studies, $I^2 = 66\%$]. No variation was detected in other secondary outcomes. The authors concluded that for individuals with non-surgical HCC, Yttrium-90 TARE was not related to a significant effect on survival, progression-free survival, TTP, control rate, and the incidence of gastrointestinal ulcers but was still of substantially lower rates of grade \leq 3 AE. More RCTs are necessary to portray the most favorable treatment better.

In a 2021 evidence based Canadian Journal of Health Technologies (CADTH) review, Young et al. evaluated the evidence regarding the clinical effectiveness of transarterial embolization (TARE) using yttrium-90 (90Y) microspheres in patients with intermediate or advanced stage HCC. Five publications met the criteria for the clinical assessment of this

review and included 4 systematic review with meta-analyses, and 1 non- randomized study. The results showed that TARE using 90Y microspheres is a therapeutic option for patients with recurrent or inoperable HCC. Patients generally did not experience a difference in overall survival, progression free survival and tumor response when compared to transarterial chemoembolization (TACE) or sorafenib or leviatinib therapies. Furthermore, patients receiving TARE experienced similar rates of adverse events compared to TACE. The comparative safety to systemic treatment was unclear as included studies did not statistically compare these results.

Abdel-Rahman and Elsayed (2020) conducted a systematic review and meta-analysis on six RCTs (N = 1340) to determine the benefits and harms of yttrium-90 microsphere RE compared with placebo, no intervention, or other available interventions in people with advanced liver cancer. The primary outcomes measured were median OS rate, quality of life and serious AEs. Secondary outcomes measured were cancer-related mortality, TTP of the tumor and tumor response. One RCT compared RE plus sorafenib versus sorafenib alone in individuals with advanced hepatocellular carcinoma. The authors found very low-certainty evidence that RE combined with sorafenib might be associated with higher rates of non-serious AEs compared to sorafenib alone. The median OS was 11.4 months in the sorafenib group and 12.1 months in the RE plus sorafenib group (HR 1.01, 95% CI 0.81 to 1.25; P = 0.95). Two RCTs compared RE versus sorafenib for unresectable hepatocellular carcinoma in individuals with locally advanced hepatocellular carcinoma. There was a one-year mortality rate of 62% in the RE group and 60% in the sorafenib group. The authors found low certainty evidence suggesting that RE achieved OS and a DCR that was comparable to sorafenib alone. The risk of non-serious AEs was lower with RE. Three RCTs compared RE versus chemoembolization in individuals with intermediate-stage hepatocellular carcinoma. The 1-year survival was 70% for both groups. The authors found low-certainty evidence suggesting that the risk of serious AEs is similar between RE and chemoembolization. (Author Salem et al. 2016 which was previously discussed in this policy and was included in the 2022 Hayes report, is included in this review; Abdel-Rahman is discussed in Hayes, 2021.)

A Hayes comparative effectiveness review compared clinically relevant outcomes following TARE with yttrium-90 (⁹⁰Y) versus outcomes following TACE, drug eluting bead-TACE (DEB-TACE), and sorafenib for individuals with primary unresectable HCC. Evidence from retrospective comparative studies suggested that ⁹⁰Y-TARE has comparable efficacy on survival outcomes, potentially superior efficacy on tumor response, and better tolerance, compared with TACE in intermediate HCC. Evidence comparing TARE with sorafenib suggests equivalence between the groups on survival and tumor progression outcomes but a potential benefit favoring TARE over sorafenib on tumor response and treatment toxicity. The available evidence regarding the comparison of TARE with DEB-TACE or comparing TARE with resin (SIR-Spheres) versus glass microspheres (TheraSphere) is insufficient to permit conclusions regarding comparative effectiveness and safety. An updated literature search was performed on September 30, 2020. One post-hoc analysis of a randomized controlled trial (SARAH), 2 retrospective cohort studies, 4 SRs and meta-analyses, 1 systematic review, and 2 cost-effectiveness studies were retrieved. The evidence remains insufficient to permit conclusions regarding comparative effectiveness and safety. In the 2022 update, Hayes identified 10 newly published studies with no change to their current Hayes rating. (Hayes, 2019; updated 2022)

Katsanos et al. (2017) conducted a systematic review and network meta-analysis of different embolization options for unresectable HCC. Medical databases were searched for RCTs evaluating bland TAE, drug-eluting bead transarterial chemoembolization (DEBTACE), or TARE, either alone or combined with adjuvant chemotherapy, or local liver ablation, or external radiotherapy for unresectable HCC up to June 2017. Fifty-five RCTs with 5,763 people with preserved liver function and unresectable HCC were included in the evidence review. The authors' review found that all embolization strategies achieved a significant survival gain over control treatment. Estimated median survival was 13.9 months in control, 18.1 months in TACE, 20.6 months with DEB-TACE, 20.8 months with TAE, 30.1 months in TACE plus external radiotherapy, 33.3 months in TACE plus liver ablation and 24.3 months in TARE. Comparative safety analysis demonstrated that TARE with a beta-emitter was the safest treatment, whereas combined TACE and liver ablation had the most favorable safety and effectiveness profile. TACE, DEB-TACE, TARE and adjuvant systemic agents did not improve objective response over bland embolization alone. The authors concluded that TACE, DEB-TACE, TARE and adjuvant systemic agents neither improved tumor objective response nor granted any individual survival benefit compared to bland particle embolization TAE. Combinations of TACE with external radiation or liver ablation achieved the best tumor response and survival. The quality of evidence remains mostly low to moderate because of clinical diversity.

A systematic review (Kallini et al. 2017, included in the 2021b&c ECRI reports) was conducted to compare the safety profiles of TheraSphere® (glass) and SIR-Spheres® (resin) Y90 microspheres for the treatment of hepatocellular carcinoma. Baseline characteristics and AEs of all grades related to gastrointestinal, hepatobiliary, and respiratory systems were collected. Thirty-one observational studies were included in the review. In the AEs of all grades, more people treated with resin microspheres reported gastric ulcers, hepatic encephalopathy, cholecystitis, hepatic failure, and pleural effusion. Those treated with resin microspheres also had more hepatobiliary AEs of grade 3 or higher. In the

events related to post-embolization syndrome, glass microspheres exhibited a similar safety profile compared to resin microspheres. Ascites and nausea grade 3 or higher were recorded more frequently with glass microsphere treatment. The authors concluded that based on review of the published literature, glass microspheres exhibit a safety profile with fewer gastrointestinal and pulmonary AEs compared to resin microspheres in the treatment of hepatocellular carcinoma.

Clinical Practice Guidelines

American Association for the Study of Liver Diseases (AASLD)

In an updated 2023 practice guideline regarding the prevention, diagnosis and treatment of individuals with HCC, the AASLD states the following:

- Transarterial radioembolization (TARE) with Yttrium-90 has recently been established as an acceptable treatment for solitary unresectable HCC
- Neoadjuvant locoregional therapy (LRT) such as with TACE, TARE, ablation, and external beam radiation therapy (EBRT) is typically used as a bridge to control tumor growth and reduce the risk of waitlist dropout currently no one type of LRT is recommended over another for bridging to transplant
- TARE can be performed for subcapsular tumors in anatomic locations that may be challenging for ablation, such as subdiaphragmatic and peri-cardiac tumors and is also effective at treating microsatellites. Radiation segmentectomy can provide durable local tumor control, significantly prolong time to progression (TTP), and serve as an effective bridging therapy to liver transplantation
- TARE can be used an accepted alternative intra-arterial therapy for intermediate-stage HCC

Guidance Statements:

- Patients with BCLC Stage B HCC should be treated with transarterial chemoembolization (Level 1, Strong Recommendation)
- Radioembolization as an alternative therapy to chemoembolization in patients with BCLC Stage B HCC (Level 3, Strong Recommendation)
- Transarterial therapies should be performed in a selective/segmental fashion (over lobar treatment) whenever possible given a lower risk of hepatic dysfunction (Level 5, Strong Recommendation)

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)

In a 2019 joint practice parameter regarding SIRT or RE for treatment of liver malignancies, the above professional societies state that SIRT and RE may be indicated in the presence of unresectable or inoperable primary or secondary liver malignancies in patients with a life expectancy of at least three months. The tumor burden should be liver dominant, not necessarily exclusive to the liver. Multidisciplinary expertise is essential and includes interventional radiology, radiation oncology, nuclear medicine, medical physics, radiation safety, hepatology, gastroenterology, medical or radioembolization oncology, and surgical oncology.

Absolute contraindications:

- Inability to catheterize the hepatic artery
- Fulminant liver failure
- Initial mapping angiography and/or technetium-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy demonstrating nontarget deposition to the gastrointestinal organs that cannot be corrected by angiographic techniques
- Pretreatment hepatic arterial administration with technetium-99m MAA demonstrative of unfavorable (or unacceptable) shunt fraction between the liver and the pulmonary parenchyma. This shunt fraction must not be greater than acceptable limits specific to each brachytherapy device
- Active hepatic infection
- Therapy during pregnancy may possibly be an option in extraordinary circumstances and with multidisciplinary consult and considerations

Relative Contraindications:

- Excessive tumor burden in the liver with greater than 50% to 70% of the parenchyma replaced by tumor. In the setting of more extensive tumor burden, treatment can be considered if synthetic hepatic function is preserved

- Total bilirubin greater than 2 mg/dL (in the absence of obstructive cause), which indicates severe liver function impairment. Nonobstructive bilirubin elevations may indicate that liver metastases have caused liver impairment to the degree that risks outweigh benefits for this therapy. In contrast, patients with HCC and elevated bilirubin may be treated with radioembolization if a segmental or subsegmental infusion can be performed
- Prior radiation therapy to the liver or upper abdomen that included a significant volume of the liver (clinical judgment by the AU required)
- Care must be employed when patients are on systemic therapies that may potentiate or may alter the impact of radioembolization and should use caution when combining therapies

National Comprehensive Cancer Network (NCCN)

The NCCN, clinical practice guidelines in oncology for hepatocellular carcinoma state that arterially directed therapies include bland TAE, chemoembolization TACE and TACE with drug-eluting beads (DEB-TACE), and RE with yttrium-90 (Y-90) microspheres. The panel recommends that EBRT or SBRT be considered as an alternative to ablation and/or embolization techniques or when these therapies have failed or are contraindicated (for individuals with unresectable disease characterized as extensive or otherwise not suitable for liver transplantation and those with local disease but who are not considered candidates for surgery due to performance status or comorbidity). (NCCN, Hepatocellular Carcinoma V2. 2023)

National Institute for Health and Care Excellence (NICE)

NICE recommends the use of SIRT SIR-Spheres, and SIRT TheraSphere as an option for treating unresectable advanced HCC in adults. NICE recommends use of SIRT for adults when used for individuals with Child-Pugh grade A liver impairment when conventional transarterial therapies are inappropriate, and when the commercial arrangement is utilized in providing Sir-Spheres and SIRT TheraSpheres. Guidance from NICE states current evidence on the safety and efficacy of SIRT for primary HCC is adequate for use with normal arrangements for clinical governance, consent, and audit. (NICE, 2021)

American College of Radiology (ACR)

In the 2022 appropriateness criteria for management of liver cancer, the ACR states the following: TARE with Yttrium-90 microspheres may be appropriate for the following:

- A cirrhotic solitary tumor less than 3 cm
- Intrahepatic cholangiocarcinoma: Peripheral hepatic lobar cholangiocarcinoma, less than 3cm; no biliary ductal dilatation, macroscopic vascular invasion, regional lymphadenopathy, or distant metastases
- Ductal cholangiocarcinoma: Hilar cholangiocarcinoma, greater than 3 cm with poorly defined margins, vascular invasion, and periportal lymphadenopathy
- Solitary colorectal liver metastasis
- Multifocal bilobar colorectal carcinoma (liver dominant or isolated)

TARE with Yttrium-90 microspheres is usually appropriate for:

- A cirrhotic solitary tumor 3 to 5 cm
- Metastatic liver disease: Multifocal metastatic neuroendocrine tumor (includes carcinoid tumors as well as islet cell tumors of the pancreas)
- Cirrhotic, multifocal, bilobar disease, at least 1 tumor greater than 5 cm
- Cirrhotic solitary or multifocal disease with vascular invasion

Intrahepatic Cholangiocarcinoma

In 2023, Schaarschmidt and colleagues conducted a multicenter, retrospective study to identify factors associated with an improved median OS for individuals with ICC receiving RE at five major tertiary-care centers. Overall analyzed was 138 RE's performed in 128 individuals with ICC. The outcomes measured were clinical data, imaging characteristics, RE reports, and data from RECIST, version 1.1, at 3, 6, and 12 months after RE. The mean OS (mOS) was then compared to subgroups using the Kaplan-Meier curves and the log-rank test. As a first-line treatment, RE was performed in 25.4% of individuals, 38.4% as a second-line treatment, and 36.2% as a salvage treatment. In people receiving first-line, second line, and salvage RE, the DCR was 68.6%, 52.8%, and 54.0% after three months; 31.4%, 15.1%, and 12.0% after six months; and 17.1%, 5.7%, and 6.0% after one year, respectively. For individuals receiving RE as first-line, second line, and salvage treatment, mOS were 12.0 months (95% CI, 7.6-23.4 month), 11.8 month (95% CI, 9.1-16.6 month), and 8.4 month (95% CI, 6.3-12.7 month), respectively. No significant differences among the three groups were observed (P = 0.15). Hepatic tumor burden did not significantly influence mOS (P = 0.12). The authors concluded that RE might be an essential treatment option, especially in advanced ICC, as a second line and salvage treatment. Further research is

necessary to investigate the role of RE as a first-line treatment in the later treatment stages of the disease. In addition to ongoing studies investigating the role of RE as first-line treatment, the role of RE in the later treatment stages of the disease demands further attention.

In a phase 2, single-Arm, multicenter clinical trial Chan and associates (2022) aimed to study the efficacy and safety of administering SIRT with resin Y-90 followed by standard chemotherapy for unresectable ICC. For the study, participants were administered SIRT at a dose of 120 Gy targeted at the tumor, then commencement of gemcitabine 1.000 mg/m² and cisplatin 25 mg/ m² on days one and eight of a 21-day cycle. The outcomes measured were OS, PFS, response rate according to RECIST 1.1, toxicity, and time from SIRT to commencement of chemotherapy. Thirty-one individuals were screened, and 24 were recruited; all completed SIRT, although only 16 received chemotherapy. The study results showed that the median cycle of chemotherapy was 5 (range: 1-8). The median OS was 13.6 months (95% CI: 5.4-21.6) for the intent-to-treat population. Among 16 people undergoing chemotherapy, the median OS was 21.6 months (95% CI: 7.3-25.2), and the median PFS was nine months (95% CI: 3.2-13.1). The response rate was 25% (95% CI: 3.8-46.2%), and the DCR was 75% (95% CI: 53.8-96.2%). No new safety signal was observed, with fewer than 10% of individuals suffering from grade 3 or higher treatment-related AEs. The median time from SIRT to chemotherapy was 29 (range: 7-42) days. Eight people could not receive chemotherapy due to rapidly progressive disease (N = 4), underlying treatment-unrelated comorbidities (N = 2), and withdrawal of consent due to personal reasons (N = 2). The authors concluded that treating SIRT followed by chemotherapy is feasible and effective for unresectable ICC. However, further studies are necessary to determine the optimal sequence of SIRT and chemotherapy. Limitations of the study include a need for more diversity in the population and control arm; there needed to be analyses on tissue biomarkers relevant to the SIRT-chemotherapy combination.

Schartz et al. (2022) conducted a systematic review and meta-analysis using a random effects model to assess the use of Y-90 for unresectable ICC. The study evaluated CA19-9 response rate, DCR, down staged to resectable rate, pooled OS, pooled median PFS, and mean reported survival rates between 3 and 36 months. A total of 921 participants were included from 21 studies. The outcomes showed an 82.3% overall DCR, 11% of those were down staged to being surgically resectable, and the CA 19-9 response rate was 67.2%. PFS was 7.8 months from point of RE with the overall median survival rate being 12.7 months. The reported survival proportions were at 3,6,12,18,24, 30 and 36 months. The authors conclude RE with Y-90 for unresectable ICC remains beneficial for both disease control and survival.

Fruscione et al. (2021) performed a systematic review on the topic of neoadjuvant therapy for unresectable ICC and its association with adequate tumor downsizing to enable resectability. Ten studies (N = 132) were included in the review; 2 retrospective, single-center studies; 1 retrospective, multicenter study; 1 prospective study; 1 prospective safety study, and 5 case reports. Excluding case reports, 22 of 127 individuals (17.3%) had successful tumor downsizing; based on treatment modality. Tumor downsizing rates ranged from 13.9% (TACE alone) to 20.8% (TARE alone). Twenty-seven people underwent conversion therapy with surgical resection. The authors concluded that conversion therapy for initially unresectable ICC may offer adequate tumor downsizing for resection.

Buettner et al. (2020) conducted a retrospective cohort review (N = 115) to report outcomes of yttrium-90 (90Y) RE in individuals with unresectable ICC. Ninety participants were treated with resin microspheres (80%), 22 were treated with glass microspheres (19%), and 1 was treated with both. The median follow-up of those treated with resin microspheres was 10 months and the median follow-up of individuals treated with glass microspheres was 14 months. Median PFS for the entire cohort was 5 months. Median OS from first diagnosis was 29 months and 1-, 3-, and 5-year OS rates were 85%, 31%, and 8%, respectively. Median OS after treatment was 11 months and 1- and 3-year OS rates were 44% and 4%, respectively. Five people were able to undergo curative-intent resection after ⁹⁰Y RE (4%). The authors concluded that 90Y RE was observed to be safe in a large cohort of individuals. The OS for those with ICC treated with 90Y RE was in line with the results of other local therapy options.

A prospective, observational study performed by White et al. (2019) evaluated the outcomes of individuals with unresectable, chemotherapy-refractory ICC who were treated with TARE. Primary outcome was OS. Secondary outcomes included safety, PFS, and liver-specific progression-free survival (LPFS). The study included sixty-one people; 91% had performance status 0/1; 92% had received prior chemotherapy; and 59% had no extrahepatic disease. Median follow-up was 13.9 months [95% confidence interval (CI), 9.6-18.1]. OS was 8.7 months (95% CI, 5.3-12.1), and 37% of individuals survived to 12 months. PFS was 2.8 months (95% CI, 2.6-3.1), and LPFS was 3.1 months (95% CI, 1.3-4.8). One severe complication (abdominal pain) occurred at the time of the TARE procedure. Thirty people experienced a total of 49 AEs, of which 8% were grade ≥ 3; most common were grade 1-2 fatigue and abdominal pain. Those with advanced ICC have limited therapeutic options and a poor prognosis. The authors concluded that the results demonstrated that this treatment merits further investigation in this cohort in a larger study, including collection of patient-reported outcomes.

A retrospective study was conducted by Jia et al. (2017b) on individuals who underwent resin-based yttrium-90 (⁹⁰Y) therapy for unresectable and failed first-line chemotherapy ICC. Tumor response was assessed using modified RECIST criteria and side effects were assessed using Common Terminology Criteria for Adverse Events. Survivals were calculated from the date of diagnosis of ICC, beginning of first-line chemotherapy and first ⁹⁰Y procedure, respectively; effects of factors on survival were analyzed by Cox regression model. The aim of the study was to evaluate the value of resin-based ⁹⁰Y RE for unresectable and failed first-line chemotherapy (cisplatin plus gemcitabine) ICC. Twenty-four people were included in this study. Mean 5.6 ±1.6 cycles of first-line chemotherapy were performed prior to ⁹⁰Y treatment. There was a total of 27 treatments of ⁹⁰Y. DCR was 81.8% at 3 months. Side effects included fatigue, anorexia, nausea, abdominal pain, vomiting and fever. Radiation-induced gastrointestinal ulcer was identified in one person. The mean follow-up was 11.3 ±6.6 months, and the median survivals from the time of diagnosis of ICC, beginning of first-line chemotherapy and first ⁹⁰Y procedure were 24.0, 16.0 and 9.0 months, respectively. The 6, 12, 18, 24 and 30-month survival after ⁹⁰Y therapy were 69.9, 32.6, 27.2, 20.4 and 20.4%, respectively. The authors concluded that resin-based ⁹⁰Y RE can provide palliative control of unresectable and failed first-line chemotherapy ICC with acceptable side effects.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN clinical practice guidelines for Biliary Tract Cancers state that based on the available evidence, locoregional therapy is a treatment option that may be considered for individuals with unresectable disease or metastatic cancer without extrahepatic disease. Intra-arterial chemotherapy is recommended only in the context of a clinical trial or at experienced centers in carefully selected cases for individuals with advanced disease confined to the liver. (NCCN, V3.2023)

National Institute for Health and Care Excellence (NICE)

NICE interventional procedures guidance for SIRT for unresectable primary ICC recommendations state that the current evidence on the safety of SIRT for unresectable primary ICC shows that there are well-recognized, serious but rare safety concerns. Evidence on its efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. They recommend that further research in the form of prospective studies, including RCTs, should address patient selection, quality-of-life outcomes and OS. Patient selection for the research studies should be done by a multidisciplinary team. The procedure should only be done in specialist centers by clinicians trained and experienced in managing cholangiocarcinoma. (NICE, 2018)

Bridge to Transplant

A Hayes Health Technology Assessment report compared clinically relevant outcomes following TARE with yttrium-90 (⁹⁰Y) with other LRTs or sorafenib for individuals with primary HCC as a bridge to transplant or resection. A total of 8 studies met the inclusion criteria. All but two studies compared data retrospectively. The remaining studies consisted of 2 RCTs. Outcome measures included survival, tumor response, TTP, rate of successful downstaging or bridging, and toxicity and other complications. The assessment reports that ⁹⁰Y TARE may confer similar or greater benefits than other LRTs or sorafenib with respect to the efficacy outcomes assessed, and that ⁹⁰Y TARE is comparable or better than other LRTs or sorafenib in terms of safety. A 2021 review of literature found one additional study. The small body of low-quality evidence suggests that ⁹⁰Y TARE may have similar or better safety and efficacy outcomes than other treatments used to downstage or bridge primary individuals with HCC to transplantation or resection. (Hayes, 2019, updated 2022)

A retrospective cohort (N = 207) was conducted by Gabr et al. (2021) to evaluate the long-term outcomes of liver transplantation (LT) for individuals with HCC who were bridged and down staged using Y90. Long-term outcomes included OS, recurrence-free survival (RFS), disease specific mortality (DSM), and time-to-recurrence. A total of 169 people were bridged and 38 were down staged to LT. OS rates at three-year, 5-year, and 10-year were 84%, 77%, and 60%, respectively. Twenty-four individuals developed recurrence, with a median RFS of 120 months. DSM at 3, 5, and 10 years was 6%, 11%, and 16%, respectively. There were no differences in OS/RFS for those who were bridged or down staged. RFS was higher in people with complete and extensive versus partial tumor necrosis. The authors concluded that Y90 is an effective treatment for HCC in the setting of bridging/downstaging to LT.

Ettore et al. (2017, included in Hayes report above) retrospectively evaluated the efficacy of the Y90-RE for individuals with hepatocellular carcinoma (HCC) prior to LT. The study included one hundred forty-three participants who were transplanted for HCC, and in 22 cases they were treated with Y90-RE before LT. Three people were treated with Y90-RE within the Milan criteria, and 19 were out of criteria before Y90-RE. Four individuals had an increasing MELD score between Y90-RE and LT. Alpha-fetoprotein decreased after Y90-RE treatment in all cases. No death was observed in Y90-RE procedure or at LT. In 78.9 % of cases, a successful downstaging was observed, and in 100 % of cases bridging was achieved. From Y90-RE treatment OS was 43.9 months. From LT, overall mean survival was 30.2 months with a free

survival of 29.6 months. The authors state that LT was performed for individuals after Y90-RE treatment both as bridging and downstaging for HCC and obtained a similar overall and free survival of LT for HCC and that Y90-RE is an option to provide curative therapy for those who traditionally are not considered eligible for surgery.

Lau et al. (2011) reviewed the role of SIRT with ⁹⁰Y microspheres for HCC. The evidence was limited to cohort studies and comparative studies with historical controls. The authors concluded that ⁹⁰Y microspheres are recommended as an option of palliative therapy for large or multifocal HCC without major portal vein invasion or extrahepatic spread. They can also be used for recurrent unresectable HCC, as a bridging therapy before liver transplantation, as a tumor down staging treatment and as a curative treatment for individuals with associated comorbidities who have otherwise excisable tumors but are not candidates for surgery.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

In the NCCN guidelines on HCC, SIRT and radioembolization (TARE) with Y- 90 microspheres are listed as locoregional therapies for bridge to transplant, and is recommended for patients who are eligible to slow tumor progression and the dropout rate from transplantation waiting list, particularly in areas where wait times are long.

Liver Metastases From Other Primary Sites

There is limited evidence suggesting that treatment with TARE/SIRT using yttrium-90 (⁹⁰Y) microspheres for other indications is effective. RCTs are needed to determine the clinical utility of this treatment.

Kuei et al. (2015) conducted a systematic review to evaluate the effects of Yttrium-90 RE on non-conventional liver tumors including those secondary to breast cancer, cholangiocarcinoma, ocular and percutaneous melanoma, pancreatic cancer, renal cell carcinoma, and lung cancer. A total of 28 studies containing non-conventional primaries undergoing Yttrium-90 RE were included for review. Of the studies on SIRT of non-conventional liver metastases, breast cancer is the most studied. This review found 7 exclusively BRCLM SIRT studies in addition to 3 mixed primary studies that provide response data. Response rates were between 18%-61% and median OS between 6.6 to 13.6 months. The authors concluded that although the tumor response with SIRT was encouraging, the influence on survival remained unclear. The number of studies on the effects of SIRT on breast cancer metastasis has so far involved only small, heterogenous cohorts. To validate SIRT as a potential first-line adjuvant to chemotherapy, larger multicenter randomized control studies are needed. Eight ICC-only SIRT studies were analyzed. Yttrium-90 SIRT is considered at some centers a preferred first-line therapy for low-tumor burden ICC. Reasons for this include the benefit of being able to downstage previously unresectable ICC for curative resection. Though median OS data is shorter than that of hepatic arterial infusion, Yttrium-90 therapy carries fewer risks including not having to implant a chemoinfusion port. Four studies have been done on Yttrium-90 SIRT of melanoma liver metastases. Given the hypervascularity and aggressive nature of melanoma liver metastases, treatment with SIRT appears to be a reasonable approach at reducing disease progression. Median OS ranges from 7.6 to 10.1 months. Based on the few small cohort studies, the authors stated that SIRT has been demonstrated to be safe and effective at prolonging survival, however without further comparative studies the ideal selection criteria and benefit over other regional therapies remains uncertain. Metastatic pancreatic cancer carries a poor prognosis. Alternative LRT such as Yttrium 90 SIRT have been investigated as adjuncts for the purpose of slowing disease progression. Two small cohort, single center studies have been published. Though the limited available data makes survivability benefits unclear, initial reports are encouraging. Median survival is attributed to a 2–4-month improvement over conventional gemcitabine combination therapy alone. Improvement over the new chemotherapy regimen FOLFIRINOX has yet to be demonstrated. Response rates are consistent with established response rates with colorectal and neuroendocrine metastatic liver disease. Further studies are needed to delineate the proper selection criteria for optimal individual outcome. Experience with LRT like SIRT in the treatment of renal cell carcinoma liver metastases is very limited. In the treatment of liver metastasis from renal cell carcinoma, SIRT is limited by the rarity of liver dominant metastases and the known resistance to radiation. Data on a handful of individuals are promising for the use of SIRT for a palliative rather than curative intent. The value of Yttrium-90 SIRT of lung cancer has been seldom investigated and the available data is extremely limited. The authors concluded that the few cases of Yttrium-90 SIRT of lung cancer liver metastases demonstrate SIRT's potential as an effective salvage therapy. Clinicians must be mindful of nontarget radiation to the lungs due to potentially limited baseline pulmonary function. Further studies are needed so that the criteria in which SIRT becomes a worthwhile therapy in metastatic lung cancer can be better defined. The authors summarized that although the indications for Yttrium-90 SIRT in nonconventional liver metastases are less well defined, initial results of small studies are largely favorable. Limitations include marked cohort heterogeneity, the absence of a gold standard in response criteria, and variations in treatment dosing. These studies demonstrate that whether Yttrium-90 SIRT provides a justifiable benefit to any given person relies tremendously on both tumor type and individual status.

Larger, multi-centered randomized controlled studies are needed so that established clinical guidelines can develop that ultimately improve outcomes.

Melanoma

Alexander et al. (2022) conducted a systematic review regarding SIRT for hepatic metastases of uveal melanoma (UM) to assess the effectiveness and safety of SIRT for hepatic metastases from UM. Research from EMBASE and MEDLINE until July 2020 using terms related to SIRT and hepatic from UM was utilized and showed outcomes of SIRT for individuals with UM and one hepatic metastasis. Data was collected on OS, hepatic progression free survival (hPFS), and tumor response. The Newcastle Ottawa Scale (NOS) assessed the risk of bias. The literature reported outcomes for 268 individuals with hepatic metastases from UM using 11 studies. 170 participants achieved disease control with the median OS from the time of SIRT at 12.3 months. The median hPFS was 5.4 months with serious complications seen infrequently. Median NOS score showed a moderate risk of bias with a score of 6. Limitations include the questionable results due to retrospective data with moderate risk of bias. It was concluded further prospective studies are required to explore the role of SIRT in UM.

A systematic review was performed by Rowcroft et al. (2020) to review the evidence for the management of UM liver metastases. The primary outcome was OS, with disease free survival as a secondary outcome. Fifty-five studies were included (N = 2446) with 39 retrospective cohort studies, two RCTs and 14 prospective cohort studies. Treatment modalities included surgery, isolated hepatic perfusion (IHP), hepatic artery infusion (HAI), TACE, SIRT and immunoembolization (IE). Ten studies evaluated surgical resection. Median OS ranged from 10 to 35 months. Ten studies utilized either IHP or percutaneous IHP (PHP) to treat UM liver metastases with median OS ranging from 9 to 25 months. There were eight studies evaluating the use of HAI with OS ranging from 10 to 24 months. Seventeen studies evaluated the use of TACE. The reported OS ranged from 5 to 29 months. Six studies evaluated the use of SIRT where median OS ranged from 9 to 24 months. IE had a median OS of 21 months. The authors concluded that predominantly retrospective and uncontrolled studies suggested that surgery and locoregional techniques may prolong survival. This review is limited by the low quality of evidence available.

In 2019, Gonsalves et al. reported the results of a phase II, two parallel arm prospective trial on the safety and efficacy of radioembolization (RE) for treating UM hepatic metastases. Participants were enrolled into one of two study groups. Group A included 23 participants with no prior liver-directed or systemic therapies, and group B included 24 participants with hepatic tumor progression following immunoembolization. Inclusion criteria required confirmed UM hepatic metastases (≥ 1 cm) and an Eastern Cooperative Oncology Group performance status of less than or equal to 1. Participants underwent unilobar, fractionated whole-liver, or sequential lobar treatments every 3–5 weeks. Procedure-related complications were classified using the Society of Interventional Radiology classification system of complications by outcome. Follow up included blood tests every week for a month, every 2 weeks for 2 months, and every month afterwards. Chest abdominal and pelvic CT were performed 1 month following treatment to help detect extrahepatic disease. CT, PET, and MRI were performed every 3 months for surveillance of extrahepatic metastases and tumor response. MRI was performed at 3 months for confirmation of tumor response if there were concerns. Participants were evaluated for 1 month and every 3 months for acute and delayed toxicities, respectively. The results showed that in Group A, radiographic partial response was achieved in 9 of the 23 participants, stabilization of disease was achieved in 11, and 3 showed disease progression. None showed complete response. Median PFS was 8.1 months and the median OS was 18.5 months. New disease was detected in all participants with disease progression, and extrahepatic disease developed or progressed in 21 participants at a median of 6.6 months. For Group B, the results showed radiographic partial response was achieved in 8 participants, stabilization of disease was achieved in 6, and 10 showed disease progression. None showed complete response. Median PFS was 5.2 months, and median OS was 19.2 months. 21 developed new hepatic lesions, and extrahepatic disease developed in 22. No major treatment related toxicities occurred in either group. The authors concluded that despite greater than 90% of participants in this trial developed new hepatic and extrahepatic metastases, prolonged OS was achieved, and radioembolization is a safe and effective first or second line treatment for UM hepatic metastases. This trial is limited by a small sample size. Additional research is needed to validate these findings.

A systematic review (Jia et al. 2017a, included in the 2021a ECRI report) was conducted to assess the effectiveness of yttrium-90 (⁹⁰Y) RE in the treatment of unresectable liver metastases of melanoma. A total of 12 reports (7 observational studies and 5 abstracts from conferences) involving 255 participants were included in the analysis. The primary sites of melanoma were cutaneous (N = 22), ocular (N = 197), rectal (N = 3), and unknown (N = 33). The median DCR at 3 months was 73.6%. Among the 207 individuals for whom tumor response at 3 months was reported, complete response was seen in 1.0%, partial response was seen in 19.3%, stable disease was seen in 46.9% and progressive disease was seen in 32.9%. The median survival was 10 months and the median 1-year survival rate was 34.6%. Complications of ⁹⁰Y RE were reported in 13 cases. The most common side effects were fatigue, abdominal pain, and nausea. The authors

concluded that ⁹⁰Y RE is a promising alternative therapy for the treatment of unresectable liver metastases of melanoma, with encouraging effects on disease control and survival. Some complications can occur, and side effects are frequent but mild. A limitation of the study is the absence of randomized clinical trial data.

Breast Cancer

In a 2022 meta-analysis, Liu et al. assessed the efficacy of yttrium-90 selective internal radiation therapy (SIRT) in treating patients with breast cancer with hepatic metastasis. Twenty-four studies comprised of 412 patients were included. The results suggest that SIRT is feasible for treating breast cancer with hepatic metastasis recalcitrant to other therapies and showed an overall post embolization median survival time of 9.8 months. Patients with < 25% hepatic metastatic burden and lack of extrahepatic disease showed a better response. The tumor response and tumor control rates were 36-49% and 73-97% respectively which is similar to results shown for primary liver cancer. There were no life-threatening adverse effects reported. This meta-analysis is limited by a heterogenous patient population and disease severity, and additional high-quality studies are needed to determine comparative efficacy with other treatment approaches.

Rivera et al. (2021) conducted a systematic review of the literature on the efficacy of liver directed therapies for breast cancer related liver metastasis (BCLM). These therapies include hepatic resection, radiofrequency ablation (RFA), transarterial chemo and radioembolization (TACE/TARE), and hepatic arterial infusion (HAI). There were 51 overall studies included, 10 of which were regarding TARE in 380 total patients. With regard to TARE, 9 of the 10 studies provided RECIST response data and the evidence shows that of the 380 total patients, nine showed complete response, 143 had a partial response, 139 had disease stabilize and 44 had disease progression. Eight studies provided mean OS of 11.5 months. Three provided one year survival data of 34.5 to 86%. The authors concluded that treatment of BCLM using TARE does not show vastly improved survival across all included studies.

A systematic review (Feretis and Solodkyy 2020, included in the 2021a ECRI report) was conducted to assess the effect of RE with yttrium-90 on tumor response and to estimate survival post RE in individuals with unresectable hepatic metastases of breast cancer. Twelve studies (N = 452) were included with 236 participants having breast metastases not confined to the liver. The duration of the follow up period post-radioembolization ranged from 6 to 15.7 months. DCRs varied from 48%-100% with an estimated mean response to TARE of 81%. OS post-radioembolization ranged from 3.6 to 20.9 months with an estimated mean survival of 11.3 months. The authors concluded that TARE with yttrium microspheres has a potentially beneficial role in cases with inoperable liver metastases secondary to breast cancer. They stated that the absence of RCTs and the retrospective nature of the studies included carried the risk of selection bias. Future randomized trials are needed comparing treatments.

A large single center study by Fendler et al. (2016, included in Liu 2022 above) evaluated safety, efficacy, and prognostic factors for (90)Y-Yttrium microsphere RE of unresectable liver metastases from breast cancer (BRCLM). Eighty-one individuals underwent whole-liver (WL) RE by application of SIR-spheres (SIRTEX Medical). After RE, all participants were monitored for 3 days as inpatients for acute toxicity. Late toxicity was evaluated in all participants until 12 weeks after first RE. The primary endpoint was OS after RE. OS was defined as the interval between date of RE until the last date of contact as censored observation or until disease-related death. Toxicity grade ≥ 3 based on clinical symptoms, bilirubin, ulcer, pancreatitis, ascites, or RE-induced liver disease (REILD) occurred in $\leq 10\%$ of individuals. Two participants eventually died from REILD. Sequential lobar treatment and absence of prior angio-suppressive therapy were both associated with a lower rate of serious adverse events (SAE). Median OS after RE was 35 weeks. The authors concluded that RE for BRCLM shows encouraging local response rates with low incidence of SAE, especially in those with sequential lobar treatment or without prior angio-suppressive therapy. High hepatic tumor burden and liver transaminase levels at baseline indicate poor outcome. The retrospective design of this study may have resulted in false low-toxicity findings arising from underreporting.

Smits et al. (2013) provided a systematic overview of the current literature concerning ⁹⁰Y microspheres for individuals with BCLM. Six studies were included for analysis, with a total of 198 participants. Tumor response was scored in five studies using either RECIST (N = 3) or World Health Organization (WHO) criteria (N = 2). Overall DCRs (complete response, partial response, and stable disease) at 2-4 months post treatment ranged from 78% to 96%. Median survival, available in four studies, ranged from 10.8 to 20.9 months. In total, gastric ulceration was reported in ten people (5%) and treatment related mortality in three (2%). The authors concluded that the results from the analyzed studies consistently show that ⁹⁰Y is a safe and effective treatment option for individuals with BCLM. According to the authors, well designed, comparative studies with larger populations are needed to further describe safety and clinical outcomes of ⁹⁰Y for individuals with BCLM.

Pancreatic Cancer

A single institution retrospective cohort study (N = 26) was conducted by Kayaleh et al. (2020) to evaluate the safety, efficacy, and OS rate of individuals with liver dominant metastatic pancreatic cancer treated with TARE with ⁹⁰Y. The median OS from diagnosis was 33 months, from diagnosis of liver metastasis was 21.8 months and after TARE treatment with ⁹⁰Y was 7 months. The median HPFS was 2.7 months. Mild AEs were reported. Baseline and follow-up imaging were available for 22 of 26 individuals. At 3 months, partial response was shown in 1 individual, stable disease in 9 individuals and progressive disease in 12 individuals. The authors concluded that TARE with ⁹⁰Y glass microspheres is safe and led to a promising increase in OS in individuals with liver dominant metastatic pancreatic cancer. Larger RCT studies are needed to validate the findings. Some limitations of the study are the small size and lack of controls.

Clinical Practice Guidelines

European School of Oncology (ESO) and European Society for Medical Oncology (ESMO)

There are no randomized data supporting the effect of local therapy on survival, every patient must be informed of this when discussing a potential local therapy technique. Local therapy should only be proposed in very selected cases of good performance status (PS), with limited liver involvement and no extrahepatic lesions, after adequate systemic therapy has demonstrated control of the disease. Currently, there are no data to select the best technique for the individual patient (surgery, stereotactic RT, intrahepatic ChT, etc.). Prospective RCTs of local therapy for breast cancer liver metastases are urgently needed as the available evidence comes only from case series in highly selected patients.

National Comprehensive Cancer Network (NCCN)

The NCCN clinical practice guideline on UM states that if disease is confined to the liver, regional therapies such as chemoembolization, radioembolization, or immunoembolization should be considered. (NCCN, Melanoma: Uveal, v1. 2023)

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

The FDA has approved two commercial forms of ⁹⁰Y microspheres: TheraSphere® and SIR-Spheres®.

SIR-Spheres (Sirtex Medical) are resin ⁹⁰Y microspheres and are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of floxuridine (FUDR). SIR-Spheres received FDA premarket approval (P990065) on March 5, 2002. Supplemental approvals have been identified for the PMA Product Code NAW. Additional information is available at:

http://www.accessdata.fda.gov/cdrh_docs/pdf/p990065a.pdf. (Accessed January 29, 2024)

TheraSphere(BTG) are glass ⁹⁰Y microspheres and are indicated for radiation treatment or as a neoadjuvant to surgery or transplantation for individuals with unresectable hepatocellular carcinoma who can have placement of appropriately positioned hepatic arterial catheters. Glass ⁹⁰Y microspheres are approved by the FDA under the provisions of a Humanitarian Device Exemption (H980006). Additional information is available at:

http://www.accessdata.fda.gov/cdrh_docs/pdf/H980006b.pdf. (Accessed January 29, 2024)

The use of TheraSphere and SIR-Spheres is also regulated by the United States Nuclear Regulatory Commission (U.S. NRC), which grants a license for the use of these products. Refer to the following guidance for further information:

<https://www.nrc.gov/docs/ML1535/ML15350A099.pdf>. (Accessed January 29, 2024)

On March 17, 2021, the FDA approved TheraSphere (Boston Scientific Corporation) pre-market approval (PMA) for use as SIRT for local tumor control of solitary tumors (1-8 cm in diameter) for individuals with unresectable hepatocellular carcinoma, Child-Pugh Score A cirrhosis, well-compensated liver function, no macrovascular invasion, and good performance status. Additional information is available at:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P200029>. (Accessed January 29, 2024)

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Guideline History/Revision Information

Date	Summary of Changes
08/01/2024	<p>Title Change</p> <ul style="list-style-type: none"> Previously titled <i>Implantable Beta-Emitting Microspheres for Treatment of Malignant Tumors</i> <p>Related Policies</p> <ul style="list-style-type: none"> Removed reference link to the Medical Management Guideline titled <i>Abnormal Uterine Bleeding and Uterine Fibroids</i> <p>Coverage Rationale</p> <ul style="list-style-type: none"> Added language to indicate: <ul style="list-style-type: none"> Selective internal radiation therapy (SIRT) using yttrium-90 microspheres is proven and medically necessary for the [listed] indications in individuals with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 SIRT using yttrium-90 microspheres is unproven and not medically necessary for all other indications [not listed as proven and medically necessary in the policy] due to insufficient evidence of efficacy

Date	Summary of Changes
	<p>Medical Records Documentation Used for Reviews (previously titled <i>Documentation Requirements</i>)</p> <ul style="list-style-type: none"> Replaced list of <i>Required Clinical Information</i> with instruction to refer to the protocol titled Medical Records Documentation Used for Reviews <p>Definitions</p> <ul style="list-style-type: none"> Added definition of “Transarterial Radioembolization (TARE)” <p>Applicable Codes</p> <ul style="list-style-type: none"> Added CPT code 75894 <p>Supporting Information</p> <ul style="list-style-type: none"> Updated <i>Description of Services</i>, <i>Clinical Evidence</i>, <i>FDA</i>, and <i>References</i> sections to reflect the most current information Archived previous policy version MMG063.L

Instructions for Use

This Medical Management Guideline provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this guideline, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Management Guideline is provided for informational purposes. It does not constitute medical advice.

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Member benefit coverage and limitations may vary based on the member's benefit plan Health Plan coverage provided by or through UnitedHealthcare of California, UnitedHealthcare Benefits Plan of California, UnitedHealthcare of Oklahoma, Inc., UnitedHealthcare of Oregon, Inc., UnitedHealthcare Benefits of Texas, Inc., or UnitedHealthcare of Washington, Inc.