Implantable Beta-Emitting Microspheres for Treatment of Malignant Tumors (for Louisiana Only)

Policy Number: CS060LA.~~I~~J
Effective Date: TBD

➲ Instructions for Use

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Application

This Medical Policy only applies to the state of Louisiana.

Coverage Rationale

Transarterial radioembolization (TARE) using yttrium-90 (^{90}Y) microspheres is proven and medically necessary for the following indications:

- **When used for the following indications:**
  - **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**
- **and**
- **When the following criteria are met:**
  - **Eastern Cooperative Oncology Group (ECOG) performance status of 0,1, or 2**
- ~~Unresectable metastatic liver tumors from primary colorectal cancer (CRC)~~
- ~~Unresectable metastatic liver tumors from neuroendocrine tumors~~
- ~~Unresectable primary hepatocellular carcinoma (HCC)~~

- ~~Unresectable intrahepatic cholangiocarcinoma~~

Transarterial radioembolization (TARE) using yttrium-90 (^{90}Y) microspheres is unproven and not medically necessary for all other indications due to insufficient evidence of efficacy.

Definitions

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

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 policy 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 federal, state, or contractual requirements 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
79445	Radiopharmaceutical therapy, by intra-arterial particulate administration

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

Codes labeled with an asterisk (*) are not on the Louisiana Medicaid Fee Schedule and therefore may not be covered by the state of Louisiana Medicaid Program.

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) with yttrium-90 (90Y) is a technique that targets multiple sites of disease within the liver through high doses of ionizing radiation directly to the tumor while minimizing radiation exposure of the normal liver tissue~~.~~ (Hayes, **2020**~~2019~~).

Radioactive yttrium-90 (**^{90}Y**~~90Y~~) microspheres offer selective internal radiation therapy (SIRT) (also referred to as transarterial radioembolization [TARE], radioembolization, or brachytherapy) for secondary tumors of the liver. A trained specialist injects radioactive microspheres into hepatic arteries that supply blood to tumor(s). The goal of the procedure is to irradiate and destroy the tumor(s) while sparing normal liver tissue ~~.~~ (Hayes, 20~~1~~**20**~~9~~).

Clinical Evidence

Liver Metastases from Colorectal Cancer

A 2021**a** ECRI Clinical Evidence Assessment report on transarterial radioembolization **(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). In patients with chemorefractory colorectal cancer (CRC) metastasis who received TARE as third-line therapy, TARE (^{90}Y) improved overall survival (OS) compared with best supportive care. In patients with CRC metastasis, adding TARE to first-line treatment did not improve survival. OS was higher

with **transarterial chemoembolization (**TACE**)** than with TARE in patients with neuroendocrine tumor metastasis, based on evidence from 1 SR. The SR included only 6 retrospective cohort studies at high risk of patient selection bias. In patients 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. ~~(Authors Frilling et al. (2019) and Jia et al. (2017), which were previously cited in this policy, are included in this review) (ECRI, 2021).~~

Mulcahy et al. (2021) conducted a randomized, open-label, international, multicenter phase 3 trial regarding radioembolization with chemotherapy for colorectal liver metastases. The study evaluates the impact of transarterial Yttrium-90 radioembolization ~~(TARE)~~ in combination with second line systemic chemotherapy for colorectal liver metastases (CLM). Between May 2012 and August 2020 four hundred twenty-eight patients from 95 centers in North America, Asia, and Europe were randomly assigned either to chemotherapy with or without TARE. Out of the 215 patients assigned to the TARE group; 187 received TARE, 16 received only chemotherapy, and 12 with no treatment. The control group consisted of 213 patients; 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 study was successful as T~~the median ~~overall survival~~ (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 (progression free survival) 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~~**review was conducted** ~~conducted by Baltatzis and Siriwardena (2019) which~~ includ**inged** 4 randomized trials and 8 clinical cohort series **(Baltatzis and Siriwardena 2019, included in the 2021a ECRI report)**. The study population was comprised of 120 individuals undergoing liver resection after chemotherapy and SIRT. The conversion rate to hepatectomy in previously unresectable patients 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 in patients treated by chemotherapy and SIRT. The authors concluded that the study showed that 13.6% of patients 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 ~~cited~~ **discussed** in this policy, are included in this review~~.)~~ ~~cited in ECRI, 2021).~~

Jakobs et al. (2017) performed a study with the aim of providing further evidence for the efficacy/safety of radioembolization using yttrium-90-resin microspheres for unresectable chemorefractory liver metastases from colorectal cancer (mCRC). They followed 104 consecutively patients treated with ~~radioemolization~~radioembolization until death. ~~Overall survival (~~OS~~)~~ was calculated from the day of the first radioembolization 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 in patients who had a complete response to prior chemotherapy and 13 months in patients with a partial response

or stable disease. The authors concluded that radioembolization can achieve meaningful survival in patients with chemorefractory liver-predominant ~~metastatic colorectal cancer (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 when used as salvage therapy for chemotherapy-resistant liver metastases from colorectal cancer. Forty-five patients with hepatic metastases from colorectal cancer underwent Y-90 radioembolization after failure of systemic chemotherapy. Y-90 radioembolization was technically successful in all. Twenty-three patients had no toxicities, 6 patients had grade 3 toxicities, and no patients had grade 4 toxicity. Two patients died within 30 days of treatment from renal failure unrelated to the procedure. One patient had partial response, 34 had stable disease, and 6 had progressive disease. PET response was seen in 46% of patients with 2 patients (4%) demonstrating complete and 22 (42%) demonstrating partial metabolic response. The median survival was 186 days. Patients who had response on PET following Y-90 therapy had a median overall survival of 317 days whereas patients with no response on PET had a median overall survival of 163 days. The authors concluded that Y-90 radioembolization as a salvage therapy for chemotherapy-resistant hepatic metastases from colon cancer was safe and resulted in disease stability.

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The FOXFIRE, SIRFLOX, and FOXFIRE-global randomized studies evaluated the efficacy of combining first-line chemotherapy with SIRT using yttrium-90 resin microspheres in patients with metastatic colorectal cancer with liver metastases (Wasan et al., 2017). The studies were designed for combined analysis of overall survival. Chemotherapy-naive patients with metastatic colorectal cancer 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 of any grade occurred in 244 patients receiving FOLFOX alone and 274 patients receiving FOLFOX plus SIRT. The authors concluded that the overall survival 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 patient populations and as a consolidation therapy after chemotherapy.

The metastatic colorectal cancer liver metastases outcomes after radioembolization (MORE) study was a retrospective analysis of 606 patients with unresectable colorectal liver metastases treated with radioembolization (RE) using 90Y-labeled resin microspheres. The first analysis of this study was completed with a last patient follow-up of 77.7 months.

The authors, Kennedy et al. (2017) provide an updated survival analysis, with a last patient follow-up of 125 months. All patients with a diagnosis of metastatic colorectal cancer 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 patients, and ~~overall survival (~~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. Patients received a median (range) of 2 lines of chemotherapy. Baseline characteristics and factors significantly associated with patient survival are consistent with those reported in the first safety analysis of the MORE study. These factors include poor 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 patients with unresectable metastatic colorectal cancer.

Van Hazel et al. (2016) evaluated SIRFLOX, a randomized, multicenter trial designed to assess the efficacy and safety of adding selective internal radiation therapy (SIRT) using yttrium-90 resin microspheres to standard fluorouracil, leucovorin, and oxaliplatin (FOLFOX)-based chemotherapy in patients with previously untreated metastatic colorectal cancer. Chemotherapy-naïve patients 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 ~~progression-free survival (~~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. ~~Objective response rates (~~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 adverse events, including recognized SIRT-related effects, were reported in 73.4% and 85.4% of patients in control versus SIRT. The authors concluded that the addition of SIRT to FOLFOX-based first-line chemotherapy in patients with liver-dominant or liver-only metastatic colorectal cancer did not improve PFS at any site but significantly delayed disease progression in the liver.

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A retrospective case-control study was conducted by Kennedy et al. (2015) which assessed 11 centers who treated liver dominant ~~metastatic colorectal cancer (~~mCRC~~)~~ using radioembolization (selective internal radiation therapy) with ~~yttrium-90 (~~90Y~~)~~-labeled resin microspheres. The study consisted of 606 consecutive patients who had liver-only, limited extra-hepatic metastases or primary in situ. The patients were followed up over 8.6 months from their first ~~radioembolization (~~RE~~)~~ procedure. A median of two 90Y-RE procedures were conducted for each patient. Median survivals differed significantly between patients receiving 90Y-RE as a 2nd-, 3rd-, and 4th+ line of treatment after chemotherapy: 13.0 months, 9.0 months, and 8.1 months, respectively. Survival was also significantly determined by the severity of liver dysfunction before 90Y-RE. The authors concluded that 90Y-RE appears to have a favorable risk/benefit profile and may offer clinicians a more targeted approach for the management of liver-dominant metastatic colorectal cancer.

Benson et al. (2013) investigated the safety, response rate, progression-free and overall survival of patients with liver metastases treated with glass ^{90}Y radioembolization in a prospective, multicenter phase II study. A total of 151 patients with liver metastases (colorectal n=61, neuroendocrine n=43 and other tumor types n=47) refractory to standard of care therapies were included. Clinical, laboratory and imaging follow-up were obtained at 30 days followed by 3-month intervals for 1 year and every 6 months thereafter. The primary ~~end-point~~**endpoint** was ~~progression-free survival (~~PFS~~)~~; secondary ~~end-points~~**endpoints** included safety, hepatic progression-free survival (HPFS), response rate and overall survival. Grade 3/4 adverse events included pain (12.8%), elevated alkaline phosphatase (8.1%), hyperbilirubinemia (5.3%), lymphopenia (4.1%), ascites (3.4%) and vomiting (3.4%). Disease control rates were 59%, 93% and 63% for colorectal, ~~neuroendocrine~~ **neuroendocrine,** and other primaries, respectively. Median PFS was 2.9 and 2.8 months for colorectal and other primaries, respectively. PFS was not achieved in the neuroendocrine group. Median survival from ^{90}Y treatment was 8.8 months for colorectal and 10.4 months for other primaries. Median survival for neuroendocrine patients has not been reached. Based on these results, three international, multicenter, randomized phase III studies in colorectal and hepatocellular carcinoma have been initiated.

Clinical Practice Guidelines ~~Professional Societies~~

American Society of Clinical Oncology (ASCO)

A 2020 guideline by ASCO recommends TARE in combination with systemic chemotherapy in second line setting or beyond in patients with CRC.

National Comprehensive Cancer Network (NCCN)

~~The National Comprehensive Cancer Network (~~**NCCN**~~)~~ **clinical practice guidelines for colon and rectal cancers state Yttrium-90 microsphere selective internal radiation ~~is~~are an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases. The use of arterial-directed therapies in highly selected patients 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, v1.2022; NCCN, Rectal, v1.2022).**

National Institute for Health and Care Excellence (NICE)

~~The National Institute for Health and Care Excellence (N~~NICE~~)~~ states that SIRT is a potentially beneficial treatment for patients 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 overall survival 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

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 ¼ 0.17), grade III/IV complication (5.9% vs 9.2%, p ¼ 0.58), or 90-day mortality. There was no difference in median overall survival (OS, 35.9 months vs 50.1 months, p ¼ 0.3) or progression-free survival (PFS, 15.9 months vs 19.9 months, p ¼ 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 patients treated with SIR-Spheres. Results were included in a systematic review and meta-analysis of published results with glass or resin microspheres. Objective response rate (ORR) was defined as complete or partial response. Disease control rate (DCR) was defined as complete/partial response or stable disease. Twenty-four patients were identified. ORR and DCR in the institutional series was 14/24 and 21/24 at 3 months. Overall survival 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 radioembolization for neuroendocrine liver metastases. Prospective randomized studies to compare radioembolization with other liver directed treatment modalities are needed.

Cramer et al. (2016) conducted a prospective longitudinal study to determine the effect of Y radioembolization therapy on health-related quality of life (HRQOL) in patients 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 radioembolization. Overall survival (OS) times were calculated from first Y using the Kaplan-Meier method and analyzed using the log-rank test. Thirty patients 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. Patients 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). Patients 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 patients 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 ~~selective internal radiation therapy~~ (SIRT) in patients with unresectable liver metastases from ~~neuroendocrine tumors (~~NETLMs~~)~~. In 40 patients, 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 Response Evaluation Criteria in Solid Tumors on CT or MR images. Medical records were reviewed. Objective tumor response and disease control rates 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 overall survival 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 patient 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 radioembolization with yttrium-90 (90Y) microspheres in cases with unresectable ~~neuroendocrine tumor liver metastases (~~NETLMs~~)~~ between April 2008 and June 2013. The primary neuroendocrine tumor site was the pancreas in seven patients (23%), small bowel in six patients (20%), large bowel/rectum in five patients (17%), bronchus in two patients (7%), and unknown in 10 patients (33%) The mean follow-up was 23.0±19.4 months and the median overall survival 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 patients. Before treatment, estimated liver involvement was 37% in 11 patients, 27% in eight patients, 30% in nine patients and 76%–100% in two patients. The authors concluded that the study demonstrates the effectiveness and safety of radioembolization for the treatment of 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 radioembolization in patients 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 didn't specify. The total number of procedures with response data was 435, in 414 patients. The pooled data demonstrated a weighted objective response rate of 50%, disease control rate of 86%, and improved overall survival for patients responding to therapy. The authors concluded that ^{90}Y resin radioembolization is an effective treatment option for patients with liver-dominant metastatic neuroendocrine tumors.

Cao et al. (2010) assessed the efficacy of ^{90}Y microsphere therapy for patients with unresectable ~~neuroendocrine tumor liver metastases (~~NETLMs~~)~~. Fifty-eight patients were included in a retrospective analysis, of which 51 were evaluable at follow-up. Six patients achieved a complete response, 14 a partial response, 14 had stable disease and 17 had disease progression. Overall survival rates at 1, 2 and 3 years were 86, 58 and 47 per cent respectively. Median survival was 36 months. Extent of tumor involvement, radiographic response to treatment, extrahepatic disease and tumor grade were significant prognostic factors for overall survival.

Clinical Practice Guidelines ~~Professional Societies~~

National Comprehensive Cancer Network (NCCN)

NCCN clinical practice guidelines for neuroendocrine tumors list hepatic regional therapy, such as radioembolization, as an option for treating unresectable liver metastases. The 2B recommendation is based on lower-level evidence, although there is consensus among NCCN panel members that the intervention is appropriate (NCCN, Neuroendocrine, v4.2021).

~~Clinical Practice Guidelines~~

~~*Agency for Healthcare Research and Quality (AHRQ)*~~

~~An Agency for Healthcare Research and Quality (AHRQ) report (2012) evaluated the comparative effectiveness of various local hepatic therapies for metastases to the liver from unresectable colorectal cancer (CRC) in two patient populations: patients with refractory liver-dominant metastases who are not eligible for continued systemic chemotherapy, and patients who are candidates for local liver therapies as an adjunct to systemic chemotherapy. Local hepatic therapies included those related to ablation, embolization (including radioembolization) and radiotherapy. Twenty-four studies reporting overall survival, quality of life and various adverse events were included. In the absence of comparative data, the evidence is insufficient to permit conclusions on the comparative effectiveness of these therapies for unresectable CRC metastases to the liver. Gaps in the research base, even for critical benefits or harms, are extensive, and the quality of studies is generally questionable. Conducting RCTs (ideally head-to-head comparisons) to answer many important questions is desirable, but challenging (Belinson et al., 2012).~~

~~*National Comprehensive Cancer Network (NCCN)*~~

~~The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for colon and rectal cancers state Yttrium-90 microsphere selective internal radiation is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases. The use of arterial-directed therapies in highly selected patients 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, v2.2021; NCCN, Rectal, v1.2021).~~

~~*National Institute for Health and Care Excellence (NICE)*~~

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Primary Hepatocellular Carcinoma (HCC)

A 2021b ECRI report evaluated TARE in comparison to other treatment modalities through systematic reviews and reported outcomes in patients with unresectable primary liver

tumors at different disease stages. The studies assessed consisted of 2 ~~systematic reviews (~~SR~~)~~ on TARE vs TACE,1 SR regarding radiation therapy vs. TARE, 2 SRs and 1 ~~randomized control trial (~~RCT~~)~~ on sorafenib vs. TARE, studies on TARE alone included 1 SR and 1 SR on patients with HCC, portal vein tumor thrombosis (PVT), and intrahepatic cholangiocarcinoma and treatment with TARE. Findings include no difference in adverse events (AE) between TARE and cTACE as well as TARE and DEB-TACE. In comparing TARE and Sorafenib for intermediate-locally advanced HCC the authors reported overall survival rate did not differ between treatment options. TARE vs. Sorafenib in patients with Intermediate-locally advanced and advanced HCC serious AEs occurred more often in the sorafenib group vs. the TARE group. For patients 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 patients with HCC and PVT treated with TARE, 3-dimensional conformal radiotherapy, or stereotactic body radiotherapy. Lastly, in comparing TARE in patients with HCC and PVT a median overall survival of 9.7 months after TARE in all patients with HCC with PVT was reported. –Limitations include differences in patient population, lack of generalization across studies or patients, high risk for bias due to heterogeneity in patient population, small size, and retrospective design. ––The authors conclude TARE for patients with HCC will improve overall survival rates compared to conventional TACE~~.~~ (ECRI, 2021b).

~~A 2021 Hayes Health Technology Assessment report compared clinically relevant outcomes following transarterial radioembolization (TARE) with yttrium-90 (90Y) with other locoregional therapies (LRTs) or sorafenib in patients with primary hepatocellular carcinoma (HCC) as a bridge to transplant or resection. A total of 8 studies met the inclusion criteria. All but 2 studies compared data retrospectively. The remaining studies consisted of 2 randomized controlled trials. Outcome measures included survival, tumor response, time to progression, 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 HCC patients to transplantation or resection. (Hayes, 2021).~~

~~A retrospective cohort (n=207) was conducted by Gabr et al. (2021) to evaluate the long-term outcomes of liver transplantation (LT) for patients with HCC who were bridged and downstaged using Y90. Long-term outcomes included overall survival (OS), recurrence-free survival (RFS), disease specific mortality (DSM), and time-to-recurrence. A total of 169 patients were bridged and 38 were downstaged to LT. OS rates at three-year, 5-year, and 10-year were 84%, 77%, and 60%, respectively. Twenty-four patients 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 patients who were bridged or downstaged. RFS was higher in patients 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.~~

Abdel-Rahman and Elsayed (2020) conducted a systematic review and meta-analysis on six ~~randomized controlled trials (~~RCTs~~)~~ (n=1340) to determine the benefits and harms of yttrium-90 microsphere radioembolization compared with placebo, no intervention, or other available interventions in people with advanced liver cancer. The primary outcomes

measured were median overall survival rate, quality of life and serious adverse events. Secondary outcomes measured were cancer-related mortality, time to progression of the tumor and tumor response. One RCT compared radioembolization plus sorafenib versus sorafenib alone in individuals with advanced hepatocellular carcinoma. The authors found very low-certainty evidence that radioembolization combined with sorafenib might be associated with higher rates of non-serious adverse events compared to sorafenib alone. The median overall survival was 11.4 months in the sorafenib group and 12.1 months in the radioembolization plus sorafenib group (HR 1.01, 95% CI 0.81 to 1.25; P = 0.95). Two RCTs compared radioembolization versus sorafenib for unresectable hepatocellular carcinoma in individuals with locally advanced hepatocellular carcinoma. There was a one-year mortality rate of 62% in the radioembolization group and 60% in the sorafenib group. The authors found low certainty evidence suggesting that radioembolization achieved overall survival and a disease control rate that was comparable to sorafenib alone. The risk of non-serious adverse events was lower with radioembolization. Three RCTs compared radioembolization 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 adverse events is similar between radioembolization and chemoembolization. (Author Salem et al. ~~(~~2016~~,)~~ which was previously **discussed** ~~cited~~ in this policy, is included in this review; Abdel-Rahman is **discussed** ~~cited~~ in Hayes, 2021).

A 2020 Hayes comparative effectiveness review compared clinically relevant outcomes following ~~transarterial radioembolization (~~TARE~~)~~ with yttrium-90 (90Y) versus outcomes following ~~transarterial chemoembolization (~~TACE~~)~~, drug eluting bead-TACE (DEB-TACE), and sorafenib in patients with primary unresectable ~~hepatocellular carcinoma (~~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 systematic reviews 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 (Hayes, 2020**; updated 2021**).

Katsanos et al. (2017) conducted a systematic review and network meta-analysis of different embolization options for unresectable ~~hepatocellular carcinoma (~~HCC~~)~~. Medical databases were searched for randomized controlled trials evaluating bland transarterial embolization (TAE), ~~transarterial chemoembolization (TACE), drug-eluting bead chemoembolization (~~DEBTACE~~)~~, or ~~transarterial radioembolization (~~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 patients 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 patient survival benefit compared to bland particle embolization ~~(~~TAE~~)~~. Combinations of TACE with external radiation or liver ablation achieved the best tumor response and patient 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 ECRI report)** was conducted ~~by Kallini et al. (2017)~~ to compare the safety profiles of TheraSphere® (glass) and SIR-Spheres® (resin) Y90 microspheres for the treatment of hepatocellular carcinoma. Baseline characteristics and adverse events of all grades related to gastrointestinal, hepatobiliary, and respiratory systems were collected. Thirty-one observational studies were included in the review. In the adverse events of all grades, more patients treated with resin microspheres reported gastric ulcers, hepatic encephalopathy, cholecystitis, hepatic failure, and pleural effusion. Patients treated with resin microspheres also had more hepatobiliary adverse events 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 adverse events compared to resin microspheres in the treatment of hepatocellular carcinoma.

~~Ettorre et al. (2017) retrospectively evaluated the efficacy of the Y90-radioembolization (RE) in patients with hepatocellular carcinoma (HCC) prior to liver transplantation (LT). The study included one hundred forty-three patients who were transplanted for HCC, and in 22 cases the patients were treated with Y90-RE before LT. Three patients were treated with Y90-RE within the Milan criteria, and 19 patients were out of criteria before Y90-RE. Four patients had an increasing MELD score between Y90-RE and LT. Alpha-fetoprotein decreased after Y90-RE treatment in all cases. No patient 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 overall survival 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 in patients 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 patients who traditionally are not considered eligible for surgery.~~

A systematic review and meta-analysis was conducted by Lobo et al. (2016) to compare clinical outcomes of transarterial radioembolization ~~(~~TARE~~)~~ to transarterial chemoembolization ~~(~~TACE~~)~~ for treatment of unresectable hepatocellular carcinoma ~~(~~HCC~~)~~. Primary outcome was overall survival rate for up to 4 years. Secondary outcomes included post-treatment complications and treatment response. The search strategy yielded 172 studies, five met selection criteria and included 553 patients with unresectable HCC, 284 underwent TACE and 269 underwent TARE. Meta-analysis showed no statistically significant difference in survival for up to 4 years between the two groups. TACE required at least one day of hospital stay compared to TARE which was mostly an outpatient procedure. TACE had more post-treatment pain than TARE, but less subjective fatigue. There was no difference between the two groups in the incidence of post-treatment nausea, vomiting, fever, or other complications. In addition, there was no difference in partial or complete response rates between the two groups. TARE appears to be a safe alternative

treatment to TACE with comparable complication profile and survival rates. Larger prospective randomized trials, focusing on patient-reported outcomes and cost-benefit analysis are required to consolidate these results.

Zhang et al. (2015) conducted a meta-analysis to evaluate the safety and efficacy of ~~transarterial radioembolization (~~TARE~~)~~ versus ~~transarterial chemoembolization (~~TACE~~)~~ for unresectable ~~hepatocellular carcinoma (~~HCC~~)~~. PubMed, EMBASE, Web of science and the Cochrane Library were searched for clinical trials comparing TARE with TACE for unresectable HCC. Response rate, ~~overall survival (~~OS~~)~~, time to progression (TTP), hospitalization time days and clinical complications were analyzed and compared. Seven case control studies and one cohort study were eligible for inclusion criteria. A total of 1,499 patients were included among the eight studies, with 451 patients in the TARE group and 1,048 patients in TACE group. The meta-analysis showed that the OS was significantly better in the TARE with Y90 group than in the TACE group. It demonstrated a 26% reduction in the risk of death in patients treated with TARE. The time to progression was significantly better in the TARE with Y90 group than in the TACE group. The hospitalization time days were significantly shorter in the TARE with Y90 group than in the TACE group. For over-all tumor control, the meta-analysis of case control studies suggested that the patients in the TARE group had a significantly better response than those in the TACE ~~group~~**group,** but the pooled response rate of the cohort study favored the TACE group. The TARE treatments lead to lower abdominal pain than TACE. The authors concluded that the current meta-analysis suggested that TARE (Y90) is significantly better in OS, 3-year OS rates, TTP, hospitalization time days and some complications for patients with HCC. The use of TARE (Y90) for HCC patients is promising. They suggest that further multi-center, well-designed RCTs are needed to improve the treatment benefits for HCC patients.

~~An Agency for Healthcare Research and Quality (AHRQ) report (2013) evaluated the comparative effectiveness of various local hepatic therapies for patients with unresectable primary hepatocellular carcinoma (HCC) who are not candidates for surgical resection or liver transplantation. Local hepatic therapies included those related to ablation, embolization (including radioembolization) and radiotherapy. Forty-eight studies reporting overall survival, quality of life and various adverse events were included. Of the 13 interventions included in the report, only 1 comparison had sufficient evidence to receive a rating above insufficient and it did not include radioembolization. For all other outcomes and comparisons, there was insufficient evidence to permit conclusions on the comparative effectiveness of local hepatic therapies for unresectable HCC. Additional randomized controlled trials are necessary for all comparisons (Belinson et al., 2013).~~

~~In a retrospective case-control study, Moreno-Luna et al. (2012) compared the outcomes and safety of transarterial radioembolization (TARE) versus transarterial chemoembolization (TACE) in patients with unresectable hepatocellular carcinoma (HCC). Sixty-one patients treated with TARE were retrospectively matched by age, sex~~**sex,** ~~and liver dysfunction with 55 TACE-treated patients. Complete tumor response was more common after TARE (12%) than after TACE (4%). When complete response was combined with partial response and stable disease, there was no difference between TARE and TACE. Median survival did not differ between the two groups (15.0 months for TARE and 14.4 months for TACE). Two-year survival rates were 30% for TARE and 24% for TACE. TARE patients reported more fatigue but had less fever than TACE patients. Treatment with TARE required less hospitalization than treatment with TACE.~~

Xie et al. (2012) performed a meta-analysis comparing the efficacy of ~~transcatheter arterial chemoembolization (~~TACE~~)~~ and microsphere embolization for treating unresectable ~~hepatocellular carcinoma (~~HCC~~)~~. Thirteen studies were included in the evaluation. A total of 597 patients were treated with microsphere embolization and 1,233 patients with chemoembolization. The data showed that microsphere embolization therapy was significantly better for longer overall survival, 1-year survival, longer time to progression and complete or partial response rate than that of chemoembolization treatment.

Sangro et al. (2011) conducted a multicenter analysis to evaluate the main prognostic factors driving survival after radioembolization using ^{90}Y resin microspheres in patients with hepatocellular carcinoma. In total, 325 patients were treated, predominantly as whole-liver (45.2%) or right-lobe (38.5%) infusions. The median overall survival was 12.8 months (10.9-15.7), which varied significantly by disease stage, Eastern Cooperative Oncology Group (ECOG) performance status, hepatic function, tumor burden and presence of extrahepatic disease. The most significant independent prognostic factors for survival were ECOG status, tumor burden (nodules >5), international normalized ratio >1.2, and extrahepatic disease. Common adverse events ~~were:~~were fatigue, nausea/vomiting, and abdominal pain. Grade 3 or higher increases in bilirubin were reported in 5.8% of patients. All-cause mortality was 0.6% and 6.8% at 30 and 90 days, respectively. The authors concluded that this analysis provides robust evidence of the survival achieved with radioembolization, including those with advanced disease and few treatment options.

Clinical Practice Guidelines ~~Professional Societies~~

American Association for the Study of Liver Diseases (AASLD)

The AASLD developed guidance regarding the diagnosis, staging, and treatment of patients with ~~hepatocellular carcinoma (~~HCC~~)~~. For cirrhotic patients with HCC of T2 or T3 stage and no vascular involvement who are not candidates for transplantation or resection, the AASLD recommends a locoregional therapy over no treatment; the strength of the recommendation was strong, but TARE was given very-low-quality evidence rating compared with moderate for ~~transarterial chemoembolization (~~TACE~~)~~. No form of locoregional control was recommended over another, but the recommendation was conditional and based on a very-low overall level of evidence. The AASLD did not issue guidance regarding the use of locoregional therapies for HCC versus systemic therapy, due to the lack of evidence to inform the balance of benefits and harms in patients with macrovascular invasion and/or metastatic disease (Heimbach et al., 2018); Marrero et al., 2018).

American College of Radiology (ACR), the American Brachytherapy Society (ABS), the American College of Nuclear Medicine (ACNM), the American Society for Radiation Oncology (ASTRO), the Society of Interventional Radiology (SIR), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI)

A 2021 Practice parameter was developed for ~~selective internal radiation therapy (~~SIRT~~)~~ **or radioembolization for treatment of liver malignancies. The practice parameter for SIRT or radioembolization for treatment of liver malignancies was updated according to processes on the ACR website by the committee of Practice Parameters Interventional and Cardiovascular Radiology of the ACR Commission on Interventional and Cardiovascular, Committee on Practice Parameters and Technical Standards-Nuclear Medicine and Molecular Imaging of the ACR Commission on Nuclear Medicine and Molecular Imaging and the Committee on Practice Parameters-Radiation Oncology of the ACR Commission on Radiation Oncology in collaboration with ABS, ACNM, ASTRO, SIR, and SNMMI. The purpose of the practice**

parameter is to serve as a tool in the proper application of radioembolization which focuses on best practices and principles for the effective utilization of radioembolization. The practice parameter includes clinical implementation from personnel qualifications, quality assurance standards, indications, and recommended documentation.

A 2019 Practice parameter for ~~selective internal radiation therapy (~~SIRT~~)~~ or radioembolization for treatment of liver malignancies states that the treatment goal of radioembolization should be tailored to the individual patient, whether it is palliative or a bridge to surgical resection or liver transplantation. The most common clinical utility of radioembolization is in the treatment of HCC and liver-dominant metastatic CRC and neuroendocrine tumors.
Indications are not limited to the following:

- The presence of unresectable or inoperable primary or secondary liver malignancies (particularly CRC and NET metastases).
- The tumor burden should be liver dominant, not necessarily exclusive to the liver.
- Patients should also have a performance status that will allow them to benefit from such therapy.
- A life expectancy of at least 3 months.

American Hepato-Pancreato-Biliary Association, the Society of Surgical Oncology, the Society for Surgery of the Alimentary Tract

Schwarz et al. (2010) published the statements of the Consensus Conference on Multidisciplinary Treatment of Hepatocellular Carcinoma sponsored by the American Hepato-Pancreato-Biliary Association and co-sponsored by the Society of Surgical Oncology and the Society for Surgery of the Alimentary Tract. The consensus document reviewed the four most widely used modalities for treating advanced ~~disease: (TACE~~disease: TACE~~)~~, sorafenib, external beam radiation therapy and microsphere radioembolization. The consensus on ^{90}Y microspheres includes the following:

- ^{90}Y is a safe microembolization treatment and can be administered in the outpatient setting.
- ^{90}Y could be considered for treating hepatocellular carcinoma in the following scenarios:
  - Downstaging/bridging to transplantation or resection
  - Portal vein thrombosis
  - Advanced disease

There are no level 1 data for ^{90}Y compared to other regional therapies. Considerations of efficacy and safety (given cirrhosis) must be made on an individual basis.

National Comprehensive Cancer Network (NCCN)

NCCN clinical practice guidelines for hepatobiliary cancers state that all hepatocellular carcinomas, irrespective of their location in the liver, may be amenable to embolization (chemoembolization, bland embolization, radioembolization with yttrium-90 microspheres) provided that the arterial blood supply to the tumor may be isolated without excessive non-target treatment. General patient selection criteria for embolization procedures include unresectable/inoperable disease with tumors not amenable to ablation therapy only, and the absence of large-volume extrahepatic disease. Patients with unresectable/inoperable disease, who are eligible to undergo embolization therapy and have tumor lesions > 5 centimeters (cm), should be considered for treatment using arterial embolic approaches. Those patients with lesions 3–5 cm can be considered for combination therapy with ablation and arterial embolization (NCCN, hepatobiliary v5.2021).

National Institute for Health and Care Excellence (NICE)

~~The National Institute for Health and Care Excellence (~~**NICE**~~)~~ **recommends the use of** ~~selective internal radiation therapy (~~SIRT~~)~~ **SIR-Spheres, and SIRT TheraSphere as an option for treating unresectable advanced** ~~hepatocellular carcinoma (~~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).**

Radioembolization Brachytherapy Oncology Consortium (REBOC)

In 2007, REBOC, an independent group of experts from the fields of interventional radiology, radiation oncology, nuclear medicine, medical ~~oncology~~**oncology, and surgical oncology issued clinical guidelines for ^{90}Y microsphere brachytherapy with the purpose to standardize the indications, techniques, multimodality treatment approaches and dosimetry to be used for ^{90}Y microsphere hepatic brachytherapy. The recommendations state that success in treatment of tumors in the liver by radioembolization relies on the presence of appropriate indications to ensure that patients receive safe and effective therapy. Because the nature of primary and secondary hepatic malignancies differs, therapy should be tailored to the disease. Patients with hepatic metastases from primary sites other than colorectal should be offered standard systemic treatment options with known survival benefit before ^{90}Y treatment. In the case of primary liver tumors, patients should undergo a thorough evaluation to determine the optimal treatment strategy.**

Key findings include the following:

- **Sufficient evidence exists to support the safety and effectiveness of ^{90}Y microsphere therapy in selected patients.**
- **Candidates for radioembolization are patients with unresectable primary or metastatic hepatic disease with liver-dominant tumor burden and a life expectancy >3 months.**

- **In metastatic colorectal cancer, radioembolization therapy can be given**
- **(1) alone after failure of first-line chemotherapy,**
- **—(2) with floxuridine (FUDR) during first-line therapy or**
- **(3) during first- or second-line chemotherapy on a clinical trial.**

Initiation of clinical trials is essential to further define the safety and role of ^{90}Y microspheres in the context of currently available therapies (Kennedy et al., 2007).

~~The National Institute for Health and Care Excellence (NICE) states that TheraSphere could be used to treat patients with operable and inoperable HCC, as an alternative or adjunct to 1 of several options currently offered (including liver resection, transplantation, local ablation, chemoembolisation and transcatheter therapies, and systemic therapies), depending on multiple factors including the patient's general health and tumor stage. The evidence from 11 studies summarized in the briefing is of mixed quality and shows that patients treated with TheraSphere do not show significantly different overall survival times compared with those treated with conventional transarterial chemoembolisation (TACE) with lipiodol (NICE, 2016[WRM1]).~~

~~Lau et al. (2011) reviewed the role of SIRT with ^{90}Y microspheres for hepatocellular carcinoma (HCC). The evidence was limited to cohort studies and comparative studies with historical controls. The authors concluded that ^{90}Y 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 patients with associated comorbidities who have otherwise excisable tumors but are not candidates for surgery.~~

~~Schwarz et al. (2010) published the statements of the Consensus Conference on Multidisciplinary Treatment of Hepatocellular Carcinoma sponsored by the American Hepato-Pancreato-Biliary Association and co-sponsored by the Society of Surgical Oncology and the Society for Surgery of the Alimentary Tract. The consensus document reviewed the four most widely used modalities for treating advanced disease: transarterial chemoembolization (TACE), sorafenib, external beam radiation therapy and microsphere radioembolization. The consensus on ^{90}Y microspheres includes the following:~~

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  - ~~Advanced disease~~

~~There are no level 1 data for ^{90}Y compared to other regional therapies. Considerations of efficacy and safety (given cirrhosis) have to~~must be made on an individual basis.~~

~~Clinical Practice Guidelines~~

~~*National Comprehensive Cancer Network (NCCN)*~~

~~National Comprehensive Cancer Network (NCCN) clinical practice guidelines for hepatobiliary cancers state that all hepatocellular carcinomas, irrespective of their location in the liver, may be amenable to embolization (chemoembolization, bland embolization, radioembolization with yttrium-90 microspheres) provided that the arterial blood supply to the tumor may be isolated without excessive non-target treatment. General patient selection criteria for embolization procedures include unresectable/inoperable disease with tumors not amenable to ablation therapy only, and the absence of large-volume extrahepatic disease. Patients with unresectable/inoperable disease, who are eligible to undergo embolization therapy and have tumor lesions > 5 centimeters (cm), should be considered for treatment using arterial embolic approaches. Those patients with lesions 3-5 cm can be considered for combination therapy with ablation and arterial embolization (NCCN, hepatobiliary v~~51~~.2021).~~

~~Liver Metastases from Neuroendocrine Tumors~~

~~A retrospective, multi-institutional review of literature comparison of individuals with unresectable neuroendocrine liver metastases (NELM) undergoing transarterial chemoembolization (TACE) (n=197) versus transarterial radioembolization (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 ¼ 0.17), grade III/IV complication (5.9% vs 9.2%, p ¼ 0.58), or 90-day mortality. There was no difference in median overall survival (OS, 35.9 months vs 50.1 months, p ¼ 0.3) or progression-free survival (PFS, 15.9 months vs~~

~~19.9 months, p ¼ 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 systematic review and meta-analysis of published literature was conducted by Devcic et al. (2014) to evaluate the efficacy of (90)Y resin radioembolization in patients 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 didn't specify. The total number of procedures with response data was 435, in 414 patients. The pooled data demonstrated a weighted objective response rate of 50%, disease control rate of 86%, and improved overall survival for patients responding to therapy. The authors concluded that ^{90}Y resin radioembolization is an effective treatment option for patients with liver-dominant metastatic neuroendocrine tumors.~~

~~Cramer et al. (2016) conducted a prospective longitudinal study to determine the effect of Y radioembolization therapy on health-related quality of life (HRQOL) in patients with neuroendocrine tumor liver metastases (NETLM). Baseline Short-Form 36 HRQOL scores were evaluated for significant change at 1, 3, 6, 12, and 24 months3-, 6-, 12-, and 24-months following Y radioembolization. Overall survival (OS) times were calculated from first Y using the Kaplan-Meier method and analyzed using the log-rank test. Thirty patients 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. Patients 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). Patients 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 patients 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 selective internal radiation therapy (SIRT) in patients with unresectable liver metastases from neuroendocrine tumors (NETLMs). In 40 patients, 54 evaluable SIRT procedures were performed;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 Response Evaluation Criteria in Solid Tumors on CT or MR images. Medical records were reviewed. Objective tumor response and disease control rates 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 overall survival 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 patient 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 radioembolization with yttrium-90 (90Y) microspheres in cases with unresectable neuroendocrine tumor liver metastases (NETLMs) between April 2008 and June 2013. The primary neuroendocrine tumor site was the pancreas in seven patients (23%), small bowel in six patients (20%), large bowel/rectum in five patients (17%), bronchus in two patients (7%), and unknown in 10 patients (33%) The mean follow-up was 23.0±19.4 months and the median overall survival 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 patients. Before treatment, estimated liver involvement was 37% in 11 patients, 27% in eight patients, 30% in nine patients and 76%-100% in two patients. The authors concluded that the study demonstrates the effectiveness and safety of radioembolization for the treatment of unresectable NETLMs.~~

~~A systematic review and meta-analysis of published literature was conducted by Deveic et al. (2014) to evaluate the efficacy of (90)Y resin radioembolization in patients 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 didn't specify. The total number of procedures with response data was 435, in 414 patients. The pooled data demonstrated a weighted objective response rate of 50%, disease control rate of 86%, and improved overall survival for patients responding to therapy. The authors concluded that ^{90}Y resin radioembolization is an effective treatment option for patients with liver-dominant metastatic neuroendocrine tumors.~~

~~Cao et al. (2010) assessed the efficacy of ^{90}Y microsphere therapy for patients with unresectable neuroendocrine tumor liver metastases (NETLMs). Fifty-eight patients were included in a retrospective analysis, of which 51 were evaluable at follow-up. Six patients achieved a complete response, 14 a partial response, 14 had stable disease and 17 had disease progression. Overall survival rates at 1, 2 and 3 years were 86, 58 and 47 per cent respectively. Median survival was 36 months. Extent of tumor involvement, radiographic response to treatment, extrahepatic disease and tumor grade were significant prognostic factors for overall survival.~~

~~*National Comprehensive Cancer Network (NCCN)*~~

~~NCCN clinical practice guidelines for neuroendocrine tumors list hepatic regional therapy, such as radioembolization, as an option for treating unresectable liver metastases. The 2B recommendation is based on lower-level evidence, although there is consensus among NCCN panel members that the intervention is appropriate (NCCN, Neuroendocrine, v~~4~~2.2020)~~1~~).~~

Intrahepatic Cholangiocarcinoma

Schartz et al. (2022) conducted a systematic review and meta-analysis using a random effects model ~~describing~~to assess the use of Y-90 for unresectable intrahepatic cholangiocarcinoma (ICC). The study evaluated CA19-9 response rate, disease control rate (DCR), down staged to resectable rate, pooled ~~overall median survival (OS)~~, pooled median progression free survival (PFS), and mean reported survival rates between 3 and 36 months. A total of 921 patients were included from 21 studies. The outcomes showed an 82.3% overall DCR, 11% of patients 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 radioembolization 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 radioembolization 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 ~~intrahepatic cholangiocarcinoma (~~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 patients (17.3%) had successful tumor downsizing; based on treatment modality. Tumor downsizing rates ranged from 13.9% (transarterial chemoembolization alone) to 20.8% (transarterial radioembolization alone). Twenty-seven patients 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) radioembolization in individuals with unresectable ~~intrahepatic cholangiocarcinoma (~~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 patients treated with resin microspheres was 10 months and the median follow-up of patients 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 patients were able to undergo curative-intent resection after 90Y radioembolization (4%). The authors concluded that 90Y radioembolization was observed to be safe in a large cohort of patients. The OS in patients with ICC treated with 90Y radioembolization 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 patients with unresectable, chemotherapy-refractory ICC who were treated with ~~transarterial radioembolization (~~TARE~~)~~. Primary outcome was overall survival. Secondary outcomes included safety, ~~progression free survival (~~PFS~~)~~, and liver-specific progression-free survival (LPFS). The study included sixty-one patients; 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). Overall survival was 8.7 months (95% CI, 5.3-12.1), and 37% of patients 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 patients experienced a total of 49 adverse events, of which 8% were grade ≥3; most common were grade 1-2 fatigue and abdominal pain. Patients 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 patient cohort in a larger study, including collection of patient-reported outcomes.

A retrospective study was conducted by Jia et al. (2017b) on patients who underwent resin-based yttrium-90 (90Y) therapy for unresectable and failed first-line chemotherapy ~~intrahepatic cholangiocarcinoma (~~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 radioembolization for unresectable and failed first-line chemotherapy (cisplatin plus gemcitabine) ICC. Twenty-four patients were included in this study. Mean 5.6 ± 1.6 cycles of first-line chemotherapy were performed prior to 90Y treatment. There ~~were~~ **was** a total of 27 treatments of 90Y. Disease control rate 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 patient. 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~~**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 radioembolization can provide palliative control of unresectable and failed first-line chemotherapy ICC with acceptable side effects.

In a single-center study, Mosconi et al. (2016) retrospectively analyzed the data of 23 consecutive patients with intrahepatic cholangiocarcinoma (ICC) undergoing 90Y-TARE between July 2010 and September 2015. The aim of the study was to assess overall survival (OS), tumor response and the safety of radioembolization with yttrium-90 (90Y-TARE). After 90Y-TARE, the patients were regularly evaluated at 1 and 3 months, and thereafter at 3-month intervals. At each visit, the clinical and toxicity data were recorded, and CT or MRI was performed. Survival was calculated from the date of the 90Y-TARE procedure. Target and overall ~~Response Evaluation Criteria in Solid Tumors (~~RECIST~~)~~, modified RECIST (mRECIST) and the European Association for the Study of the Liver (EASL) treatment responses were assessed. Significantly prolonged OS was recorded for patients with a response based on mRECIST and EASL criteria while RECIST responses were not found to be associated with survival. The overall median survival was 17.9 months. The cumulative survival rate was 67.9% at 1 year and 20.6% at 2 years. The authors concluded that in unresectable ICC, 90Y-TARE is safe and offers a survival benefit. They identified a number of study limitations.

Al-Adra et al. (2015) systematically reviewed the existing literature surrounding treatment of unresectable ~~intrahepatic cholangiocarcinoma (~~ICC~~)~~ with yttrium-90 microspheres. A comprehensive search of electronic databases for ICC treatment was performed and 12 primary studies meeting the inclusion criteria were identified. These included seven prospective case series and five retrospective cohort studies with relevant data regarding radioembolization therapy with yttrium-90 microspheres. A total of 298 patients were assessed with a median follow-up of 10.8 months. Most of the patients previously received chemotherapy (54%) and/or underwent surgical resection (33%). The overall weighted median survival was 15.5 months. Tumor response based on radiological studies demonstrated a partial response in 28% and stable disease in 54% of patients at three months. The ability to offer surgical resection to previously unresectable disease was reported in three studies (n=73) and surgery was performed on seven patients post-radioembolization. The most common types of morbidity following radioembolization therapy with yttrium-90 microspheres were fatigue (33%), abdominal pain (28%) and nausea (25%). The authors concluded that the overall survival of patients with ICC after treatment with yttrium-90 microspheres is higher than historical survival rates and shows similar survival to those patients treated with systemic chemotherapy and/or trans-arterial chemoembolization therapy. They state that the use of yttrium-90 microspheres could be considered as a treatment option for ICC. Future randomized trials comparing systemic chemotherapy, TACE and local radiation will be required to identify the optimal treatment modality for unresectable ICC.

Clinical Practice Guidelines ~~Professional Societies~~

National Comprehensive Cancer Network (NCCN)

NCCN clinical practice guidelines for hepatobiliary cancers state that locoregional therapies such as TARE with yttrium-90 microspheres have been shown to be safe and effective option in patients with unresectable intrahepatic cholangiocarcinomas (NCCN, Hepatobiliary v5.2021).

National Institute for Health and Care Excellence (NICE)

~~National Institute for Health and Care Excellence (NICE)~~

~~The National Institute for Health and Care Excellence (~~**NICE**~~)~~ **interventional procedures guidance for selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma recommendations state that the current evidence on the safety of** ~~selective internal radiation therapy (~~**SIRT**~~)~~ **for unresectable primary intrahepatic cholangiocarcinoma 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 randomized controlled trials, should address patient selection, quality-of-life outcomes and overall survival. 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 2021 Hayes Health Technology Assessment report compared clinically relevant outcomes following ~~transarterial radioembolization (~~**TARE**~~)~~ **with yttrium-90 (90Y) with other locoregional therapies (LRTs) or sorafenib in patients with primary** ~~hepatocellular carcinoma (~~**HCC**~~)~~ **as a bridge to transplant or resection. A total of 8 studies met the inclusion criteria. All but 2 studies compared data retrospectively. The remaining studies consisted of 2 randomized controlled trials. Outcome measures included survival, tumor response, time to progression, 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 HCC patients to transplantation or resection.~~ **(Hayes, 2021).**

A retrospective cohort (n=207) was conducted by Gabr et al. (2021) to evaluate the long-term outcomes of liver transplantation (LT) for patients with HCC who were bridged and ~~downstaged~~**down staged using Y90. Long-term outcomes included** ~~**overall survival (OS)**~~**, recurrence-free survival (RFS), disease specific mortality (DSM), and time-to-recurrence. A total of 169 patients were bridged and 38 were** ~~**downstaged**~~**down staged to LT. OS rates at three-year, 5-year, and 10-year were 84%, 77%, and 60%, respectively. Twenty-four patients 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 patients who were bridged or** ~~**downstaged**~~**down staged. RFS was higher in patients 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) retrospectively evaluated the efficacy of the Y90-radioembolization (RE) in patients with hepatocellular carcinoma (HCC) prior to ~~liver transplantation (~~**LT**~~)~~**. The study included one hundred forty-three patients who were transplanted for HCC, and in 22 cases the patients were treated with Y90-RE before LT. Three patients were treated with Y90-RE within the Milan criteria, and 19 patients were out of criteria before Y90-RE. Four patients had an increasing MELD score between Y90-RE and LT. Alpha-fetoprotein**

decreased after Y90-RE treatment in all cases. No patient 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 overall survival 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 in patients 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 patients who traditionally are not considered eligible for surgery.

Lau et al. (2011) reviewed the role of SIRT with ^{90}Y microspheres for ~~hepatocellular carcinoma (~~HCC~~)~~. The evidence was limited to cohort studies and comparative studies with historical controls. The authors concluded that ^{90}Y 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 patients with associated comorbidities who have otherwise excisable tumors but are not candidates for surgery.

Liver Metastases from Other Primary Sites

There is limited evidence suggesting that treatment with ~~transarterial radioembolization (~~TARE~~)~~ using yttrium-90 (90Y) microspheres for other indications is effective. Randomized controlled trials are needed to determine the clinical utility of this treatment.

Alexander et al. (2022) conducted a systematic review regarding selective internal radiation therapy for hepatic metastases of uveal melanoma (UM) to assess the effectiveness and safety of ~~selective internal radiation therapy (~~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 in patients with UM and one hepatic metastasis. Data was collected on overall survival (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 patients with hepatic metastases from UM using 11 studies. 170 patients 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.
~~2022~~

A single institution retrospective cohort study (n=26) was conducted by Kayaleh et al.~~,~~ (202**0**~~1~~) to evaluate the safety, efficacy, and overall survival rate of individuals with liver dominant metastatic pancreatic cancer treated with TARE with ~~yttrium-90 (~~Y-90~~)~~. The median overall survival from diagnosis was 33 months, from diagnosis of liver metastasis was 21.8 months and after TARE treatment with Y-90 was 7 months. The median hepatic progression-free survival was 2.7 months. Mild adverse events 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 Y-90 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.

A systematic review (Feretis and Solodkyy ~~(~~2020**, included in the 2021a ECRI report**) **was conducted** ~~conducted a systematic review~~ to assess the effect of radioembolization with yttrium-90 on tumor response and to estimate patient survival post radioembolization 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. Disease control rates varied from 48%-100% with an estimated mean response to TARE of 81%. Overall survival 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 randomized controlled trials and the retrospective nature of the studies included carried the risk of selection bias. Future randomized trials are needed comparing treatments. ~~(Cited in ECRI, 2021).~~

A systematic review was performed by Rowcroft et al. (2020) to review the evidence for the management of uveal melanoma (UM) liver metastases. The primary outcome was overall survival, with disease free survival as a secondary outcome. Fifty-five studies were included (n=2446) with 39 retrospective cohort studies, two randomized controlled trials and 14 prospective cohort studies. Treatment modalities included surgery, isolated hepatic perfusion (IHP), hepatic artery infusion (HAI), ~~transarterial chemoembolization (~~TACE~~)~~, ~~selective internal radiotherapy (~~SIRT~~)~~ and i~~I~~mmunoembolization (IE). Ten studies evaluated surgical resection. Median ~~overall survival (~~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. Immunoembolization (IE) had a median OS of 21 ~~months .The~~**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.

A systematic review (Jia et al. 2017a, included in the 2021a ECRI report) was conducted to assess the effectiveness of yttrium-90 (^{90}Y) radioembolization in the treatment of unresectable liver metastases of melanoma. A total of 12 reports (7 observational studies and 5 abstracts from conferences) involving 255 patients 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 disease control rate at 3 months was 73.6%. Among the 207 patients 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 radioembolization were reported in 13 cases. The most common side effects were fatigue), abdominal pain, and nausea. The authors concluded that ^{90}Y radioembolization 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.

A large single center study by Fendler et al. (2016) evaluated safety, ~~efficacy~~ **efficacy,** and prognostic factors for (90)Y-Yttrium microsphere ~~radioembolization (~~RE~~)~~ of unresectable liver metastases from breast cancer (BRCLM). Eighty-one patients underwent whole-liver (WL) radioembolization by application of SIR-spheres (SIRTEX Medical). After radioembolization, all patients were monitored for 3 days as inpatients for acute toxicity. Late toxicity was evaluated in all patients until 12 weeks after first

radioembolization. The primary endpoint was ~~overall survival (~~OS~~)~~ after radioembolization. OS was defined as the interval between date of radioembolization 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 radioembolization-induced liver disease (REILD) occurred in ≤10% of patients. Two patients 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 overall survival 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 patients 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.

Kuei et al. (2015) conducted a systematic review to evaluate the effects of Yttrium-90 radioembolization 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 radioembolization were included for review. Of the studies on ~~selective internal radiation therapy (~~SIRT~~)~~ of non-conventional liver metastases, breast cancer is the most studied. This review found 7 exclusively ~~breast cancer liver metastases (~~BRCLM~~)~~ SIRT studies in addition to 3 mixed primary studies that provide response data. Response rates were between 18%-61% and median overall survival 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 patient cohorts. ~~In order to~~**To** validate SIRT as a potential first-line adjuvant to chemotherapy, larger multicenter randomized control studies are needed. Eight ~~intrahepatic cholangiocarcinoma (~~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 overall survival 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 ~~hypervascular~~ **hypervascularity** and aggressive nature of melanoma liver metastases, treatment with SIRT appears to be a reasonable approach at reducing disease progression. Median overall survival 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 locoregional therapies 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~~ **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 patient selection criteria for optimal patient outcome. Experience with locoregional therapies 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 patients

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 ~~looked into~~ **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 or not~~whether Yttrium-90 SIRT provides a justifiable benefit to any given patient relies tremendously on both tumor type and patient status. Larger, multi-centered randomized controlled studies are needed so that established clinical guidelines can develop that ultimately improve patient outcomes.

Smits et al. (2013) provided a systematic overview of the current literature concerning ^{90}Y microspheres for ~~breast cancer liver metastases (~~BCLM~~)~~ patients. Six studies were included for analysis, with a total of 198 patients. Tumor response was scored in five studies using either ~~Response Evaluation Criteria In Solid Tumors (~~RECIST~~)~~ (n=3) or World Health Organization (WHO) criteria (n=2). Overall disease control rates (complete response, partial ~~response~~ **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 patients (5%) and treatment related mortality in three patients (2%). The authors concluded that the results from the analyzed studies consistently show that ^{90}Y is a safe and effective treatment option for BCLM patients. According to the authors, well designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes of ^{90}Y for BCLM patients.

Clinical Practice Guidelines ~~Professional Societies~~

National Comprehensive Cancer Network (NCCN)

~~National Comprehensive Cancer Network (NCCN)~~**The National Comprehensive Cancer Network ~~(~~NCCN~~)~~ clinical practice guidelines on uveal melanoma reviewed multiple retrospective studies and one prospective phase II study which reported results for patients with liver metastases from uveal melanoma treated with hepatic radioembolization. Response rates from the retrospective studies varied widely (6%–100%), but disease control rate was consistently greater than 50%. The phase II study** reported ~~objective response rate (ORR)~~ **of 39% in the 23 patients who received radioembolization as first-line treatment for liver metastasis, and ORR of 33% in the 24 patients who received radioembolization after progression on immunoembolization. The disease control rate was 87% and 58%, respectively. They concluded that radioembolization was well tolerated, with most toxicities being grade 1–2 and self-limiting, and no treatment-related deaths (NCCN, Uveal, v2. 2021).**

~~Kucuk et al. (2011) evaluated the success of SIRT with 90Y microspheres in liver metastases of different tumors. Seventy-eight patients (49 M; 29 F; mean age: 62.4 ± 2.3 years) received intraarterial radionuclide therapy with 90Y microspheres for liver metastasis or primary hepatocellular carcinoma (HCC). Twenty-five patients had primary HCC. The remaining patients had unresectable multiple liver metastases of different~~

~~cancers (35 colorectal, 7 gastric, 4 breast, 1 pancreas, 1 renal cell, 1 esophagus cancer, 3 neuroendocrine tumor and 1 malignant melanoma). Treatment response was evaluated by fluorine-18 fluorodeoxyglucose (F18-FDG) positron emission tomography/computed tomography (PET/CT) six weeks after treatment. Patients were divided into two groups according to the disease stage;~~stage: ~~those with only liver metastases (H) and those with metastases in other organs (EH). In the evaluation of treatment response, 43(55%) patients were responders (R) and 35 (45%) patients were non-responders (NR). The mean overall survival time of the R group was calculated as 25.63 ± 1.52 months and the NR group's 20.45 ± 2.11. The mean overall survival time of the H group was computed as 25.66 ± 1.52 months and the EH group's 20.76 ± 1.97. The authors concluded that SIRT is a useful treatment method which can contribute to the lengthening of survival times in patients with primary or metastatic unresectable liver malignancies. F18-FDG PET/CT is seen to be a successful imaging method in evaluating treatment response for predicting survival times in this patient group. Larger, prospective, randomized studies are needed to confirm these results.~~

~~Clinical Practice Guidelines~~

~~*National Comprehensive Cancer Network (NCCN)*~~

~~The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on uveal melanoma reviewed multiple retrospective studies and one prospective phase II study which reported results for patients with liver metastases from uveal melanoma treated with hepatic radioembolization. Response rates from the retrospective studies varied widely (6%-100%), but disease control rate was consistently greater than 50%. The phase II study reported objective response rate (ORR) of 39% in the 23 patients who received radioembolization as first-line treatment for liver metastasis, and ORR of 33% in the 24 patients who received radioembolization after progression on immunoembolization. The disease control rate was 87% and 58%, respectively. They concluded that radioembolization was well tolerated, with most toxicities being grade 1-2 and self-limiting, and no treatment-related deaths (NCCN, Uveal, v3. 2020).~~

~~Clinical Practice Guidelines~~

~~American Association for the Study of Liver Diseases (AASLD)~~

~~The AASLD developed guidance regarding the diagnosis, staging, and treatment of patients with hepatocellular carcinoma (HCC). For cirrhotic patients with HCC of T2 or T3 stage and no vascular involvement who are not candidates for transplantation or resection, the AASLD recommends a locoregional therapy over no treatment; the strength of the recommendation was strong, but TARE was given a very-low-quality evidence~~very-low-quality evidence rating ~~compared with moderate for transarterial chemoembolization (TACE). No form of locoregional control was recommended over another, but the recommendation was conditional and based on a very-low overall level of evidence. The AASLD did not issue guidance regarding the use of locoregional therapies for HCC versus systemic therapy, due to the lack of evidence to inform the balance of benefits and harms in patients with macrovascular invasion and/or metastatic disease (Heimbach et al., 2018); Marrero et al., 2018).~~

~~American College of Radiology (ACR), the American Brachytherapy Society (ABS), the American College of Nuclear Medicine (ACNM), the American Society for Radiation Oncology (ASTRO), the Society of Interventional Radiology (SIR), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI)~~

~~A 2021 Practice parameter was developed for selective internal radiation therapy (SIRT) or radioembolization for treatment of liver malignancies. The practice parameter for SIRT or radioembolization for treatment of liver malignancies was updated according to~~

processes on the ACR website by the committee of Practice Parameters Interventional and Cardiovascular Radiology of the ACR Commission on Interventional and Cardiovascular, Committee on Practice Parameters and Technical Standards-Nuclear Medicine and Molecular Imaging of the ACR Commission on Nuclear Medicine and Molecular Imaging and the Committee on Practice Parameters-Radiation Oncology of the ACR Commission on Radiation Oncology in collaboration with ABS, ACNM, ASTRO, SIR, and SNMMI. The purpose of the practice parameter is to serve as a tool in the proper application of radioembolization which focuses on best practices and principles for the effective utilization of radioembolization. The practice parameter includes clinical implementation from personnel qualifications, quality assurance standards, indications, and recommended documentation. A 2019 Practice parameter for selective internal radiation therapy (SIRT) or radioembolization for treatment of liver malignancies states that the treatment goal of radioembolization should be tailored to the individual patient, whether it is palliative or a bridge to surgical resection or liver transplantation. The most common clinical utility of radioembolization is in the treatment of HCC and liver-dominant metastatic CRC and neuroendocrine tumors.

Indications are not limited to the following:

- The presence of unresectable or inoperable primary or secondary liver malignancies (particularly CRC and NET metastases). The tumor burden should be liver dominant, not necessarily exclusive to the liver. Patients should also have a performance status that will allow them to benefit from such therapy.
- A life expectancy of at least 3 months.

American Society of Clinical Oncology (ASCO)

A 2020 guideline by ASCO recommends TARE in combination with systemic chemotherapy in second-linesecond line setting or beyond in patients with CRC.

National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for colon and rectal cancers state Yttrium-90 microsphere selective internal radiation is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases. The use of arterial-directed therapies in highly selected patients 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, v1.2022; NCCN, Rectal, v1.2022).

National Comprehensive Cancer Network (NCCN) clinical practice guidelines for hepatobiliary cancers state that locoregional therapies such as TARE with yttrium-90 microspheres have been shown to be safe and effective option in patients with unresectable intrahepatic cholangiocarcinomas (NCCN, Hepatobiliary v5.2021).

National Comprehensive Cancer Network (NCCN)The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on uveal melanoma reviewed multiple retrospective studies and one prospective phase II study which reported results for patients with liver metastases from uveal melanoma treated with hepatic radioembolization. Response rates from the retrospective studies varied widely (6%-100%), but disease control rate was consistently greater than 50%. The phase II study reported objective response rate (ORR) of 39% in the 23 patients who received radioembolization as first-line treatment for liver metastasis, and ORR of 33% in the 24 patients who received radioembolization after progression on immunoembolization. The disease control rate was 87% and 58%, respectively. They concluded that radioembolization was well tolerated, with most

~~toxicities being grade 1-2 and self-limiting, and no treatment-related deaths (NCCN, Uveal, v2. 2021).~~

~~The National Institute for Health and Care Excellence (NICE) interventional procedures guidance for selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma recommendations state that the current evidence on the safety of selective internal radiation therapy (SIRT) for unresectable primary intrahepatic cholangiocarcinoma 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 randomized controlled trials, should address patient selection, quality of life outcomes and overall survival. 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[WRM2]).~~

~~Radioembolization Brachytherapy Oncology Consortium (REBOC)~~

~~In 2007[WRM3], REBOC, an independent group of experts from the fields of interventional radiology, radiation oncology, nuclear medicine, medical oncologyoncology, and surgical oncology issued clinical guidelines for ^{90}Y microsphere brachytherapy with the purpose to standardize the indications, techniques, multimodality treatment approaches and dosimetry to be used for ^{90}Y microsphere hepatic brachytherapy. The recommendations state that success in treatment of tumors in the liver by radioembolization relies on the presence of appropriate indications to ensure that patients receive safe and effective therapy. Because the nature of primary and secondary hepatic malignancies differs, therapy should be tailored to the disease. Patients with hepatic metastases from primary sites other than colorectal should be offered standard systemic treatment options with known survival benefit before ^{90}Y treatment. In the case of primary liver tumors, patients should undergo a thorough evaluation to determine the optimal treatment strategy.~~
~~Key findings include the following:~~

- ~~Sufficient evidence exists to support the safety and effectiveness of ^{90}Y microsphere therapy in selected patients.~~
- ~~Candidates for radioembolization are patients with unresectable primary or metastatic hepatic disease with liver-dominant tumor burden and a life expectancy >3 months.~~
- ~~In metastatic colorectal cancer, radioembolization therapy can be given (1) alone after failure of first-line chemotherapy, (2) with floxuridine (FUDR) during first-line therapy or (3) during first- or second-line chemotherapy on a clinical trial.~~
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~~Initiation of clinical trials is essential to further define the safety and role of ^{90}Y microspheres in the context of currently available therapies (Kennedy et al., 2007).~~

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 ^{90}Y microspheres; TheraSphere® and SIR-Spheres®.

SIR-Spheres® (Sirtex Medical) are resin ^{90}Y 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. Additional information is available at: http://www.accessdata.fda.gov/cdrh_docs/pdf/p990065a.pdf. **(Accessed February 24, 2022)** ~~(Accessed March 16, 2020)~~

TheraSphere® (BTG) are glass ^{90}Y microspheres and are indicated for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma who can have placement of appropriately positioned hepatic arterial catheters. Glass ^{90}Y 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 February 24, 2022)** ~~(Accessed March 16, 2020)~~

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. See the following guidance for further information: http://pbadupws.nrc.gov/docs/ML1217/ML12179A353.pdf. **(Accessed February 24, 2022)** ~~(Accessed March 16, 2020)~~

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Policy History/Revision Information

Date	Summary of Changes
TBD	**Coverage Rationale** • Revised list of proven and medically necessary indications for transarterial radioembolization (TARE) using yttrium-90 (^{90}Y) microspheres; replaced: ○ "Unresectable *metastatic* liver *tumors* from *primary* colorectal *cancer (CRC)*" with "unresectable liver *metastases* from colorectal *carcinoma in individuals with Limited Extra-Hepatic Disease who are Refractory to or relapsed following systemic chemotherapy*" ○ "Unresectable *metastatic* liver *tumors* from neuroendocrine tumors" with "unresectable liver *metastases* from neuroendocrine tumors *when systemic therapy has failed to control symptoms*" ○ "Unresectable primary hepatocellular carcinoma (HCC)" with "primary hepatocellular carcinoma (HCC) *that is* unresectable *and limited to the liver or* primary hepatocellular carcinoma (HCC) *as a bridge to liver transplantation*" • Revised coverage criteria; added criterion requiring the *Eastern Cooperative Oncology Group (ECOG)* performance status of 0,1, or 2 **Applicable Codes** • Added notation to indicate CPT/HCPCS code S2095 are not on the State of Louisiana Fee Schedule and therefore are not covered by the State of Louisiana Medicaid Program **Definitions** • Added definition of: ○ Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status ○ Limited Extra-Hepatic Disease ○ Refractory **Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information Archived previous policy version CS060LA.I

Instructions for Use

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