

Implantable Beta-Emitting Microspheres for Treatment of Malignant Tumors

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Community Plan Policy

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Coverage Rationale

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

- 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 (⁹⁰Y) microspheres is unproven and not medically necessary for all other indications due to insufficient evidence of efficacy.

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 the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction
79445	Radiopharmaceutical therapy, by intra-arterial particulate administration

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

Description of Services

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

Transarterial radioembolization (TARE) 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, 2019).

Radioactive yttrium-90 (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, 2019).

Clinical Evidence

Liver Metastases from Colorectal Cancer

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.

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 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.

Maleux et al. (2016) performed a retrospective study to assess the technical and clinical outcomes, overall survival and prognostic factors for prolonged survival after yttrium-90 (⁹⁰Y) radioembolization as a salvage therapy for patients with chemorefractory liver-only or liver dominant colorectal metastases. Demographic, laboratory, imaging and dosimetry data were collected. Eighty-eight patients were selected for angiographic workup; 71 patients underwent catheter-directed 90Y microsphere infusion into the hepatic artery 25 days after angiographic workup. Thirty day toxicity included fatigue, abdominal discomfort, nausea, fever, diarrhea, liver function abnormalities and elevated bilirubin. Gastric ulcer was found in five patients. A late complication was radioembolization-induced portal hypertension (REIPH) in three patients. Median time to progression in the liver was 4.4 months. Estimated survival at six and 12 months was 65% and 30%, respectively, with a 50% estimated survival after 8.0 months. Prognostic factors for worse survival were high preprocedural bilirubin, alkaline phosphatase and tumor

volume levels. The authors concluded that 90Y microsphere radioembolization for chemorefractory colorectal liver metastases has an acceptable safety profile with a 50% estimated survival after 8.0 months.

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.

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.

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 ⁹⁰Y 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 was progression-free survival (PFS); secondary end-points 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 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 ⁹⁰Y 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.

Hepatic intra-arterial injection of the beta-emitting isotope 90Y bound to resin microspheres (radioembolization) delivers therapeutic radiation doses to liver metastases with minimal damage to adjacent tissues. Hendlisz et al. (2010) conducted a

prospective, multicenter, randomized phase III trial in patients with unresectable, chemotherapy-refractory liver-limited metastatic colorectal cancer (mCRC) comparing arm A (fluorouracil [FU] protracted intravenous infusion 300 mg/m² days 1 through 14 every 3 weeks) and arm B (radioembolization plus intravenous FU 225 mg/m² days 1 through 14 then 300 mg/m² days 1 through 14 every 3 weeks) until hepatic progression. The primary end point was time to liver progression (TTLP). Cross-over to radioembolization was permitted after progression in arm A. Forty-six patients were randomly assigned and 44 were eligible for analysis (arm A, n = 23; arm B, n = 21). Median follow-up was 24.8 months. Median TTLP was 2.1 and 5.5 months in arms A and B, respectively. Median time to tumor progression (TTP) was 2.1 and 4.5 months, respectively. Grade 3 or 4 toxicities were recorded in six patients after FU monotherapy and in one patient after radioembolization plus FU treatment. Twenty-five of 44 patients received further treatment after progression, including 10 patients in arm A who received radioembolization. Median overall survival was 7.3 and 10.0 months in arms A and B, respectively. The authors concluded that radioembolization with ⁹⁰Y-resin microspheres plus FU is well tolerated and significantly improves TTLP and TTP compared with FU alone. They further concluded that this procedure is a valid therapeutic option for chemotherapy-refractory liver-limited mCRC.

Cosimelli et al. (2010) conducted a prospective multicenter phase II study evaluating radioembolization using ⁹⁰Y resin microspheres in patients with unresectable, chemotherapy refractory colorectal liver metastases (mCRC). Of 50 eligible patients, 38 (76%) had received ≥ 4 lines of chemotherapy. Early and intermediate adverse events (mostly fever and pain) were observed in 16 and 22% of patients respectively. Two died due to renal failure or liver failure. One patient (2%) had a complete response, 11 (22%) partial response, 12 (24%) stable disease and 22 (44%) progressive disease. Four (8%) were non-evaluable. Median overall survival was 12.6 months. Two-year survival was 19.6%.

The National Institute for Health and Care Excellence (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).

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).

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, v2.2020a; NCCN, v2.2020b).

Primary Hepatocellular Carcinoma (HCC)

A 2019 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 (Hayes, 2019a).

A 2019 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 for evaluation of 90Y TARE versus other LRTs in patients with primary unresectable HCC who were being treated with the intent of downstaging or bridging to transplantation or resection. 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 (Hayes, 2019b).

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 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.

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.

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 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.

Salem et al. (2016) performed a single center, randomized; phase 2 study to compare the effects of transarterial chemoembolization (cTACE) and Y90 radioembolization in patients with hepatocellular carcinoma (HCC). Forty-five patients with Barcelona Clinic Liver Cancer (BCLC) stages A or B HCC were assigned randomly to groups that received Y90 therapy or cTACE. The primary outcome was time to progression (TTP) and secondary outcomes included safety, rate of response (based on tumor size and necrosis criteria), and Kaplan–Meier survival time. The median follow-up evaluation was 15.7 months for TACE and 21 months for Y90. Patients in the Y90 radioembolization group had significant longer median TTP (>26 mo.) than patients in the cTACE group (6.8 mo.). A greater number of patients in the cTACE group developed diarrhea (21%) than in the Y90 group or hypoalbuminemia (58% in the cTACE group vs 4% in the Y90 group). Similar proportions of patients in each group had a response to therapy, marked by necrosis (74% in the cTACE group vs 87% in the Y90 group). There were 7 transplants at a median of 7.6 months for TACE and 13 transplants at a median of 8.8 months for Y90. The rates of transplantation were 87% after Y90 vs 70% after cTACE. Twenty-five patients did not receive a liver transplant. The median censored to liver transplantation, was 17.7 months for the cTACE group vs 18.6 months for the Y90 group. The authors concluded that Y90 prolongs TTP when compared with cTACE for early intermediate stage HCC, suggesting more complete treatment of targeted lesions, tumor control and possible reduction of drop-out from transplant waitlists.

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).

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, v4.2019a).

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 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 ⁹⁰Y 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: 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.

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

Hilgard et al. (2010) reviewed the evidence regarding the safety and efficacy of radioembolization with ⁹⁰Y glass microspheres in patients with advanced hepatocellular carcinoma (HCC). One hundred eight consecutive patients with advanced HCC and liver cirrhosis were included. Complete responses were identified in 3% of patients, partial responses in 37%, stable disease 53% and disease progression in 6% of patients. Time-to-progression was 10.0 months, and the median overall survival was 16.4 months. The authors concluded that radioembolization with ⁹⁰Y glass microspheres for patients with advanced HCC is a safe and effective treatment which can be utilized even in patients with compromised liver function. Because time-to-progression and survival appear to be comparable to systemic therapy in selected patients with advanced HCC, randomized controlled trials in combination with systemic therapy are warranted.

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 ⁹⁰Y microspheres includes the following:

- ⁹⁰Y is a safe microembolization treatment and can be administered in the outpatient setting.
- ⁹⁰Y 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 ⁹⁰Y compared to other regional therapies. Considerations of efficacy and safety (given cirrhosis) have to be made on an individual basis.

The National Institute for Health and Care Excellence (NICE) states that current evidence on the efficacy and safety of SIRT for primary hepatocellular carcinoma is adequate for use with normal arrangements for clinical governance, consent and audit (NICE, 2013).

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).

Liver Metastases from Neuroendocrine Tumors

Frilling et al. (2019) performed a retrospective case series 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.

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 ⁹⁰Y 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 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.

Cao et al. (2010) assessed the efficacy of ⁹⁰Y 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.

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, v1.2019b).

Intrahepatic Cholangiocarcinoma

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.

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.

A retrospective study was conducted by Jia et al. (2017) 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 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 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.

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 (category 2B) (NCCN, v1.2019a).

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).

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.

A systematic review was conducted by Jia et al. (2017) to assess the effectiveness of yttrium-90 (⁹⁰Y) 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 ⁹⁰Y 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.

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 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 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 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 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 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.

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; 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.

Smits et al. (2013) provided a systematic overview of the current literature concerning ⁹⁰Y 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 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 ⁹⁰Y 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 ⁹⁰Y for BCLM patients.

A large single center study by Fendler et al. (2016) evaluated safety, 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 $\leq 10\%$ of patients. Two patients eventually died from REILD. Sequential lobar treatment and absence of prior angi-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 angi-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.

Sato et al. (2008) performed radioembolization on 137 patients with non-resectable liver metastases who had failed standard of care polychemotherapy. Primary sites origins of malignancy included colon (n=51), breast (n=21), neuroendocrine (n=19), and others. Clinical toxicities included fatigue (56%), vague abdominal pain (26%), and nausea (23%). At follow-up imaging, according to World Health Organization (WHO) criteria, there was a 42.8% response rate (2.1% complete response, 40.7% partial response). There was a biologic tumor response, defined as any decrease in tumor size, of 87%. Differences in survival were seen with different tumor type, ECOG performance status, tumor burden, imaging findings (hypovascular or hypervascular tumors at angiography and cross-sectional imaging), and number of tumors. Median survival rate for patients with colorectal cancer, neuroendocrine tumors, and noncolorectal, nonneuroendocrine tumors were 457, 776, and 207 days, respectively. Survival differences by tumor type were not statistically significant.

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 a 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).

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 and surgical oncology issued clinical guidelines for ⁹⁰Y microsphere brachytherapy with the purpose to standardize the indications, techniques, multimodality treatment approaches and dosimetry to be used for ⁹⁰Y 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 ⁹⁰Y 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 ⁹⁰Y 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 ⁹⁰Y microspheres in the context of currently available therapies (Kennedy et al., 2007).

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 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.

U.S. Food and Drug Administration (FDA)

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

The FDA has approved two commercial forms of ⁹⁰Y microspheres; TheraSphere[®] and SIR-Spheres[®]. SIR-Spheres (Sirtex Medical) are resin ⁹⁰Y microspheres and are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of floxuridine (FUdR). SIR-Spheres received FDA premarket approval (P990065) on March 5, 2002. Additional information is available at:

http://www.accessdata.fda.gov/cdrh_docs/pdf/p990065a.pdf.

TheraSphere (BTG) are glass ⁹⁰Y 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 ⁹⁰Y microspheres are approved by the FDA under the provisions of a Humanitarian Device Exemption (H980006). Additional information is available at: http://www.accessdata.fda.gov/cdrh_docs/pdf/H980006b.pdf.

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>.

Centers for Medicare and Medicaid Services (CMS)

Medicare does not have a National Coverage Determination (NCD) for implantable beta-emitting microspheres used in the treatment of malignant tumors. Local Coverage Articles (LCDs)/Local Coverage Articles (LCAs) exist; see the LCAs for [Treatment with Yttrium-90 Microspheres](#) and [Coding Radiopharmaceutical Agents](#). (Accessed March 16, 2020)

References

- Al-Adra D, Gill R, Axford S. Treatment of unresectable intrahepatic cholangiocarcinoma with yttrium-90 radioembolization: A systematic review and pooled analysis. *Eur J Surg Oncol*. 2015 Jan; 41(1): 120–127.
- 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). Practice parameter for selective internal radiation therapy (SIRT) or radioembolization for treatment of liver malignancies. October 2019.
- Barbier CE, Garske-Román U, Sandström M, et al. Selective internal radiation therapy in patients with progressive neuroendocrine liver metastases. *Eur J Nucl Med Mol Imaging*. 2016 Jul;43(8):1425-31.
- Belinson S, Yang Y, Chopra R, et al. Local therapies for unresectable primary hepatocellular carcinoma. Comparative Effectiveness Review No. 114. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-2007-10058-I.) AHRQ Publication No. 13-EHC069-EF. Rockville, MD: Agency for Healthcare Research and Quality. May 2013.
- Belinson S, Chopra R, Yang Y, et al. Local hepatic therapies for metastases to the liver from unresectable colorectal cancer. Comparative Effectiveness Review No. 93. (Prepared by Blue Cross and Blue Cross Blue Shield Association Technology Evaluation Center under Contract No. 290-2007-10058-I.) AHRQ Publication No. 13-EHC014-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2012.
- Benson AB 3rd, Geschwind JF, Mulcahy MF, et al. Radioembolisation for liver metastases: results from a prospective 151 patient multi-institutional phase II study. *Eur J Cancer*. 2013 Oct;49(15):3122-30.
- Bruix, Jordi and Sherman, Morris. Management of hepatocellular carcinoma: An update. *American Association for the Study of Liver Diseases Practice Guidelines*. 2011.
- Cao CQ, Yan TD, Bester L, et al. Radioembolization with yttrium microspheres for neuroendocrine tumour liver metastases. *Br J Surg*. 2010 Apr;97(4):537-43.
- Cosimelli M, Golfieri R, Cagol PP, et al. Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. *Br J Cancer*. 2010 Jul 27;103(3):324-31.
- Cramer B, Xing M, Kim HS. Prospective longitudinal quality of life assessment in patients with neuroendocrine tumor liver metastases treated with 90Y radioembolization. *Clin Nucl Med* 2016 Dec;41(12):e493-e497.
- Devic Z, Rosenberg J, Braat AJ, et al. The efficacy of hepatic 90Y resin radioembolization for metastatic neuroendocrine tumors: a meta-analysis. *J Nucl Med*. 2014 Sep;55(9):1404-10.
- Ettore GM, Levi Sandri GB, Laurenzi A et al. Yttrium-90 radioembolization for hepatocellular carcinoma prior to liver transplantation. *World J Surg* 2017 Jan;41(1):241-249. Fendler WP, Lechner H, Todica A, et al. Safety, efficacy and prognostic factors after radioembolization of hepatic metastases from breast cancer: A large single center experience in 81 patients. *J Nucl Med*. 2016 Jan 7.
- Frilling A, Clift AK, Braat AJAT, et al. Radioembolisation with 90Y microspheres for neuroendocrine liver metastases: an institutional case series, systematic review and meta-analysis. *HPB (Oxford)*. 2019 Jul;21(7):773-783.
- Hayes, Inc. Hayes Comparative Effectiveness Review. Radioactive Yttrium-90 Microspheres for Treatment of Primary Unresectable Liver Cancer. Lansdale, PA: Hayes, Inc. Jun 11, 2019a.
- Hayes, Inc. Hayes Medical Technology Directory. Radioactive Yttrium-90 microspheres for the treatment of primary unresectable liver cancer for downstaging or as a bridge to transplantation or surgery. Lansdale, PA: Hayes, Inc.; September 11, 2019b.
- Hayes, Inc. Hayes Medical Technology Directory. Radioactive yttrium-90 microspheres for treatment of secondary liver cancer. Lansdale, PA: Hayes, Inc.; March 31, 2015. Updated April 29, 2019c.
- Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology*. 2018 Jan;67(1):358-380.
- Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *J Clin Oncol*. 2010 Aug 10;28(23):3687-94.

Hilgard P, Hamami M, Fouly AE, et al. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. *Hepatology*. 2010 Nov;52(5):1741-9.

Jia Z, Jiang G, Zhu C, et al. A systematic review of yttrium-90 radioembolization for unresectable liver metastases of melanoma. *Eur J Radiol*. 2017 Jul;92:111-115.

Jia Z, Paz-Fumagalli R, Frey G, et al. Resin-based Yttrium-90 microspheres for unresectable and failed first-line chemotherapy intrahepatic cholangiocarcinoma: preliminary results. *J Cancer Res Clin Oncol* 2017 March;143(3):481-489.

Jakobs TF, Paprottka KJ, Raeßler F, et al. Robust evidence for long-term survival with 90Y radioembolization in chemorefractory liver-predominant metastatic colorectal cancer. *Eur Radiol* 2017 Jan;27(1):113-119.

Kallini JR, Gabr A, Thorlund K et al. Comparison of the adverse event profile of TheraSphere[®] with SIR-Spheres[®] for the treatment of unresectable hepatocellular carcinoma: a systematic review. *Cardiovasc Intervent Radiol*. 2017; 40(7):1033-1043.

Kalva SP, Rana RS, Liu R, et al. Yttrium-90 radioembolization as salvage therapy for liver metastases from colorectal cancer. *Am J Clin Oncol* 2017 Jun;40(3):288-293.

Katsanos K, Kitrou P, Spiliopoulos S, et al. Comparative effectiveness of different transarterial embolization therapies alone or in combination with local ablative or adjuvant systemic treatments for unresectable hepatocellular carcinoma: A network meta-analysis of randomized controlled trials. *PLoS One*. 2017 Sep 21;12(9):e0184597.

Kennedy AS, Ball D, Cohen SJ, et al. Multicenter evaluation of the safety and efficacy of radioembolization in patients with unresectable colorectal liver metastases selected as candidates for (90)Y resin microspheres. *J Gastrointest Oncol*. 2015 Apr;6(2):134-42.

Kennedy A, Cohn M, Coldwell DM, et al. Updated survival outcomes and analysis of long-term survivors from the MORE study on safety and efficacy of radioembolization in patients with unresectable colorectal cancer liver metastases. *J Gastrointest Oncol*. 2017 Aug;8(4):614-624.

Kennedy A, Nag S, Salem R, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. *Int J Radiat Oncol Biol Phys*. May 2007 1;68(1):13-23.

Kucuk ON, Soydal C, Lacin S, et al. Selective intraarterial radionuclide therapy with yttrium-90 (Y-90) microspheres for unresectable primary and metastatic liver tumors. *World J Surg Oncol*. 2011 Aug 6;9:86.

Kuei Andrew, Saab Sammy, Cho Sung-Ki, et al. Effects of Yttrium-90 selective internal radiation therapy on non-conventional liver tumors. *World J Gastroenterol* 2015 July 21; 21(27): 8271-8283.

Lau WY, Lai EC, Leung TW. Current role of selective internal irradiation with yttrium-90 microspheres in the management of hepatocellular carcinoma: a systematic review. *Int J Radiat Oncol Biol Phys*. 2011 Oct 1;81(2):460-7.

Lobo L, Yakoub D, Picado O, et al. Unresectable hepatocellular carcinoma: Radioembolization versus chemoembolization: A systematic review and meta-analysis. *Cardiovasc Intervent Radiol*. 2016 Sep 1.

Maleux G, Deroose C, Laenen A, et al. Yttrium-90 radioembolization for the treatment of chemorefractory colorectal liver metastases: technical results, clinical outcome and factors potentially influencing survival. *Acta Oncol* 2016;55(4):486-495.

Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 Practice Guidance by the American Association for the study of liver diseases. *Hepatology*. 2018 Aug;68(2):723-750.

Moreno-Luna LE, Yang JD, Sanchez W, et al. Efficacy and safety of transarterial radioembolization versus chemoembolization in patients with hepatocellular carcinoma. *Cardiovasc Intervent Radiol*. 2012 Oct 24.

Mosconi C, Gramenzi A, Ascanio S, et al. Yttrium-90 radioembolization for unresectable/recurrent intrahepatic cholangiocarcinoma: a survival, efficacy and safety study. *Br J Cancer* 2016 July 26;115(3):297-302.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Colon cancer Version 2.2020a.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Hepatobiliary cancers Verison 4.2019a.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Neuroendocrine tumors Version 1.2019b.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Rectal cancer Version 2.2020b.

National Institute for Health and Care Excellence (NICE). IPG672. Selective internal radiation therapy for non-resectable colorectal metastases in the liver. March 2020.

National Institute for Health and Care Excellence (NICE). IPG460. Selective internal radiation therapy for primary hepatocellular carcinoma. July 2013.

National Institute for Health and Care Excellence (NICE). IPG630. Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma. October 2018.

National Institute for Health and Care Excellence (NICE). MIB63. SIR-Spheres for treating inoperable hepatocellular carcinoma Medtech innovation briefing Published: 30 March 2016.

National Institute for Health and Care Excellence (NICE). MIB62. TheraSphere for treating operable and inoperable hepatocellular carcinoma. Medtech innovation briefing. Published: 30 March 2016.

Peker A, Çiçek O, Soydal Ç, et al. Radioembolization with yttrium-90 resin microspheres for neuroendocrine tumor liver metastases. *Diagn Interv Radiol* 2015; 21:54–59.

Salem R, Gordon AC, Mouli S, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology* 2016 Dec;151(6):1155-1163.

Sangro B, Carpanese L, Cianni R, et al. European Network on Radioembolization with yttrium-90 Resin Microspheres (ENRY). Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology*. 2011 Sep 2;54(3):868-78.

Sato KT, Lewandowski RJ, Mulcahy MF, et al. Unresectable chemorefractory liver metastases: radioembolization with ⁹⁰Y microspheres - safety, efficacy and survival. *Radiology*. 2008 May;247(2):507-15.

Schwarz RE, Abou-Alfa GK, Geschwind JF, et al. American Hepato-Pancreato-Biliary Association; Society of Surgical Oncology; Society for Surgery of the Alimentary Tract. Nonoperative therapies for combined modality treatment of hepatocellular cancer: expert consensus statement. *HPB (Oxford)*. 2010 Jun;12(5):313-20.

Smits ML, Prince JF, Rosenbaum CE, et al. Intra-arterial radioembolization of breast cancer liver metastases: a structured review. *Eur J Pharmacol*. 2013 Jun 5;709(1-3):37-42.

van Hazel GA, Heinemann V, Sharma NK, et al. SIRFLOX: Randomized phase III trial comparing first-line mFOLFOX6 (Plus or Minus Bevacizumab) versus Theraspher/Sir-Sphere Jul 16 24.

White J, Carolan-Rees G, Dale M, et al. Yttrium-90 transarterial radioembolization for chemotherapy-refractory intrahepatic cholangiocarcinoma: a prospective, observational study. *J Vasc Interv Radiol*. 2019 Aug;30(8):1185-1192.

Xie F, Zang J, Guo X, et al. Comparison of transcatheter arterial chemoembolization and microsphere embolization for treatment of unresectable hepatocellular carcinoma: a meta-analysis. *J Cancer Res Clin Oncol*. 2012 Mar;138(3):455-62.

Zhang Y, Li Y, Ji H et al. Transarterial Y90 radioembolization versus chemoembolization for patients with hepatocellular carcinoma: A meta-analysis. *BioScience Trends*. 2015; 9(5):289-298.

Policy History/Revision Information

Date	Summary of Changes
08/01/2020	Template Update <ul style="list-style-type: none">Reformatted policy; transferred content to new template
04/01/2020	Supporting Information <ul style="list-style-type: none">Updated <i>Clinical Evidence</i> and <i>References</i> sections to reflect the most current informationArchived previous policy version 2019T0445Q

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare

reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence ([Medicare IOM Pub. No. 100-16, Ch. 4, §90.5](#)).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.