IMPLANTABLE BETA-EMITTING MICROSPHERES FOR TREATMENT OF MALIGNANT TUMORS

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INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Medical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Medical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines 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.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBS. However, if such plans choose to provide coverage for benefits which are deemed EHBS, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBS is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

Yttrium-90 (90Y) microsphere radioembolization 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)
Yttrium-90 (²⁹⁰Y) microsphere radioembolization is unproven and not medically necessary for all other indications.

Limited evidence suggests that treatment with intrahepatic microsphere radiation (IMR) might shrink tumors and relieve symptoms in some patients, sometimes enough to render some inoperable tumors operable. However, limited available evidence has not shown improved survival. In addition, the treatment's potential impact on quality of life has not been studied. No studies have yet compared the effects of IMR therapy with alternative treatments, such as chemoembolization. Randomized controlled trials are needed to determine the clinical utility of this treatment.

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 Coverage Determination Guidelines may apply.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>37243</td>
<td>Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intra procedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction</td>
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<tr>
<td>79445</td>
<td>Radiopharmaceutical therapy, by intra-arterial particulate administration</td>
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<table>
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<tr>
<th>HCPCS Code</th>
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<tr>
<td>S2095</td>
<td>Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres</td>
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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.

Intrahepatic microsphere radiation (IMR) therapy or selective internal radiation therapy (SIRT) is a palliative treatment for inoperable liver tumors designed to inhibit tumor growth and preserve remaining liver function by delivering radiation locally. During IMR therapy, a physician threads a catheter inserted at the femoral artery into the hepatic artery and injects millions of microscopic beads that contain the radioactive element ⁹⁰Y. The microspheres become lodged in the liver's capillaries. The beta radiation, which penetrates about half an inch, is delivered directly to tumors and is less toxic to adjacent, healthy tissue than radiation delivered by other means. After about two weeks, the radiation dissipates, but the beads remain in the liver permanently. Physicians monitor patients' liver function during follow-up examinations. (ECRI, 2015)

CLINICAL EVIDENCE

Liver Metastases from Colorectal Cancer and Hepatocellular Carcinoma (HCC)

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.

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).

A separate 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) 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) 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, v2. 2015, updated v2. 2016).

NCCN clinical practice guidelines for colon and rectal cancers state that the role of liver-directed therapies, such as arterial radioembolization with 90Y microspheres, in the treatment of colorectal metastases is controversial. Some institutions use arterially directed radioembolization in select patients with chemotherapy-resistant/refractory disease, without obvious systemic disease, and with predominant hepatic metastases. The use of arterial-directed therapies in highly selected patients remains a category 3 recommendation based on the limited amount of evidence and different institutional practice patterns. A category 3 recommendation indicates that there is major disagreement among NCCN panel members that the intervention is appropriate (NCCN, v 3.2015a; NCCN, v 3.2015b, updated v2.2016).

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-naive 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.

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.

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 patients 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 $^{90}$Y 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 $^{90}$Y 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.

Hepatic intra-arterial injection of the beta-emitting isotope $^{90}$Y bound to resin microspheres (radioembolization) delivers therapeutic radiation doses to liver metastases with minimal damage to adjacent tissues. Hendliz 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/m(2) days 1 through 14 every 3 weeks) and arm B (radioembolization plus intravenous FU 225 mg/m(2) days 1 through 14 then 300 mg/m(2) 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 $^{90}$Y -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 $^{90}$Y 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%.

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:

- $^{90}$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) have to be made on an individual basis.

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, but more research and data collection is required to demonstrate its efficacy. The evidence on its efficacy in chemotherapy-naive patients is inadequate in quantity. Clinicians should offer eligible patients who have not been previously treated by chemotherapy entry into well-designed research studies. For patients who are not eligible or who prefer not to enter a research trial, the procedure should be used with special arrangements for clinical governance, consent and audit. For patients who have previously been treated with chemotherapy, comparative trials are needed to determine whether SIRT prolongs survival compared with best standard treatment, and to determine its effect on quality of life. There is also a need to identify which subgroups of patients are likely to derive clinical benefit from SIRT (NICE, 2011).

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, 2013b Reaffirmed 2016).
Liver Metastases from Neuroendocrine Tumors

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, v1.2015, updated v2. 2016).

A meta-analysis of 12 studies concluded that 90Y resin radioembolization is an effective treatment option for patients with liver-dominant metastatic neuroendocrine tumors. The pooled data demonstrated a high response rate and improved survival for patients responding to therapy (Devvic et al., 2014).

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.

Liver Metastases from Other Primary Sites

The overall quality of evidence on the safety and efficacy of 90Y radioembolization for the treatment of unresectable intrahepatic cholangiocarcinoma (ICC) is low due to few studies, small sample sizes and weak study designs. No randomized controlled trials were identified. Future research needs include larger, better designed studies with comparisons to standard and alternative therapies, standardization of treatment protocols and longer follow-up periods.

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 POLFIRINOX 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.

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.

NICE states that current evidence on the safety and efficacy of SIRT for primary ICC is limited in both quantity and quality. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research (NICE 2013a).

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 metastases of 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 tomodraphy/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 $^{90}$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 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.

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 ≤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.

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 (hypo-vascular 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, non-neuroendocrine tumors were 457, 776, and 207 days, respectively. Survival differences by tumor type were not statistically significant.

**Professional Societies**

**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 $^{90}$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 fluorouracil (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)
American College of Radiology (ACR) / Society of Interventional Radiology (SIR)

In a joint guideline with the Society of Interventional Radiology (SIR), ACR states that indications for radioembolization with microspheres include, but are not limited to:

- The presence of unresectable and/or inoperable primary or secondary liver malignancies. 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, i.e., an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 or Karnofsky Performance Status (KPS) of 70 or more.
- A life expectancy of at least three months (ACR, 2014).

ACR appropriateness criteria on the radiologic management of hepatic malignancies rated SIRT (a broad category that includes radioembolization with \(^{90}\text{Y}\) microspheres) as a 5 for solitary hepatocellular tumors less than 3 cm in diameter, 7 for solitary hepatocellular tumors 5 cm in diameter and 7 for more than one hepatocellular tumor with at least one greater than 5 cm in diameter. Ratings of 4, 5 and 6 represent a treatment that may be appropriate and ratings of 7, 8 and 9 represent a treatment that is usually appropriate (ACR, 2011).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

The FDA has approved two commercial forms of \(^{90}\text{Y}\) microspheres; TheraSphere® and SIR-Spheres®.

SIR-Spheres (Sirtex Medical) are resin \(^{90}\text{Y}\) 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](http://www.accessdata.fda.gov/cdrh_docs/pdf/p990065a.pdf). (Accessed November 10, 2016)

TheraSphere (BTG) are glass \(^{90}\text{Y}\) 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 \(^{90}\text{Y}\) 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](http://www.accessdata.fda.gov/cdrh_docs/pdf/H980006b.pdf). (Accessed November 10, 2016)

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](http://pbadupws.nrc.gov/docs/ML1217/ML12179A353.pdf). (Accessed November 10, 2016)

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 Determinations (LCDs) exist. See the LCDs for Treatment with Yttrium-90 Microspheres.

(Accessed November 16, 2016)

REFERENCES


Implantable Beta-Emitting Microspheres for Treatment of Malignant Tumors
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Policies and Guidelines:

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