

Radioembolization, Transarterial Embolization (TAE), and Transarterial Chemoembolization (TACE)

Effective: November 1, 2020

Next Review: July 2021

Last Review: September 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Radioembolization, transarterial embolization (TAE), and transarterial chemoembolization (TACE) involve delivery of small radioactive, chemotherapeutic, or inert beads for treatment of various conditions.

MEDICAL POLICY CRITERIA

- I. Radioembolization may be considered **medically necessary** for any of the following:
 - A. Locations other than the liver; or
 - B. Primary or metastatic liver tumors, when any of the following are met:
 1. Unresectable primary liver tumors (hepatocellular carcinoma [HCC]); or
 2. As a bridge to transplantation in primary HCC; or
 3. Unresectable hepatic metastases from neuroendocrine or colorectal tumors, or melanoma when any of the following are met:
 - a. Neuroendocrine tumors (carcinoid and noncarcinoid) when both of the following criteria (i. and ii.) are met:

- i. The disease is liver-dominant and diffuse (defined as tumor tissue spread throughout the affected organ) and symptomatic; and
 - ii. Systemic therapy has failed to control symptoms, or the patient is not a candidate for systemic therapy.
 - b. Colorectal tumors, including but not limited to adenocarcinoma when both of the following criteria (i. and ii.) are met:
 - i. The disease is liver-dominant, progressive, and diffuse (diffuse is defined as tumor tissue spread throughout the affected organ); and
 - ii. The patient is refractory to or not a candidate for chemotherapy.
 - c. Melanoma (ocular/uveal or cutaneous) when the disease is liver-dominant, progressive, and diffuse.
 4. Unresectable primary intrahepatic cholangiocarcinoma.
- II. Transarterial embolization (TAE) with non-radioactive agents may be considered **medically necessary** for any indication.
 - III. Transarterial chemoembolization (TACE) may be considered **medically necessary** for any indication.
 - IV. Radioembolization for the treatment of primary and metastatic tumors of the liver is considered **investigational** for all other scenarios not meeting the policy criteria above.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Neuroendocrine tumors are rare, slow-growing, hormone-secreting tumors that may occur in numerous locations in the body.^[1] Neuroendocrine tumors include the following:

- Carcinoid Tumors
- Islet Cell Tumors (also known as Pancreatic Endocrine Tumors)
- Neuroendocrine Unknown Primary
- Adrenal Gland Tumors
- Pheochromocytoma/paraganglioma
- Poorly Differentiated (High Grade or Anaplastic)/Small Cell
- Multiple Endocrine Neoplasia, Type 1 (also known as MEN-1 syndrome or Wermer's syndrome)
- Multiple Endocrine Neoplasia, Type 2 a or b (also known as pheochromocytoma and amyloid producing medullary thyroid carcinoma, PTC syndrome, or Sipple syndrome)

Neuroendocrine tumors may also be referred to by their location (e.g., pulmonary neuroendocrine tumors; gastroenteropancreatic neuroendocrine tumors)

Some appendiceal carcinoids, also called adeno carcinoids, goblet cell carcinoids or crypt cell carcinoids, have mixed histology, including elements of adenocarcinoma. While these biphasic tumors have both neuroendocrine and adenocarcinoma components, the National Comprehensive Cancer Network (NCCN) recommends they be managed according to colon cancer guidelines.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

For requests pertaining to primary or metastatic liver tumors:

- Description of the planned therapy including the approach and the embolization agent to be used
- Specific description of the disease including the following:
 - Tumor type (primary vs. metastatic)
 - Extent and location of disease including whether the tumor is liver-dominant, progressive, and diffuse, and the presence or absence of extra-hepatic disease
 - For neuroendocrine metastases, description of the presence or absence of tumor-related symptoms
- Rationale for the determination that the patient is not a surgical candidate or the tumor is unresectable
- Prior treatments, if any, and tumor response
- Rationale for the determination that the patient is not a candidate for initial or continued systemic therapy
- For treatment of hepatocellular carcinoma, specify if whether treatment is proposed as a bridge to transplantation

CROSS REFERENCES

1. [Charged-Particle \(Proton\) Radiotherapy](#), Medicine, Policy No. 49
2. [Radiofrequency Ablation \(RFA\) of Tumors Other than Liver](#), Surgery, Policy No. 92
3. [Cryosurgical Ablation of Miscellaneous Solid Tumors](#), Surgery, Policy No. 132
4. [Magnetic Resonance \(MR\) Guided Focused Ultrasound \(MRgFUS\) and High Intensity Focused Ultrasound \(HIFU\) Ablation](#), Surgery, Policy No. 139
5. [Microwave Tumor Ablation](#), Surgery, Policy No. 189
6. [Ablation of Primary and Metastatic Liver Tumors](#), Surgery, Policy No. 204

BACKGROUND

TRANSARTERIAL EMBOLIZATION

According to the National Cancer Institute, transarterial embolization is defined as:^[2]

A procedure in which the blood supply to a tumor or an abnormal area of tissue is blocked. During transarterial embolization, a small incision (cut) is made in the inner thigh and a catheter (thin, flexible tube) is inserted and guided into an artery near the tumor or abnormal tissue. Once the catheter is in place, small particles made of tiny gelatin sponges or beads are injected. This blocks the artery and stops the flow of blood to the tumor or abnormal area of tissue. Transarterial embolization is used to treat some types of liver cancer, kidney cancer, and neuroendocrine tumors. It may also be used to treat uterine fibroids, aneurysms, and other conditions. Also called arterial embolization and TAE.

Types of transarterial embolization include bland embolization, chemoembolization, and

radioembolization. This policy is predominantly focused on information and evidence regarding radioembolization, which is also a form of radiation therapy.

Transarterial embolization (TAE) with non-radioactive (bland embolization) agents and transarterial chemoembolization (TACE) are also used to treat some types of cancer and other conditions. These techniques may be considered medically necessary.

RADIOEMBOLIZATION

Radioembolization, formerly referred to as selective internal radiation therapy or “SIRT”, is the intra-arterial delivery of small beads (microspheres) impregnated with yttrium-90 via the bloodstream. This technique is used to treat cancer – most commonly cancer in the liver, which is the focus of this policy. In treating cancer in the liver, the microspheres, which become permanently embedded, are delivered to tumor preferentially to normal liver, as the hepatic circulation is uniquely organized, whereby tumors greater than 0.5 cm rely on the hepatic artery for blood supply while normal liver is primarily perfused via the portal vein. Yttrium-90 is a pure beta-emitter with a relatively limited effective range and short half-life that helps focus the radiation and minimize its spread. Radioembolization is generally reserved for patients with adequate functional status (ECOG 0-2), adequate liver function and reserve, Child Pugh score A or B, and liver-dominant metastases. Candidates for radioembolization are initially examined by hepatic angiogram to identify and map the hepatic arterial system, and at that time, a mixture of albumin particles is delivered via the hepatic artery to simulate microspheres. After, single-photon emission CT gamma imaging is used to detect possible shunting of the albumin particles into gastrointestinal or pulmonary vasculature.

Hepatic tumors can arise either as primary liver cancer or by metastasis to the liver from other organs. Potentially curative local treatments include surgical resection with tumor-free margins, liver transplantation, ablative techniques, and external-beam radiation therapies. Unfortunately, most hepatic tumors are unresectable at diagnosis, due either to their anatomic location, size and number of lesions, concurrent nonmalignant liver disease, or insufficient hepatic reserve.

The use of external beam radiotherapy, 3-D or more advanced radiotherapy approaches such as intensity-modulated radiotherapy [IMRT]) may be of limited use in patients with diffuse, multiple lesions due to the low tolerance of normal liver to radiation compared to the higher doses of radiation needed to kill the tumor.

Various nonsurgical and non-external irradiation based ablative techniques have been investigated that seek to cure or palliate unresectable hepatic tumors by improving locoregional control. These techniques rely on extreme temperature changes, particle and wave physics (microwave or laser ablation), or arterial embolization therapy including chemoembolization, bland embolization, or radioembolization.

UNRESECTABLE PRIMARY LIVER CANCER [HEPATOCELLULAR CARCINOMA (HCC)]

The majority of patients with HCC present with unresectable disease and treatment options are limited secondary to the chemoresistance of HCC and the intolerance of normal liver parenchyma to tumoricidal radiation doses.

Other Treatment Options

- Radioembolization. In general, radioembolization is used for unresectable HCC that is greater than 3 cm.

- Transarterial chemoembolization (TACE) therapy. Results of two randomized controlled trials have shown a survival benefit using TACE versus supportive care in patients with unresectable HCC.^[3,4]
- Transarterial embolization (TAE). In one study, patients were randomly assigned to TACE, TAE, or supportive care. One-year survival rates for TACE, TAE, and supportive care were 82%, 75%, and 63%, respectively and two-year survival rates were 63%, 50%, and 27%, respectively.
- Targeted therapies. A 2007 multicenter, randomized, double-blind placebo controlled Phase III trial that enrolled 602 patients with advanced HCC randomly assigned patients to receive sorafenib versus placebo.^[5] Overall survival (OS) was significantly longer in the sorafenib group compared with placebo (10.7 versus 7.9 months, respectively; hazard ratio for sorafenib: 0.69; $p < 0.001$).

UNRESECTABLE METASTATIC COLORECTAL CARCINOMA

The role of local (liver-directed) therapy (including radioembolization, chemoembolization, and conformal radiation therapy) for complete tumor removal or destruction is widely accepted in clinical practice. Incomplete “debulking” of unresectable metastatic disease in the liver remains controversial.^[6]

Fifty to sixty percent of patients with colorectal cancer develop metastases, either synchronously or metachronously. Emphasis on treating patients with potentially curable disease is on complete destruction or removal of all tumor tissue. The majority of patients diagnosed with metastatic colorectal disease are initially classified as having unresectable disease.

Other Treatment Options

- In patients with metastatic disease limited to the liver, preoperative chemotherapy is sometimes used in an attempt to downsize the metastases in order to convert the metastatic lesions to a resectable status (conversion chemotherapy).
- In patients with unresectable disease that cannot be converted to resectable disease, the primary treatment goal is palliative, with survival benefit shown with both second and third-line systemic chemotherapy.^[7]
- Advances in chemotherapy have doubled the median survival in this population from less than one year to more than two years.
- Palliative chemotherapy by combined systemic and hepatic artery infusion therapy (HAI) may increase disease-free intervals for patients with unresectable hepatic metastases from colorectal cancer.
- Ablation techniques (see Cross References)
- Radiation therapy (see Cross References).

UNRESECTABLE METASTATIC NEUROENDOCRINE TUMORS

Neuroendocrine tumors are an uncommon, heterogeneous group of mostly slow-growing, hormone-secreting malignancies, with an average patient age of 60 years. Primary neuroendocrine tumors vary in location, but most are either carcinoids (which most commonly arise in the midgut) or pancreatic islet cells. Carcinoid tumors, particularly if they metastasize to the liver, can result in excessive vasoactive amine secretion including serotonin and are commonly associated with the carcinoid syndrome (diarrhea, flush, bronchoconstriction, and

right valvular heart failure).

Although they are considered to be indolent tumors, at the time of diagnosis, up to 75% of patients have liver metastases. The five-year survival rates with metastases to the liver are less than 20%. Less than 10% of patients are eligible for resection as most patients have diffuse, multiple lesions.

Conventional therapy is largely considered to be palliative supportive care to control, eradicate, or debulk hepatic metastases, often to palliate carcinoid syndrome or local pain from liver capsular stretching.

Other Treatment Options

- Medical treatment includes somatostatin analogs, like octreotide or lanreotide, or systemic chemotherapy. Although patients often achieve symptom relief with octreotide, the disease eventually becomes refractory, with a median duration of symptom relief of approximately 13 months, with no known effect on survival. Systemic chemotherapy for these tumors has shown modest response rates of limited duration, is better for pancreatic neuroendocrine tumors compared to carcinoids, and is frequently associated with significant toxicity.^[8]
- Radiofrequency or cryosurgical tumor ablation (see Cross References)
- Transarterial chemoembolization (TACE) therapy. Chemoembolization has shown response rates of nearly 80%, but the effect is of short duration and a survival benefit has not been demonstrated.^[8]
- TAE with non-radioactive agents
- Radiation therapy (see Cross References)

UNRESECTABLE INTRAHEPATIC CHOLANGIOCARCINOMA

Cholangiocarcinomas are tumors that arise from the epithelium of the bile duct and are separated into intrahepatic and extrahepatic types. Intrahepatic cholangiocarcinomas appear in the hepatic parenchyma and are also known as peripheral cholangiocarcinomas.^[9] Resection is the only treatment with the potential for cure and five-year survival rates have been in the range of 20% to 43%.

Other Treatment Options

Patients with unresectable disease may select among fluoropyrimidine-based or gemcitabine-based chemotherapy, fluoropyrimidine chemoradiation, or best supportive care.

MISCELLANEOUS METASTATIC TUMORS

Small case reports have been published on the use of radioembolization in many other types of cancer with metastases, including breast, head, and neck (including parotid gland), pancreaticobiliary, anal, thymic, thyroid, endometrial, lung, kidney, gastric, small bowel, esophageal, ovarian, cervical, prostatic, bladder, and for melanoma, sarcoma and lymphoma.^[10]

REGULATORY STATUS

Currently, two commercial forms of yttrium-90 microspheres are available: a glass sphere, TheraSphere® (MDS Nordion, Inc. used under license by BTG International) and a resin sphere, SIR-Spheres® (Sirtex Medical Limited). Noncommercial forms are mostly used outside

the U.S. While the commercial products use the same radioisotope (yttrium-90) and have the same target dose (100 Gy), they differ in microsphere size profile, base material (i.e., resin vs. glass), and size of commercially available doses. These physical characteristics of the active and inactive ingredients affect the flow of microspheres during injection, their retention at the tumor site, spread outside the therapeutic target region, and dosimetry calculations.

Note also that the U.S. Food and Drug Administration (FDA) granted premarket approval of SIR-Spheres® for use in combination with 5-fluorouridine (5-FUDR) chemotherapy by HAI to treat unresectable hepatic metastases from colorectal cancer. In contrast, TheraSphere® was approved by humanitarian device exemption (HDE) for use as monotherapy to treat unresectable hepatocellular carcinoma (HCC). In January 2007, this HDE was expanded to include patients with hepatocellular carcinoma who have partial or branch portal vein thrombosis. For these reasons, results obtained with one product do not necessarily apply to other commercial (or noncommercial) products.

EVIDENCE SUMMARY

This evidence review does not include summaries for transarterial embolization (TAE) with non-radioactive or transarterial chemoembolization (TACE), which may be considered medically necessary.

The principal health outcomes associated with treatment of malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment.

In order to understand the impact of radioembolization (RE) on these outcomes, well-designed randomized controlled trials (RCTs) are needed that compare this therapy with standard medical and/or surgical treatment of tumors in the liver.

RADIOEMBOLIZATION FOR UNRESECTABLE PRIMARY LIVER CANCER [HEPATOCELLULAR CARCINOMA (HCC)]

The following literature review on RE for unresectable HCC focused on systematic literature reviews and comparative studies (randomized and nonrandomized).

Systematic Reviews

Various meta-analyses have been performed to compare the effects of TACE, drug-eluting bead (DEB) plus TACE (DEB-TACE), and RE in patients with unresectable HCC, each of which performed slightly different analyses (e.g., pairwise vs indirect comparisons and assessment of different outcomes or comparator groups). Results of these meta-analyses are summarized below.

Abdel-Rahman (2020) conducted a meta-analysis of RCTs comparing RE alone or combined with other systemic or locoregional treatments to placebo, no treatment, or other similar interventions in patients with unresectable HCC.^[11] Six RCTs (total n=1340) were identified, all of which were assessed by authors as being at high risk of bias. The authors reported the certainty of evidence as low to very low. Meta-analysis was able to be performed using data from more than one RCT for few comparisons. Based on meta-analysis of two RCTs, disease control rate was not significantly different between RE and sorafenib (relative risk [RR], 0.94;

95% confidence interval [CI] 0.84 to 1.05), though RE was associated with less hand-foot skin reactions (RR, 0.02; 95% CI 0.00 to 0.06), skin rash (RR, 0.11; 95% CI 0.04 to 0.34), diarrhea (RR, 0.11, 95% CI 0.04 to 0.34), and hypertension (RR, 0.10; 95% CI 0.01 to 0.88). Based on meta-analysis of three RCTs, the risk of serious adverse events did not differ between RE and TACE (RR, 1.47; 95% CI 0.66 to 3.25). Meta-analysis could not be performed for other comparisons; thus, results of other included trials are described individually in the section below on RCTs.^[12,13]

Venerito (2020) performed a meta-analysis to assess the noninferiority of SIRT as monotherapy or followed by sorafenib versus sorafenib monotherapy on OS.^[14] A noninferiority margin of 1.08 in terms of hazard ratio (HR) was prespecified. Three RCTs were included (total n=1,243), and meta-analysis demonstrated SIRT with or without sorafenib was noninferior to sorafenib monotherapy in OS (median, 10.2 and 9.2 months; HR, 0.91; 95% CI 0.78 to 1.05). Treatment-related severe adverse events were reported in 28.9% vs 43.3% of patients treated with SIRT and sorafenib monotherapy, respectively (p<0.01).

Yang (2020) conducted a meta-analysis of RCTs to compare effects of DEB-TACE, TACE, and RE on the primary outcome of overall survival.^[15] Compared with TACE, RE was associated with similar one-year OS (RR, 0.91; 95% CI 0.79 to 1.05), but a better OS than TACE at two years (RR, 0.87; 95% CI 0.80 to 0.95) and three years (RR, 0.90; 95% CI 0.85 to 0.96). Overall survival was not significantly different between RE and DEB-TACE at one year (RR, 0.83, 95% CI 0.68 to 1.02), but DEB-TACE was associated with better OS at two years than RE (RR, 0.40; 95% CI 0.19 to 0.84). However, pooled HRs indicated that RE was superior to TACE in overall survival (HR, 0.84; 95% CI 0.70 to 1.00) and that DEB-TACE was superior to RE in overall survival (HR, 0.59; 95% CI 0.38 to 0.91).

Tao (2017) reported on a network meta-analysis comparing nine minimally invasive surgeries for treatment of unresectable hepatocellular carcinoma (HCC).^[16] The interventions included were transarterial chemoembolization (TACE), TACE plus sorafenib, sorafenib, TACE plus high-intensity focused ultrasound, TACE plus percutaneous ethanol injection, drug-eluting bead (DEB) plus TACE (DEB-TACE), yttrium-90 radioembolization (90Y RE), TACE plus external-beam radiation therapy (EBRT), and ethanol ablation. The network included 17 studies with 2669 patients and four studies with 230 patients including 90Y RE. In a pairwise meta-analysis, patients treated with 90Y RE were more likely to achieve complete remission than those who received TACE (odds ratio [OR], 4.5; 95% CI 1.3 to 15.1). However, in the network meta-analysis, there was no significant difference between the corresponding eight treatments and TACE with respect to complete remission, partial response, stable disease, and objective response rate. The treatments were ranked for several outcomes using surface under the cumulative ranking curves (SUCRA). TACE plus EBRT had the highest SUCRA ranking in complete remission (77%), partial response (89%), progressive disease (95%), and objective response rate (81%).

Ludwig (2017) conducted an indirect meta-analysis of studies that indirectly compared DEB-TACE with 90Y RE for HCC.^[17] Fourteen studies (total N=2065 patients) comparing DEB-TACE or 90Y RE with conventional TACE for primary HCC treatment were included. The pooled estimate of median survival was 23 months for DEB-TACE and 15 months for RE. The estimated one-year survival was significantly higher for DEB-TACE (79%) than for RE (55%; OR=0.57; 95% CI 0.36 to 0.92; p=0.02). Survival did not differ statistically significantly at two or three years but did favor DEB-TACE. At two years, survival was 61% for DEB-TACE and 34%

or RE (OR=0.65; 95% CI 0.29 to 1.44; p=0.29) and at three years survival was 56% and 21% (OR=0.71; 95% CI 0.21 to 2.55; p=0.62), respectively.

Two systematic reviews published in 2016 compared RE with TACE for the treatment of unresectable HCC. Lobo (2016) selected five retrospective observational studies (total n=533 patients).^[18] Survival at one year did not differ statistically between RE (42%) and TACE (46%; RR, 0.93; 95% CI 0.81 to 1.08; p=0.33). At two years, the survival rate was higher for RE (27% vs 18%; RR=1.36; 95% CI 1.05 to 1.76; p=0.02), but there was no statistically significant difference in survival rates at three, four, or five years. Postprocedural complications were also similar in the two groups. Facciorusso (2016) included 10 studies (total n=1557 patients), two of which were randomized controlled trials (RCTs).^[17] The OR for survival was not statistically significant at one year (OR=1.0; 95% CI 0.8 to 1.3; p=0.93) but favored RE in years two (OR=1.4; 95% CI 1.1 to 1.90; p=0.01) and three (OR=1.5; 1.0 to 2.1; p=0.04).

Vente (2009) conducted a meta-analysis evaluating tumor response and survival in patients who received yttrium-90 glass or resin microsphere radioembolization for the treatment HCC or metastases from colorectal cancer (CRC).^[19] (See below under unresectable metastatic CRC section for the data from the meta-analysis as pertains to that disease.) Included studies were from 1986 onward and presented tumor response measured by CT scans and data on median survival times. To allow comparability of results with regard to tumor response, the category of “any response” was introduced, and included complete response, partial response, and stable disease. Overall tumor response could only be assessed as any response because response categories were not uniformly defined in the analyzed studies.

In 14 articles, clinical data were presented on tumor response and survival for 425 patients with HCC who had received yttrium-90 radioembolization. Treatment with resin microspheres was associated with a significantly higher proportion of any response than glass microsphere treatment (0.89 vs. 0.78, respectively; p=0.02). Median survival was reported in seven studies in which survival time was defined as survival from microsphere treatment or from diagnosis or recurrence of HCC. Median survival from microsphere treatment varied between 7.1 and 21.0 months, and median survival from diagnosis or recurrence was 9.4–24.0 months.

The authors of the meta-analysis concluded that yttrium-90 radioembolization is associated with high response rates, both in salvage and first-line settings, but that the true impact on survival will only become known after publication of several ongoing and/or to-be-initiated Phase III studies, as well as the results of trials in which yttrium-90 radioembolization and modern chemotherapy agents are combined with novel biologic agents.

In May 2013 a comparative effectiveness review of local therapies (i.e., ablation, embolization, and radiotherapy) for patients with unresectable HCC was conducted by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center for the Agency for Healthcare Research and Quality (AHRQ).^[20] The review sought to report on overall survival and quality of life outcomes and adverse events. Transplant candidates were excluded from this review. Three prospective case series and one retrospective case series with a total of 187 participants met inclusion criteria for review. There were no randomized controlled trials and no comparative trials that met inclusion criteria. Therefore, the strength of evidence was rated as insufficient to evaluate the outcomes of interest. One study reported a 1-year survival rate of 75%; three studies reported a median survival range of 11 to 15 months. Quality of life, local recurrence, and disease progression were not reported in any of the included studies. Adverse events were rare and no liver failure or hepatic abscess was

reported. The authors recommended studies that compare various embolization techniques including radioembolization.

Randomized Controlled Trials

In 2014, Kolligs reported results of a small pilot randomized controlled trial (RCT) comparing RE with TACE for the treatment of unresectable HCC, the SIR-TACE study.^[12] The study included 28 subjects with unresectable HCC, preserved liver function, and an Eastern Cooperative Oncology Group [ECOG] Performance Status of 2 or less, with no vascular invasion or extrahepatic spread, who had five or fewer liver lesions or a single lesion of 10 cm or less. Patients were randomized to RE (n=13) or TACE (n=15). Over posttreatment follow up, PR rates were 13.3% for TACE and 30.8% for RE, with rates of disease control (CR, SD, PR) of 73.3% for TACE and 76.9% for RE. Median progression-free survival (PFS) was 3.6 months for TACE and 3.7 months for RE.

In 2014, Pitton reported results from a small RCT comparing RE with TACE with drug eluting beads TACE (DEB-TACE) for the treatment of unresectable HCC.^[13] The study included 24 patients, 12 randomized to each group. No deaths occurred within 30 days of the procedure for either group. There were no statistically significant differences between the groups in terms of in PFS (180 days for RE vs 216 for TACE; p=0.619) and overall survival (OS; 592 days for RE vs 788 for TACE; p=0.927).

Nonrandomized Comparison Studies

Facciorusso (2020) performed a retrospective analysis that compared patients with HCC treated with RE plus sorafenib (n=45) with propensity score-matched patients treated with sorafenib alone (n=90).^[21] No significant differences were identified in median OS (10 vs. 10 months; p=0.711), median PFS (six versus seven months; p=0.992), and objective response rate (45.5% versus 42.8%; p=1).

Padia (2017) reported on a single-center, retrospective study (2010-2015) comparing segmental RE with segmental chemoembolization in 101 patients with localized, unresectable HCC not amenable to ablation.^[11] Patients receiving chemoembolization had poorer ECOG Performance Status ratings and Child-Pugh class while those receiving RE had larger and more infiltrative tumors. Overall complete remission was 84% with RE and 58% with chemoembolization (p=0.001). Median PFS was 564 days and 271 days (p=0.002) and median OS was 1198 days and 1043 days (p=0.35), respectively, for the RE group and the chemotherapy group.

In 2016, Soydal reported a retrospective study comparing outcomes of patients receiving RE and TACE for HCC.^[22] Each group included 40 patients. RE patients had a mean survival of 39 months versus 31 months for TACE (p=0.014). There was no significant difference in chronic complications and recurrence of disease.

In 2016, Oladeru reported a retrospective study based on SEER registry data comparing survival outcomes of patients receiving RE and external beam radiation of HCC.^[23] A total of 189 patients with unresectable HCC (77 receiving RE, 112 external beam radiotherapy) receiving treatment between 2004 and 2011 were evaluated. Median OS for RE was 12 months versus 14 months for external beam radiotherapy. Median disease-specific survival was identical for both groups at 14 months. After adjustment for differences between patients,

multivariable survival analysis showed no association of treatment and OS or disease-specific survival.

In 2015, El Fouly reported results of a nonrandomized study comparing yttrium-90 RE with TACE among 86 patients with intermediate stage, nonresectable HCC.^[24] Sixty-three patients at one institution were treated with TACE, while 53 patients at a second institution were treated with RE. Median OS in for TACE and RE was not significantly different between groups (18 months for TACE vs 16.4 months for RE); similarly median time to progression (TTP) was not significantly different between groups (6.8 months for TACE vs 13.3 months for RE). TACE patients had higher numbers of treatment sessions, hospital times, and rates of adverse events. Also in 2015, Gramenzi conducted a retrospective cohort study to compare RE with yttrium-90 with sorafenib for intermediate- or advanced-stage HCC.^[25] Patients with HCC refractory to other therapies and no metastases or systemic chemotherapy were included, 74 of whom were treated with sorafenib and 63 treated with RE. Median OS between groups was similar (14.4 months for sorafenib-treated patients vs. 13.2 months for RE-treated patients). After propensity-score matching of 32 subjects in each group, there were no significant differences in median OS or one-, two-, and three-year survival rates between groups.

RADIOEMBOLIZATION AS A BRIDGE TO LIVER TRANSPLANTATION FOR PRIMARY HCC

Systematic Reviews

Kulik (2018) published a systematic review of 18 comparative studies and 31 noncomparative studies that included patients with unresectable HCC who needed a liver transplant and received transplant alone or some type of bridging therapy as well.^[16] Of the 18 comparative studies, two studies (n=257 patients) reported on the incidence of dropout from transplantation wait-lists, and patients receiving bridging therapy. This group had reduced risk of dropout due to disease progression compared with those receiving transplantation alone (RR=0.32). Between-group differences were not statistically significant for mortality (five comparative studies; n=531 patients) or recurrence rate (10 comparative studies; n=889 patients). Subgroup analysis was conducted for types of bridging therapy: for all-cause mortality after transplantation, the RR was 1.124 with TAE compared with transplantation alone (one cohort). For disease recurrence, the RR for this bridging therapy type was 2.374 compared with transplantation alone. No RCTs were identified, and most of the selected studies had a high risk of bias on patient selection, adequate follow-up, and funding source when reported.

Randomized Controlled Trials

Salem (2016) reported on results of a phase 2 RCT comparing conventional TACE and TheraSphere radioembolization (Y90) for treatment of unresectable, unablatable HCC.^[14] Twenty-four patients were assigned to Y90 and 21 patients to conventional TACE; the ultimate goal of treatment for these patients was liver transplantation. The primary outcome was time to progression using intention-to-treat analysis. Median follow-up was 17 months. In the conventional TACE group, there were seven transplants at a median of nine months (range, 3 to 17 months). In the Y90 group, there were 13 transplants at a median of nine months (range, 4 to 15 months). Median time to progression exceeded 26 months in the Y90 group and 6.8 months in the conventional TACE group (hazard ratio, 0.12; 95% CI 0.03 to 0.56; p=0.007). Median survival was 19 months in Y90 and 18 months in conventional TACE (p=0.99). Adverse events were similar between groups, with the exception of more diarrhea (21% vs 0%) and hypoalbuminemia (58% vs 4%) in the conventional TACE group. A limitation of the

OS analysis was the censoring of the survival outcome at liver transplantation given that transplantation is related to the treatment effect.

In 2014, Kulik reported results of a pilot RCT of yttrium-90 RE with or without sorafenib for patients with HCC awaiting liver transplantation.^[26] The study randomized 23 subjects; after accounting for losses due to self-withdrawal from the study, failure to confirm HCC, and death, the modified intention-to-treat (ITT) population included 10 subjects randomized to RE alone and 10 randomized to RE with sorafenib. Overall, 17 of 20 patients underwent liver transplantation, with no difference in median time-to-transplant between groups. However, the addition of sorafenib was associated with increased peritransplant biliary complications, and acute rejection.

Nonrandomized Studies

Gabr (2020) performed a retrospective review that reported on long-term outcomes of liver transplantation for patients with HCC who were bridged or downstaged with RE.^[27] From 2004 to 2018, 207 patients underwent transplant after RE. Median OS from transplant was 12.5 years, with median time to liver transplantation of 7.5 months (interquartile range, 4.4 to 10.3). Overall, 169 patients were bridged and 38 were downstaged to liver transplant. Overall survival rates at 3, 5, and 10 years were 84%, 77%, and 60%, respectively.

Zori (2020) performed a retrospective cohort analysis that compared patients with HCC undergoing bridging locoregional therapy with RE (n=28) or TACE (n=37) prior to liver transplant.^[28] Three-year survival was not significantly different with RE vs TACE (92.9% vs. 75.7%; p=0.052). However, microvascular invasion occurred in 3.6% versus 27% of patients treated with RE versus TACE (p=0.013).

In a 2013 retrospective review, Tohme reported on 20 consecutive HCC patients on liver transplant waiting lists who received radioembolization as bridge therapy.^[29] When radioembolization began, Milan criteria (extent of disease) for liver transplantation were met by 14 patients and sustained until transplantation. Of the six patients who did not meet Milan criteria initially, radioembolization was able to downstage two patients to meet Milan criteria. Complete or partial radiologic response to radioembolization on modified Response Evaluation Criteria In Solid Tumors (RECIST) occurred in nine patients. Additionally, on pathologic examination, five patients who met Milan criteria had complete tumor necrosis with no evidence of viable tumor.

In 2014, Ramanathan reported on multimodality therapy, including radioembolization, for 715 HCC patients of which 231 were intended for transplant.^[30] In the intention-to-treat with transplantation arm, 60.2% were able to receive a transplant. Survival rates posttransplant were 97.1% and 72.5% at one and five years, respectively. Tumor recurrence rates were 2.4%, 6.2%, and 11.6% at one, three, and five years, respectively. Since this study included multimodality therapy, it is not possible to isolate the effect of radioembolization.

Lewandowski (2009) compared RE with chemoembolization in the efficacy of downstaging 86 patients with HCC from stage T3 to T2 (potentially making patients liver transplant candidates).^[31] Patients were treated with either radioembolization using yttrium-90 microspheres (n=43) or TACE (n=43). Median tumor size was similar between the two treatment groups (5.7 and 5.6 cm, for TACE vs. radioembolization, respectively.) Partial response rates were 61% versus 37% for radioembolization vs. TACE, respectively, with

downstaging from T3 to T2 in 58% of patients treated with RE versus 31% with TACE ($p < 0.05$).

RADIOEMBOLIZATION FOR UNRESECTABLE METASTATIC COLORECTAL CARCINOMA (CRC)

Systematic Reviews

A 2010 technology assessment^[7], a 2009 Cochrane review^[32], and a 2009 systematic review with meta-analysis^[19] all concluded that data from large Phase III trials were needed in order to fully understand the impact of radioembolization on survival in patient with CRC metastases in the liver.

Two additional systematic reviews were published in 2013:

Rosenbaum considered radioembolization, either as monotherapy or concomitant with chemotherapy, to be an emerging treatment for CRC liver metastases, with a limited amount of data from heterogeneous studies.^[33] This review evaluated 13 articles on radioembolization as monotherapy and 13 studies on radioembolization combined with chemotherapy for chemoresistant, unresectable CRC liver metastasis. Heterogeneity between studies prohibited pooling of data. This heterogeneity included varying patient inclusion criteria such as the amount of intrahepatic and extrahepatic tumor burden, patient performance status, previous systemic treatments, and protocols for assessing tumor response. CR, PR, and stable disease (SD) rates ranged from 29% to 90% with radioembolization alone and from 59% to 100% for radioembolization with chemotherapy. At 12 months, survival ranged from 37% to 59% with radioembolization alone and from 43% to 74% for radioembolization combined with chemotherapy. As with prior reviews, the authors concluded that additional data is needed from high-quality randomized trials.

In contrast to the prior systematic reviews, Saxena considered the evidence sufficient to recommend increased utilization of radioembolization as salvage treatment for CRC liver metastases.^[34] The review evaluated a total of 979 patients in 20 studies including two RCTs^[35,36]. The majority of patients had previously undergone at least three lines of chemotherapy (range 2-5). After radioembolization, the average reported CRs and PRs from 16 studies was 0% (range, 0% to 6%) and 31% (range, 0% to 73%), respectively. The median time to intrahepatic progress was nine months (range 6 to 16 months) and the median survival time was 12 months (range 8.3 to 36 months). The mean rate of acute toxicity was 40.5% (range 11% to 100%); most cases were mild and did not require intervention. Despite concluding that radioembolization was safe and effective, the authors noted the need for continued evaluation of clinical outcomes.

Randomized Controlled Trial

A phase 3 RCT by van Hazel (2016) of 530 patients compared patients receiving modified FOLFOX chemotherapy and FOLFOX chemotherapy plus SIRT in patients with previously untreated liver-dominant metastatic disease.^[37] Bevacizumab was allowed as additional treatment at the discretion of the treating physician. About 40% of patients had extrahepatic metastases at randomization. About 28% of patients had more than 25% liver involvement of metastases. The primary end point was overall (any site) progression-free survival (PFS). Secondary end points included liver-specific outcomes such as PFS in the liver, tumor response rate, and liver resection rate. The primary end point of PFS at any site showed no

difference between groups (10.2 months vs 10.6 months control vs RE; hazard ratio, 0.93; $p=0.43$). Secondary liver-specific end points of median PFS in the liver and objective response rate in the liver were improved in the RE group (liver PFS, 12.6 months vs 20.5 months control versus RE; liver response rate, 68.8% vs 78.7% control vs RE). Wasan (2017) analyzed OS from this study in combination with two other studies of chemotherapy with and without RE.^[38] Overall, 549 patients were randomly assigned to FOLFOX alone and 554 patients were assigned FOLFOX plus SIRT. Overall survival was not significantly different between groups (HR, 1.04; 95% CI 0.90 to 1.19).

Nonrandomized Studies

Since the systematic reviews were published, a number of additional nonrandomized studies have reported outcomes of RE for patients with CRC liver metastases who failed or were not candidates for chemotherapy.^[39-42] The majority of these were noncomparative studies which precluded conclusions on the survival benefit of RE compared to other treatments. There was a wide range of clinical response to RE; although the rate of complete response was low, partial response averaged 35% and stable disease was reported in 32-71% of patients. The few studies that compared RE to best supportive care reported a statistically significant survival benefit with RE. The rates of Grade 3 to 4 toxicities ranged from 0% to 39% and included absolute lymphocyte, alkaline phosphatase, bilirubin, and albumin. Factors associated with poorer prognosis included large tumor volume, poor radiological response to treatment, and the number of prior chemotherapy treatments.

The most recent comparative study, published by Mokkarala (2019), performed a propensity score-matched retrospective analysis of patients with colorectal metastases treated with DEB-TACE ($n=47$) or RE ($n=155$).^[43] Extra-hepatic metastasis was more frequent with DEB-TACE (68.1% vs. 47.7%; $p=0.014$), as was occurrence of ≥ 10 liver lesions (42.2% vs. 68.8%; $p=0.001$). Toxicity was not significantly different between DEB-TACE and RE (27% vs. 9.1%, respectively; $p=0.057$). Treatment with DEB-TACE was not a prognostic factor for survival (HR, 0.94; 95% CI 0.54 to 1.65).

RADIOEMBOLIZATION FOR MELANOMA METASTASES IN THE LIVER

The evidence related to the use of RE for melanoma consists of relatively small observational studies, many of which focus on patients with uveal melanoma in whom the liver is the most common site of metastatic disease.

Systematic Reviews

Rowcroft (2019) planned to perform a meta-analysis of studies of patients with liver-only metastases of uveal melanoma treated with systemic therapy, isolated hepatic perfusion, hepatic artery infusion, TACE, SIRT, and immunoembolization.^[44] However, due to heterogeneity in available data, meta-analysis was not performed. The authors descriptively reported that six non-comparative retrospective cohort studies ($n=150$; range, 8 to 71) evaluated the use of SIRT, which reported median OS ranged from 9 to 24 months.

Randomized Controlled Trials

No randomized controlled trials were identified for radioembolization of melanoma metastases in the liver.

Nonrandomized Comparative Studies

Gonsalves (2019) performed a prospective study of patients with liver metastases of uveal melanoma treated with RE.^[45] Among patients who were treatment-naïve, complete response, partial response, or stable disease was achieved in 20 of 23 patients (87.0%; 95% CI 66.4%, 97.2%), median progression-free survival from liver metastasis was 8.1 months (95% CI 6.4, 11.8), and median OS was 18.5 months (95% CI 11.3 to 23.5). Among patients who progressed after immunoembolization, complete response, partial response, or stable disease was achieved in 14 of 24 patients (58.3%; 95% CI 36.3%, 77.9%), median PFS from liver metastasis was 5.2 months (95% CI 3.7 to 9.8), and median OS was 19.2 months (95% CI 11.5 to 24.0).

In 2014, Xing conducted a retrospective observational study to compare outcomes for patients with unresectable melanoma (both uveal and cutaneous) liver metastases refractory to standard chemotherapy treated with either yttrium-90 RE (n=28) or best supportive care (n=30).^[46] The groups were similar at baseline in terms of Child-Pugh class, ECOG performance status scores, age, sex, and race. However, patients treated with RE had significantly larger tumor size at baseline than those treated with best supportive care (mean, 7.28 cm vs 4.19 cm; p=0.02). Median OS from diagnosis of melanoma liver metastases was longer in RE-treated subjects (19.9 mo. vs 4.8 mo.; p<0.000), as was the median OS from diagnosis of the primary melanoma (119.9 months vs 26.1 months; p<0.001). Pre- and post-treatment imaging studies were available for 24/28 (85.7%) of those treated with RE. Of those, no patients had a CR; five patients (17.9%) had PR, nine patients (32.1%) had SD, and 10 patients (35.7%) had PD. Two patients receiving RE had major (grade 5) clinical toxicities (ascites and hepatic encephalopathy and eventual mortality). Significant factors for longer OS were ≤ 10 metastatic liver lesions, absence of extrahepatic metastases, and Child-Pugh class A. Although this study was retrospective and included small sample sizes, it included relatively long-term follow-up and provided comparison between RE and best supportive care.

Nonrandomized Non-comparative Studies

In 2014, Eldredge-Hindy retrospectively evaluated outcomes for the use of yttrium-90 RE in 71 patients with biopsy-confirmed uveal melanoma liver metastases.^[47] The median time from the diagnosis of liver metastases to RE was 9.8 months (95% CI 7.4 to 12.2 months), and 82% of patients had received prior liver-directed therapies. Sixty-one patients (86%) had CT or magnetic resonance imaging (MRI) evaluation of treatment response at three months post-RE. Of those, five patients (8%) had a PR, 32 patients (52%) had SD, and 24 patients (39%) had DP. Median OS RE was 12.3 months (range, 1.9 to 49.3 months).

Small studies (n=8 to 32) have reported on use of RE in patients with hepatic metastases from melanoma.^[48-54] Five of the studies included only patients with ocular melanoma, and two included patients with ocular, cutaneous, or other site melanoma. Three studies excluded those patients with poor performance status. Median age was in the 50s for four studies and 61 in one study. One article did not describe any previous treatment and one described it incompletely. Four studies reported tumor response data, by RECIST criteria.

- Treatment response. Among 32 patients in the study by Gonsalves, one patient had a CR (3%), one had a PR, 18 patients had SD (56%) and 12 patients had PD (38%). In the study of 13 patients published by Klingenstein, none had a CR, eight had a PR (62%), two had SD (15%) and three had PD (23%). Nine of 11 patients in the article by Kennedy provided response data: one had CR, six had PR, one had SD and one had PD. Of the eight patients in the Schelhorn study, four (50%) had SD and four (50%) had PD. Memon reported PD

and SD in 13 (81%) patients and PD in three (19%) patients. Ponti reported disease control at six months post-RE in 52% of patients.

- Survival. Median survival in Gonsalves, Klingenstein, Schelhorn, Ponti, and Kennedy were 10.0 months, 19 months, 20 months, 18 months, and not yet reached, respectively.
- Toxicity. Gonsalves reported four patients (12.5%) with grade 3 to 4 liver toxicity and Ponti reported grade 3 to 4 biologic and clinical toxicities in 24% of patients. Klingenstein observed one patient with marked hepatomegaly. Kennedy described one grade 3 gastric ulcer. Memon reported Grade 3 toxicity in two (12%) (absolute lymphocyte toxicity) and one (7%) (aspartate aminotransferase toxicity) patients; and grade 4 bilirubin toxicity in one patient. One study^[51] (n=12) did not include any toxicity data.

RADIOEMBOLIZATION FOR UNRESECTABLE METASTATIC NEUROENDOCRINE TUMORS

Systematic Reviews

Frilling (2019) reported results from a case series of 24 patients that were then included in a meta-analysis of patients treated with SIRT for neuroendocrine liver metastases.^[55] Overall, 26 additional studies were included in the meta-analyses, which reported a fixed effects weighted averages for objective response rate of 51% (95% CI 47% to 54%) and disease control rate (complete response, partial response, or stable disease) of 88% (95% CI 85% to 90%).

A 2012 systematic review evaluated the safety and efficacy of chemoembolization, bland embolization, and radioembolization in patients with unresectable metastatic neuroendocrine tumors (mNET) in the liver.^[56] A total of 37 studies with 1575 total patients were reviewed for response to treatment, survival outcome, and toxicity. The authors reported that each of these therapies were found to be safe and effective, and recommended additional prospective trials to compare relative efficacy and toxicity.

In 2014, a meta-analysis of 12 studies that met inclusion criteria reported complete and partial responses of 50% for radioembolization of metastatic neuroendocrine tumors (mNET) in the liver.^[57] Weighted average disease control was 86%. It was noted that patients with pancreatic mNET was marginally associated with poorer response (p=0.03). The authors concluded that the meta-analysis confirmed the effectiveness of radioembolization of hepatic mNET.

Randomized Controlled Trials

No randomized controlled trials were found for radioembolization of metastatic neuroendocrine tumors in the liver.

Nonrandomized Comparative Studies

Egger (2020) performed a retrospective cohort analysis comparing patients with neuroendocrine liver metastases treated with RE (n=51) or TACE (n=197).^[58] Between RE and TACE, there were no differences in overall morbidity (13.7% vs. 22.6%, respectively; p=0.17), grade 3/4 complication (5.9% vs. 9.2%; p=0.58), 90-day mortality (9.8% vs 5.2%; p=0.21), median OS (35.9 months vs. 50.1 months; p=0.3), or progression-free survival (15.9 vs. 19.9 months; p=0.37). However, disease control rate was greater for TACE compared with RE (96% vs. 83%, p<0.01).

Engelman retrospectively compared locoregional therapies including transarterial, liver-directed therapies including RE, hepatic artery embolization (HAE), and hepatic artery chemoembolization (HACE) in 42 patients treated for metastatic neuroendocrine tumors.^[59] Treatment decisions were at the discretion of the referring physician and interventional radiologist, but the decision to proceed with therapy was typically based on progression of symptoms nonresponsive to octreotide therapy or rapid progression of liver tumor burden on imaging. Seventeen patients had HACE, 13 had HAE, and 12 had RE. Among the 27 patients with symptoms from their liver metastases, there were no statistically significant differences in symptom improvement at three months after first liver-directed therapy across treatment modalities (6/13 for HACE; 4/8 for HAE; 5/6 for RE; $p=0.265$). There were no differences between treatment modalities in radiographic response at six months postprocedure ($p=0.134$), TTP ($p=0.968$), or OS ($p=0.30$).

Nonrandomized Non-Comparative Studies

In 2015 Peker reported on 30 patients with unresectable hepatic mNET who received resin-based RE.^[60] Post-treatment response was assessed by imaging using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Mean follow-up was 23 months. Median OS was 39 months (range 12.6-65.4 months) with 1- and 2-year survival rates of 71% and 45%, respectively. PR was 43%, CR 3%, SD 37%, and PD 17%. The following were not significant prognostic factors: extrahepatic disease, radiographic response, age, and primary NET site.

In 2010, Cao reported the outcomes of 58 patients with unresectable neuroendocrine liver metastases from two different hospitals treated with yttrium-90 microspheres (SIR-Spheres) from 2003 to 2008. Data were examined retrospectively from a database.^[61] Response was assessed with radiographic evidence before and after radioembolization and measured by RECIST guidelines. Patients typically had a CT scan within three months of treatment and every three to six months until disease progression or death. Systemic chemotherapy was routinely given at one institution but not the other. Mean patient age at the time of radioembolization was 61 (range: 29-84 years), and 67% of patients were men. Primary tumor site was variable and included small bowel, pancreas, colon, thyroid, lung, and unknown. Thirty-one patients underwent surgical resection of their primary tumor, which was classified as low-grade in 15, intermediate-grade in seven, and high-grade in seven. Forty-three percent of patients had extrahepatic metastatic disease at study entry. Prior therapies before radioembolization included liver resection in 19 patients, TAE or TACE in six, ablation or percutaneous ethanol injection in 10, previous chemotherapy in 20, concurrent chemotherapy in 34, and post-radioembolization chemotherapy in five patients. Median follow-up was 21 months (range 1-61 months). Fifty-one patients were evaluable, and six achieved a complete response, 14 a partial response, 14 had stable disease, and 17 had disease progression. Overall survival (OS) rates at one, two, and three years were 86, 58, and 47%, respectively. Median survival was 36 months (range: 1-61 months). Prognostic factors for survival included extent of tumor involvement of the liver, radiographic response to treatment, presence of extrahepatic disease at the time of radioembolization, histological grade of tumor, and whether patients were responders (versus nonresponders) to radioembolization. Factors that were not significant prognostic features included age, sex, ECOG status, and previous therapy.

King reported outcomes in patients treated in a single-institution prospective study.^[8] Thirty-four patients with unresectable neuroendocrine liver metastases were given radioactive microspheres [SIR-Spheres] and concomitant seven-day systemic infusion of 5-FU, between

2003 and 2005. Mean patient age was 61 years (range: 32-79 years), and 65% were men. Mean follow-up was 35.2 +/- 3.2 months. The mean interval from diagnosis of hepatic metastases and treatment with SIR therapy was 36.6 +/- 6.7 months. Primary tumor sites were variable and included bronchus (n=1), thyroid (n=2), gastrointestinal (n=15), pancreas (n=8), and unknown (n=8). Subjective changes from baseline hormone symptoms were reported every three months. Twenty-four patients (71%) had, at baseline assessment, symptoms of carcinoid syndrome, including diarrhea, flushing, or rash. At three months, 18 of 33 patients (55%) reported improvement of symptoms, as did 16 of 32 (50%) at six months. Radiologic tumor response was observed in 50% of patients and included six CR (18%), and 11 PR (32%). Mean OS was 29.4 +/- 3.4 months.

RADIOEMBOLIZATION FOR INTRAHEPATIC CHOLANGIOCARCINOMA

Systematic Reviews

In 2015, Al-Adra reported results from a systematic review of studies reporting outcomes for RE for ICC.^[62] The review included 12 publications, seven of which were published in abstract form only. Of the peer reviewed manuscripts, three were described as prospective cohort studies.^[63-65] The overall weighted median survival was 15.5 months (range 7 to 22.2 months), based on 11 included studies. A weighted mean PR was seen in 28% of patients and stable disease was seen in 54% at three months posttreatment.

In 2015, Boehm conducted a meta-analysis to compare hepatic artery-based therapies including hepatic arterial infusion (HAI), TACE, DEB-TACE, and yttrium-90 RE for unresectable ICC.^[66] Twenty studies met inclusion criteria, five of which evaluated yttrium-90 RE. Median OS across studies was 22.8 months for HAI, 13.9 months for RE, 12.4 months for TACE, and 12.3 months for DEB-TACE. CR or PR occurred in 56.9% of patients treated with HAI, compared with 27.4% of those treated with RE and 17.3% of those treated with TACE. While HAI showed the highest median OS, it also had the highest rate of grade III and IV toxicity.

Randomized Controlled Trials

No randomized controlled trials were found for radioembolization of ICC.

Nonrandomized Studies

Additional nonrandomized studies published after the above systematic reviews are included here.

Jia (2017) retrospectively reviewed all 24 patients who underwent Y90 RE for unresectable and failed first-line chemotherapy for ICC at a single institution.^[15] Mean follow-up was 11 months (range, 3 to 36 months). Median OS from time of diagnosis was 24 months (range, 18 to 30 months) and from the RE procedure was nine months (range, 6 to 12 months). Survival rates at 6, 12, and 30 months was 70%, 33%, and 20%, respectively.

Mosconi (2016) retrospectively analyzed 23 consecutive patients with unresectable or recurrent ICC at a single institution.^[21] Overall median survival was 18 months (95% CI 14 to 21 months). Survival was significantly longer in treatment-naive patients (52 months) than in those who received other treatments before RE (16 months; p=0.009).

Rayar (2015) reported successful downstaging after RE in eight patients with unresectable ICCs. Initial unresectability was due to involvement of hepatic veins or portal veins of the future liver remnant.^[67] After RE there was significant decrease in tumor volume and all patients were subsequently able to undergo successful resection. At median follow-up of 15.6 months (range 4 to 40.7 months) after medical treatment and 7.2 months (range 0.13 to 36.4 months) after surgery, five patients were still alive, one of which was alive at 40 months after medical treatment. Two patients had tumor recurrence.

RADIOEMBOLIZATION FOR METASTATIC BREAST TUMORS

Systematic Reviews

One systematic review included six studies with a total of 198 patients with breast cancer metastases in the liver.^[68] Five studies reported tumor response. Overall disease control (complete response, partial response, and stable disease) at two to four months post-treatment ranged from 78% to 96%. Median survival was reported in four studies and ranged from 10.8 to 20.9 months. Adverse effects included gastric ulceration in 10 patients (5%) and treatment-related mortality in three patients (2%). The authors concluded that these studies showed safety and effectiveness of treatment and strongly encouraged comparative studies, in particular, combining radioembolization with systemic therapy.

Nonrandomized Studies

Table 1. Retrospective Case Series of Radioembolization for Liver Metastases in Breast Cancer

Study (Year)	Populations	Outcomes
Pieper (2016) ^[69]	44 women with unresectable liver-dominant breast metastases who had failed 2+ lines of chemotherapy who underwent yttrium-90 RE at a single center from 2006-2015	ORR: 29% Disease control rate: 71% Median TTP: 101 d Median survival: 184 d Grade 2 toxicity: 1 (cholecystitis) Grade 3 toxicity: 1 (duodenal ulceration)
Gordon (2014) ^[70]	75 women with stable extrahepatic disease who had hepatic tumor progression after systemic chemotherapy treated with yttrium-90 RE at a single center	30-day mortality: 4% Median OS: 6.6 mo (95% CI 5.0 to 9.2 mo) Median hepatic TTP: 3.2 mo (95% CI 1.2 to 8.5 mo) Median distant TTP: 4.1 mo (95% CI 2.7 to 7.0 mo)
Saxena (2014) ^[71]	40 women with unresectable, chemo-resistant breast cancer-related liver metastases treated from 2006-2012 at a single institution who had received at least one line of systemic chemotherapy	Grade 1 or 2 clinical toxicity: 40% Of 38 women with ≥1 mo follow-up: CR: 5% PR: 26% SD: 39% PD: 29% Median survival: 13.6 mo
Cianni (2013) ^[72]	52 women with chemotherapy-refractory breast cancer and inoperable liver metastases; chemotherapy administered previously to all patients, surgery in 17.3%, TACE in 3.8%, and RFA in 3.8%	CR: 0% PR: 56% SD: 35% PD: 10% Median OS: 11.5 mo

Haug (2012) ^[64]	58 women with chemotherapy-refractory breast cancer and unresectable hepatic metastases	Mean follow-up: 27.5 wk CR: 0% PR: 25.6% SD: 62.8% PD: 11.6% Median OS: 47 wk
Jakobs (2008) ^[27]	30 (29 women, 1 man) patients who underwent RE with resin microspheres in a single-session, whole-liver treatment for breast cancer metastases and had failed prior polychemotherapy regimens	For 23 patients with follow-up data, after median follow-up of 4 mo: PR: 61% SD: 35% PD: 4% One death due to treatment-related hepatic toxicity after median follow-up of 14.2 mo Median OS: 11.7 mo
Bangash (2007) ^[28]	27 women with progressive liver metastases from breast cancer while on polychemotherapy	After 90-d follow-up CR: 39% PR: 39% SD: 52% PD: 9% Median survival ECOG Performance Status 0: 6.8 mo ECOG Performance Status 1-3: 2.6 mo
Coldwell (2007) ^[38]	44 patients with hepatic metastases at three hospitals who failed 1st-, 2nd-, or 3rd-line treatment for primary breast tumor and were not candidates for RFA, TACE, resection, IMRT, or SRT	After 12-wk follow-up PR: 47% No radiation-related liver failures were observed Median survival: >14 mo

CI: confidence interval; CR: complete response; ECOG: Eastern Cooperative Oncology Group; IMRT: intensity-modulated radiotherapy; ORR: response rate; OS: overall survival; PD: progressive disease; PR: partial response; RE: radioembolization; RFA: radiofrequency ablation; SD: stable disease; SRT: stereotactic radiotherapy; TACE: transarterial chemoembolization; TTP: time to progression.

OTHER METASTATIC TUMORS IN THE LIVER

Data on the use of radioembolization in other tumors metastatic to the liver are limited and included numerous methodologic limitations such as patient heterogeneity, lack of a control group, and patient numbers too small to draw meaningful conclusions. For example, a retrospective data analysis was reported in 2014 by Michl on RE for liver metastases from pancreatic cancer. Nineteen patients were included, 16 of whom had received previous palliative chemotherapy.^[73] Median local PFS in the liver was 3.4 months (range 0.9-45.0). Median OS was nine months (range 0.9-53.0) and one-year survival was 24%. Adverse effects were grade ≤ 3 (e.g., nausea, vomiting, fatigue, fever, abdominal pain) in the short term and long-term effects included liver abscess, gastroduodenal ulceration, cholestasis and cholangitis, ascites, and spleen infarction. The lack of a control group precludes conclusions about any survival benefits and complication rates of RE.

RADIOEMBOLIZATION AS A BRIDGE TO HEPATIC RESECTION

In 2013, Vouche reported on 83 patients treated with radioembolization as a technique to control or limit tumor progression in unresectable, unilobar hepatic disease and to hypertrophy a small future liver remnant.^[74] Patients included in the study had right unilobar disease with HCC (n=67), cholangiocarcinoma (n=8), or metastatic CRC (n=8). One month

after radioembolization, significant right lobe atrophy ($p=0.003$), left lobe hypertrophy ($p<0.001$), and future liver remnant hypertrophy ($p<0.001$) were observed and remained during follow-up. Successful right lobectomy was later performed in five patients, and six patients received liver transplants. However, further studies are needed to assess radioembolization as a bridge to hepatic resection.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINES

All the following statements are category 2A recommendations unless specified.

Primary Hepatocellular Carcinoma

National Comprehensive Cancer Network (NCCN) guidelines for hepatocellular carcinoma principles of local regional therapy state that all patients with HCC should be evaluated for potential curative therapies.^[9] They recommend considering locoregional therapies for patients who are not candidates for surgical curative treatments, or as part of a strategy to bridge patients for other curative therapies. They also state that “all tumors irrespective of location may be amenable to arterially directed therapies [including bland TAE, TACE and TACE with drug-eluting beads, and RE with yttrium-90 microspheres] provided that the arterial blood supply to the tumor may be isolated without excessive non-target treatment.”

NCCN discussion indicates that there is limited evidence available on the utility of radioembolization as a bridge to liver transplant for patients on a liver transplant waiting list. However, most NCCN member centers use radioembolization as a bridge to transplant.

Primary Intrahepatic Cholangiocarcinoma

Recommendations for unresectable intrahepatic cholangiocarcinoma (ICC) include chemotherapy, clinical trial, and supportive care.^[9] The guideline follows that of the HCC locoregional therapy recommendations, above.

Metastatic Colorectal Cancer

Use of intra-arterial embolization including RE is a recommendation for highly selected patients with chemotherapy-resistant/-refractory disease without obvious systemic disease, with predominant hepatic metastases.^[6,75]

Metastatic Neuroendocrine Tumors

For unresectable liver metastases (carcinoid or neuroendocrine tumors of the pancreas, e.g., islet cell), recommendations include hepatic regional therapy which includes radioembolization (category 2B lower-level evidence with NCCN consensus).^[1]

Metastatic Breast Cancer

Current recommendations do not address the use of radioembolization in the treatment of metastatic breast cancer.^[76]

Metastatic Melanoma

Current recommendations do not address the use of radioembolization in the treatment of metastatic cutaneous melanoma.^[77] Regarding treating of liver metastases from uveal melanoma, the guidelines state that SIRT has been reported in retrospective studies and that more research is needed.^[78]

AMERICAN COLLEGE OF RADIOLOGY APPROPRIATENESS CRITERIA®

The American College of Radiology (ACR) published Appropriateness Criteria for radiologic management of hepatic malignancy.^[79]

Primary Hepatocellular Carcinoma

ACR Appropriateness Criteria consider radioembolization with beta-emitting Y90 beads to be an emerging treatment option for HCC, with outcomes similar to those with transarterial chemoembolization (TACE) and transarterial embolization (TAE), but with the possibility of less patient discomfort and toxicity. The guideline also reports that radioembolization has “shown the ability to effectively downstage patients for potential transplant or resection. Therefore, ACR recommendations are that radioembolization may be appropriate for solitary HCC tumor <3cm, and usually appropriate, particularly in the presence of portal vein thrombosis or extensive bilobar disease, for solitary HCC tumor of 5 cm and for multiple tumors, at least one of which is >5cm.

Metastatic Colorectal Cancer

The ACR reports that published evidence suggests that TACE and radioembolization provide similar survival benefit and may be appropriate for patients with metastatic liver-dominant colorectal tumors ≥ 5 cm, or for solitary colorectal liver metastasis.

Metastatic Neuroendocrine Tumors

The ACR reports increasing research into the use of radioembolization in this patient population, with early small studies suggesting therapeutic equivalency with more traditional arterial embolization techniques. Radioembolization is recommended as usually appropriate for symptomatic neuroendocrine metastases in the liver when medication fails to control symptoms.

AMERICAN COLLEGE OF RADIOLOGY/AMERICAN SOCIETY FOR RADIATION ONCOLOGY/SOCIETY OF INTERVENTIONAL RADIOLOGY

The list of indications in the American College of Radiology (ACR)/American Society for Radiation Oncology (ASTRO)/Society of Interventional Radiology (SIR) guidelines include, but are not limited to:^[80]

- Unresectable and/or inoperable primary or secondary liver malignancies that are liver dominant but not necessarily exclusive to the liver; and
- Performance status that will allow them to benefit from the therapy (e.g., ECOG performance status of 0 or 1 or KPS of 70 or more); and
- Life expectancy of at least three months

RADIOEMBOLIZATION BRACHYTHERAPY ONCOLOGY CONSORTIUM

Members met as an independent group of experts in interventional radiology, radiation oncology, nuclear medicine, medical oncology, and surgical oncology. Using level 2A evidence (panel consensus with low-level evidence), 14 recommendations were made. They concluded that there was sufficient evidence to support the safety and efficacy of yttrium-90 microsphere therapy and that its use requires multidisciplinary management, adequate patient selection, and meticulous angiographic technique. They also stated that the initiation of clinical trials was necessary to further define the role of yttrium-90 microsphere therapy in relation to other currently available therapies.^[81]

SUMMARY

TRANSARTERIAL EMBOLIZATION WITH NON-RADIOACTIVE AGENTS

There is enough research to show that transarterial embolization (TAE) with non-radioactive agents improves health outcomes for people with cancer and various conditions. Therefore, transarterial embolization (TAE) with non-radioactive agents may be considered medically necessary for any indication.

TRANSARTERIAL CHEMOEMBOLIZATION

There is enough research to show that transarterial chemoembolization (TACE) improves health outcomes for people with cancer and various conditions. Therefore, transarterial chemoembolization (TACE) may be considered medically necessary for any indication.

RADIOEMBOLIZATION

Primary Hepatocellular Carcinoma (HCC)

Studies have demonstrated that radioembolization is comparable to transarterial chemoembolization (TACE), which is considered to be the therapy of choice for patients with unresectable primary hepatocellular carcinoma (HCC) in terms of tumor response and overall survival. However, disadvantages of TACE include the necessity of multiple treatment sessions and hospitalization, its contraindication in patients with portal vein thrombosis, and its poorer tolerance by patients. Therefore, radioembolization may be considered medically necessary for the treatment of unresectable primary HCC or as a bridge to transplantation in primary HCC.

Metastatic Colorectal Cancer in the Liver

A major cause of morbidity and mortality in patients with colorectal disease metastatic to the liver is liver failure, as this disease tends to progress to diffuse, liver-dominant involvement. Therefore, the use of radioembolization to decrease tumor bulk and/or halt the time to tumor progression and liver failure may lead to prolonged progression free and overall survival in patients with no other treatment options (i.e., those with chemotherapy refractory liver-dominant disease). Other uses include palliation of symptoms from tumor bulk. Radioembolization for the treatment of unresectable hepatic metastases from colorectal cancer may be considered medically necessary in carefully selected patients, when criteria are met.

There is insufficient evidence on the use of radioembolization for the treatment of unresectable hepatic metastases from colorectal cancer when the patient does not meet

criteria. Therefore, radioembolization for the treatment of unresectable hepatic metastases from colorectal cancer is considered investigational when criteria are not met.

Metastatic Neuroendocrine Tumors in the Liver

Studies of radioembolization for treatment of metastatic neuroendocrine tumors in the liver have included heterogeneous patient populations, making interpretation of survival data difficult. However, relief of symptoms from carcinoid syndrome has been reported in a proportion of patients. Surgical debulking of liver metastases has shown palliation of hormonal symptoms; similarly, debulking by radioembolization may lead to symptom relief in some patients. Therefore, radioembolization for the treatment of unresectable hepatic metastases from neuroendocrine tumors may be medically necessary in carefully selected patients when criteria are met.

There is insufficient evidence on the use of radioembolization for the treatment of hepatic metastases from neuroendocrine tumors when the patient does not meet criteria. Therefore, radioembolization for the treatment of hepatic metastases from neuroendocrine tumors is considered investigational when criteria are not met.

Metastatic Melanoma in the Liver

In patients with uveal melanoma, the liver is the most common site of metastatic disease. Studies of radioembolization for treatment of metastatic melanoma (uveal or cutaneous) in the liver consists of one comparative study and several relatively small observational studies. In general, these studies predict good tumor response to radioembolization and report significant increases in overall survival compared to those treated with best supportive care. Therefore, radioembolization may be considered medically necessary for the treatment of diffuse, symptomatic hepatic metastases from melanoma when criteria are met.

There is insufficient evidence on the use of radioembolization for the treatment of hepatic metastases from melanoma when the patient does not meet criteria. Therefore, radioembolization for the treatment of hepatic metastases from melanoma is considered investigational when criteria are not met.

Primary Intrahepatic Cholangiocarcinoma (ICC)

The current evidence on the use of radioembolization (RE) in patients with primary intrahepatic cholangiocarcinoma (ICC) is limited to data from small studies that do not compare the health outcomes of RE with other treatments. These study designs make interpretation of the data on tumor response and survival difficult to interpret. However, ICC is a rare tumor, so large comparative studies may never become available. The available studies have consistently reported beneficial effects in patients who are not candidates for surgical tumor resection. Because there are currently limited treatment options for these patients, radioembolization may be medically necessary for the treatment of unresectable primary ICC. Since surgical resection is currently the preferred treatment for these tumors, radioembolization is considered investigational for resectable primary ICC.

Miscellaneous Metastatic Tumors in the Liver

The current evidence on the use of radioembolization in intrahepatic cholangiocarcinoma and metastatic tumors in the liver other than those from colorectal carcinoma, melanoma or

neuroendocrine tumors is too limited to draw meaningful conclusions due to methodologic limitations such as small numbers of heterogeneous patients. Therefore, radioembolization for these other tumors, including metastatic tumors from breast and pancreatic cancer, is considered investigational.

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82. BlueCross BlueShield Association Medical Policy Reference Manual
 "Radioembolization for Primary and Metastatic Tumors of the Liver." Policy No. 8.01.43

CODES

NOTE: CPT code 37243 can be used for both *radioactive* and *non-radioactive* embolization procedures performed for numerous conditions/locations. Embolization codes requiring prior authorization are listed on the "Pre-authorization List" web page. There may be codes related to embolization **not** included in any medical policy. Embolization codes not listed on the pre-authorization website do not require prior approval.

Codes	Number	Description
CPT	37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction
	75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
	77399	Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services
	77778	Interstitial radiation source application; complex
	79445	Radiopharmaceutical therapy, by intra-arterial particulate administration
HCPCS	C2616	Brachytherapy source, non-stranded, yttrium-90, per source
	S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres

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