

Radioembolization/Selective Internal Radiation Therapy (SIRT)

Policy MP-017

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Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial, and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.

Description:

Radioembolization (referred to as selective internal radiotherapy in older literature) delivers small beads (microspheres) impregnated with yttrium 90 intra-arterially via the hepatic artery. The microspheres, which become permanently embedded, are delivered to tumors preferentially because the hepatic circulation is uniquely organized, whereby tumors greater than 0.5 cm rely on the hepatic artery for blood supply while the normal liver is primarily perfused via the portal vein.

Yttrium 90 is a pure beta emitter with a relatively limited effective range and a short half-life that helps focus the radiation and minimize its spread. Candidates for radioembolization are initially examined by hepatic angiogram to identify and map the hepatic arterial system. At that time, a mixture of technetium 99-labeled albumin particles is delivered via the hepatic artery to simulate microspheres. Single-photon emission computed tomography is used to detect possible shunting of the albumin particles into the gastrointestinal or pulmonary vasculature.

Currently, 2 commercial forms of yttrium-90 microspheres are available: a glass sphere (TheraSphere) and a resin sphere (SIR-Spheres). Noncommercial forms are mostly used outside the United States. While the commercial products use the same radioisotope (yttrium 90) and have the same target dose (100 gray), they differ in microsphere size profile, base material (i.e., resin vs glass), and size of commercially available doses. The 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.

The Food and Drug Administration (FDA) granted premarket approval of SIR-Spheres for use in combination with 5-fluorouridine chemotherapy by hepatic arterial infusion to treat unresectable hepatic metastases from colorectal cancer. In contrast, TheraSphere's glass sphere was approved under a humanitarian device exemption for use as monotherapy to treat unresectable hepatocellular carcinoma.

Policy Statement and Criteria

1. Commercial Plans

U of U Health Plans may consider selective internal radiation therapy (SIRT) medically necessary as treatment for individuals with ALL of the following:

- A. Has an ECOG* score of 0 or 1 or KPS* score >70; and
- B. Documentation demonstrates a belief that the individual has a ≥3 month survival; and
- C. One of the following conditions (i, ii, or iii):
 - i. Primary treatment for surgical unresectable primary hepatocellular carcinoma (HCC) or, as a bridge to liver transplantation when **ALL** of the following criteria are met for either indication:
 - a) Preserved liver function defined as Child-Pugh Class A or B** ; and
 - b) Three or fewer encapsulated nodules and each nodule is ≤ 5 centimeters in diameter; and
 - c) No evidence of extra-hepatic metastases; and
 - d) No evidence of severe renal function impairment; and
 - e) No evidence of portal vein occlusion.
 - ii. Unresectable hepatic metastases from colorectal carcinoma when **ALL** of the following criteria are met:
 - a) With liver-dominant disease; and
 - b) Who are refractory to chemotherapy or are not candidates for chemotherapy or other systemic therapies.
 - iii. Hepatic metastases from neuroendocrine tumors (carcinoid and non-carcinoid) when **ALL** of the following criteria are met:
 - a) With diffuse and symptomatic disease; and
 - b) Systemic therapy has failed to control symptoms.
 - iv. Unresectable primary intrahepatic cholangiocarcinoma

U of U Health Plans considers SIRT investigational/experimental for all other indications due to insufficient evidence to support conclusions regarding the efficacy of SIRT on health outcomes.

***Eastern Cooperative Oncology Group (ECOG) and Karnofsky Performance Status (KPS)**

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any self-care; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

****Child-Pugh classification of cirrhosis**

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time			
Seconds over control	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh class A (well-compensated disease); 7 to 9 is class B (significant functional compromise); and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100 and 85%; class B: 80 and 60%; and class C: 45 and 35%.

2. Medicaid Plans

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at

<http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

3. Medicare Plans

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicare policies and coverage, please visit their search website at:

<http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or [the manual website](#)

Clinical Rationale

Hepatocellular Carcinoma (HCC)

In 2015, a nonrandomized study (El Fouly, et al.), compared radioembolization (RE) with transcatheter arterial chemo-embolization (TACE) for 86 patients with intermediate stage, nonresectable HCC. At a single institution, 63 patients were treated with TACE, while 53 patients at a second institution were treated with RE. Median overall survival (OS) for TACE (18 months) and RE (16.4 months) did not differ significantly between groups; similarly, the median time to progression did not differ significantly between groups (6.8 months for TACE vs 13.3 months for RE). TACE patients had more treatment sessions, lengthier hospital stays, and higher adverse event rates.

A retrospective cohort study (Gramenzi, et al.) conducted in 2015, compared RE with the kinase inhibitor sorafenib for intermediate- or advanced-stage HCC. Patients with HCC refractory to other therapies and no metastases or systemic chemotherapy were included, 74 of whom were treated with sorafenib and 63 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 1-, 2-, and 3-year survival rates between groups.

In 2015, the SIR-TACE study, a small pilot randomized control trial (RCT) by Kolligs, et al., reported on results comparing RE with TACE for the treatment of unresectable HCC. The trial included 28 subjects with unresectable HCC, preserved liver function, and an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 2 or less, with no vascular invasion or extrahepatic spread, who had 5 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 post-treatment follow-up, partial response rates were 13.3% for TACE and 30.8% for RE, with disease control rates (complete remission, stable disease, partial response) 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.

Another small RCT in 2015 (Pitton, et al.), also reported results comparing RE with DEB-TACE for the treatment of unresectable HCC. The study included 24 patients, with 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 days for DEB-TACE; $p=0.619$) or overall survival (OS; 592 days for RE vs 788 days for DEB-TACE; $p=0.927$).

A 2016 nonrandomized comparative study (Soydal, et al.), retrospectively assessed outcomes for patients receiving RE and TACE for HCC. Each group included 40 patients. RE patients had a mean survival of 39 months vs 31 months for TACE patients ($p=0.014$). There were no significant differences in complication or disease recurrence rates.

Another study in 2016 (Oladeru, et al.), retrospectively analyzed the SEER (Surveillance, Epidemiology, and End Results) registry data comparing survival outcomes for patients with HCC receiving RE with external-beam radiation therapy (EBRT). A total of 189 patients with unresectable HCC (77 receiving RE, 112 receiving EBRT) were treated between 2004 and 2011. Median OS for RE was 12 months and 14 months for EBRT. Median disease-specific survival was identical for both groups at 14 months. After adjustment for differences between patients, multivariable survival analysis showed no association between treatment and OS or disease-specific survival.

Two systematic reviews published in 2016 (Lobo and Facciorusso, et al.) compared radioembolization (RE) with TACE for the treatment of unresectable HCC. The first review selected 5 retrospective observational studies (total $N=533$ patients). Survival at 1 year did not differ statistically between RE (42%) and TACE (46%; relative risk [RR], 0.93; 95% CI, 0.81 to 1.08; $p=0.33$). At 2 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 3, 4, or 5 years. Postprocedural complications were also similar in the 2 groups. The second review included 10 studies (total $N=1557$ patients), two of which were randomized controlled trials (RCTs). The OR for survival was not statistically significant at 1 year ($OR=1.0$; 95% CI, 0.8 to 1.3; $p=0.93$) but favored RE in years 2 ($OR=1.4$; 95% CI, 1.1 to 1.90; $p=0.01$) and 3 ($OR=1.5$; 1.0 to 2.1; $p=0.04$).

A 2017 network meta-analysis (Tao, et al.) compared nine minimally invasive surgeries for treatment of unresectable hepatocellular carcinoma (HCC). 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 RE (90Y RE), TACE plus external-beam radiation therapy (EBRT), and ethanol ablation. The network included 17 studies with 2669 patients and 4 studies with 230 patients including 90Y RE. In the pair-wise 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% confidence interval [CI], 1.3 to 15.1). However, in the network meta-analysis, there was no significant difference between the corresponding 8 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. TACE plus EBRT had the highest surface under the cumulative ranking curves in complete remission (77%), partial response (89%), progressive disease (95%), and objective response rate (81%).

Another meta-analysis of studies (Ludwig, et al., 2017), indirectly compared DEB-TACE with 90Y RE for HCC. 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 1-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 2 or 3 years but did favor DEB-TACE. At 2 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 3 years survival was 56% and 21% ($OR=0.71$; 95% CI, 0.21 to 2.55; $p=0.62$), respectively.

A 2017 report (Padia, et al.), on a single-center, retrospective study dated from 2010 through 2015, compared segmental RE with segmental chemoembolization in 101 patients with localized, unresectable HCC not amenable to ablation. 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.

A Hayes directory report reviewed in 2018, originally published in 2014, evaluated radioactive yttrium-90 microspheres for the treatment of primary unresectable liver cancer. The report focused on studies for TARE vs TACE in which they had comparable results for survival and tumor response. Overall TARE with 90Y did have fewer hospitalization days versus TACE, however, results for re-hospitalization were inconsistent. TARE with 90Y suggested comparable safety, although evidence found more hepatic dysfunction, post-embolization syndrome, and lymphopenia, with less hematologic complications, abdominal pain, and fever than TACE. The authors concluded, transarterial radioembolization (TARE) with yttrium-90 (90Y) appears to have comparable clinical outcomes to other intra-arterial therapies (IATs), specifically transarterial chemoembolization (TACE), as well as sorafenib. However, with regards to TARE 90Y, RCTs that compare TARE 90Y to other standard treatments are needed to better understand comparative risks and benefits.

SIRT as a Bridge to Liver Transplantation for Unresectable HCC

A 2010 overview (Biolato, et al.) based the analysis of current literature, evaluated the loco-regional therapy performed by TACE in patients with HCC, either as sole, neoadjuvant to surgery or bridge therapy to orthotopic liver transplantation. Chemoembolization combines de-arterialization of the tumor and selective delivery of chemotherapeutic agents into tumor's feeding vessels during angiography. Tumor ischemia raises the drug concentration compared to infusion alone and extends the retention of the chemotherapeutic drug. As loco-regional therapy, TACE allows a complete local tumor control of 25 to 35% and permits an increase of survival in patients with intermediate HCC according to Barcelona-Clinic Liver Cancer (BCLC) classification. Excellent results were also achieved by combined therapies, such as with percutaneous ethanol injection (PEI) or radiofrequency ablation (RFA), as neoadjuvant therapy prior to liver resection and in some circumstances as a bridging tool before liver transplantation. Drug eluting beads are microspheres that can be loaded with doxorubicin and induce toxic and ischemic necrosis with the same device; that allows an increase of drug selectively exposed to tumor cells and simultaneously a reduction of systemic toxicity. Tumor embolization induces a neoangiogenic reaction with a significant growth of adjacent satellites, so the association with sorafenib has a strong rationale for a combined therapy and is currently under investigation. The authors concluded that TACE is the standard of care for treatment of intermediate HCC.

In a 2013 retrospective review (Tohme, et al.) published a report on 20 consecutive HCC patients awaiting liver transplant who received RE as bridge therapy. When RE began, Milan criteria were met by 14 patients and sustained until transplantation. Of the 6 patients who did not meet Milan criteria initially, RE was able to downstage 2 patients to meet Milan criteria. After RE, the median time to liver transplant was 3.5 months. Complete or partial radiologic response to RE, assessed using modified Response Evaluation Criteria In Solid Tumors (RECIST), occurred in 9 patients. Additionally, on pathologic examination, 5 patients had no evidence of viable tumor whose disease met the Milan criteria.

A 2014 report (Ramanathan, et al.), described various therapies, including RE, for 715 HCC patients of whom 231 were intended for transplant. In the intention-to-treat transplantation arm, 60.2% received a

transplant. Survival rates post-transplant were 97.1% and 72.5% at 1 and 5 years, respectively. Tumor recurrence rates were 2.4%, 6.2%, and 11.6% at 1, 3, and 5 years, respectively.

In a 2016 phase 2 RCT by Salem, et al., findings for comparing conventional TACE and TheraSphere radioembolization (Y90) for treatment of unresectable, unablatable HCC were reported. 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 7 transplants at a median of 9 months (range, 3-17 months). In the Y90 group, there were 13 transplants at a median of 9 months (range, 4-15 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 2018 systematic review (Kulik, et al.), reported on 18 comparative studies and 31 non-comparative studies that included patients with unresectable HCC who needed a liver transplant and received transplant alone or some type of bridging therapy as well. Of the 18 comparative studies, 2 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 (5 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 transarterial embolization (TAE) compared with transplantation alone (1 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.

Hayes researched radioactive yttrium-90 microspheres for the treatment of primary unresectable liver cancer as a bridge to transplantation or surgery in a medical directory report reviewed in 2018. The following comparisons were found: 1. Survival appeared comparable for TARE and the other treatments, suggesting that TARE and post-TARE radical treatment in general may have better survival. 2. Tumor response appears comparable for TARE and the other treatments, suggesting that TARE may have better results than TACE or sorafenib. 3. TARE may have a more favorable proportion of downstaging and time to downstaging compared with TACE. 4. TARE may have more favorable time to progression compared with TACE, but not with sorafenib. 5. TARE with 90Y suggests comparable safety, suggesting that TARE with sorafenib may lead to fewer adverse events. Based on a small body of evidence, transarterial radioembolization (TARE) with yttrium-90 (90Y) appears to have at least comparable clinical outcomes to transarterial chemoembolization (TACE), sorafenib, and no pre-transplant treatment. However, the evidence is insufficient to draw conclusions.

Intrahepatic Cholangiocarcinoma (ICC)

In a 2010 prospective study (Saxena, et al.), 25 patients were assessed with unresectable ICC who received radioembolization (RE) with Y90 resin microspheres. Extrahepatic disease was present in 48%, mean age was 57 years, and 48% of patients were female. Prior treatment included surgery in 40%, chemotherapy in 72%, radiofrequency ablation in 6.1%, and EBRT in 3.0%. By RECIST tumor response criteria, complete remission was seen in 0%, partial response in 24%, stable disease in 48%, and progressive disease in 20%. Follow-up was collected between 0.4 months and 55 months (median, 8.1

months). In the entire group, median OS was 9.3 months. Among subgroups, longer survival duration was seen in patients with peripheral tumors and those with ECOG Performance Status score of 0. The proportion of patients with both grade 3 albumin toxicity and grade 3 bilirubin toxicity was 8%. Grade 3 alkaline phosphatase toxicity was observed in 4%. One (4%) patient experienced duodenal ulcer due to malperfusion of Y90 microspheres.

A study from 2012 (Hoffmann, et al.), reported the results of RE with Y90 resin microspheres including 24 patients with nonresectable chemorefractory ICC and no extrahepatic disease. Mean age of the sample was 65.2 years, and the sample was 45.5% female. ECOG Performance Status score was 0 in 51.5%, 1 in 21.2%, and 2 in 27.3%. Previous therapy included chemotherapy in 78.8%, surgery in 36.4%, TACE in 9.1%, radiofrequency ablation in 5.1%, and EBRT in 3.0%. Tumor response was assessed by RECIST criteria. Complete remission was seen in 0%, partial response in 36.4%, stable disease in 51.5%, and progressive disease in 15.2%. Follow-up ranged from 3.1 to 44 months (median, 10 months). Median OS was 22 months and median time to progression was 9.8 months. Favorable subgroups with respect to survival included those with ECOG Performance Status score of 0, tumor burden as a percentage of liver volume of 25% or less, response by cancer antigen 19-9 criterion, and RECIST partial response. The same subgroups, except those with a cancer antigen 19-9 response, had favorable time to progression results. Data were collected retrospectively and no toxicity results were reported.

A 2013 retrospective review (Mouli, et al.) collected data from a single institution and reported on 46 patients treated with RE for ICC. Survival varied by level of disease (multifocal, infiltrative, and bilobar), and ranged from 5.7 to 15.6 months. Five patients achieved resectable status and underwent curative resection.

The findings were validated in a 2015 systematic review (Boehm, et al.), comparing hepatic artery-based therapies, including hepatic arterial infusion (HAI), TACE, DEB-TACE, and Y90 RE, for unresectable ICC. Of 20 studies that met inclusion criteria, five evaluated Y90 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. Complete remission or partial response 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.

Since that systematic review case series by Mosconi, et al.,(2016) reviewing 23 consecutive patients with unresectable or recurrent ICC at a single institution and Jia et al in 2017 involving 24 patients both demonstrated improved survival using selective internal radiation therapy with Y90 beads. Mosconi demonstrated overall median survival of 18 months (95% CI, 14 to 21 months). With survival significantly longer in treatment-naive patients (52 months) than in those who received other treatments before RE (16 months; $p=0.009$). The Jia study demonstrated median OS from the time of diagnosis was 24 months (range, 18-30 months) and from the RE procedure was 9 months (range, 6-12 months). Survival rates at 6, 12, and 30 months were 70%, 33%, and 20%, respectively.

In 2017, the use of SIRT with yttrium-90 (Y-90) resin microspheres has progressed as data increasingly speak to its utility in patients with both intermediate and late stage disease in these cancers. In anticipation of the pending completion of several prospective randomized controlled multi-center studies exploring the use of Y-90 resin microspheres in primary liver cancers, this article outlined mechanisms involved in SIRT administration and reviewed key safety and efficacy data that are currently available in the literature involving use of this therapy in both HCC and ICC. Wang, et al. concluded that interventional oncology procedures, including SIRT, have become an essential part of the multi-disciplinary approach to management of liver cancer at most major medical centers. Trans-arterial Y-90 radio-embolization is a promising treatment modality increasingly being used to treat various liver malignancies including HCC and ICC. With proper patient selection which includes patient ECOG

performance status not higher than 2 and well-preserved liver function with serum total bilirubin of less than 2 mg/dL, SIRT procedures boast benefits that outweigh the risks, with increased survival and DCRs, and maintenance of good quality of life (QOL) for patients with an unfortunate prognosis. Side effects are few and include fatigue, abdominal pain, nausea and vomiting. Grade 3 to 4 AEs such as gastro-intestinal (GI) ulcerations and radio-embolization-induced liver disease (REILD) are uncommon. The authors determined that patients with locally advanced HCC treated with SIRT, had similar efficacy with less toxicity to those treated with sorafenib. As the body of research with prospective, randomized, controlled multi-center studies with a focus on SIRT oncology procedures continues to grow, a more promising future exists for improved outcomes and survival for patients who have liver cancer with advanced disease and limited therapeutic options.

Unresectable Neuroendocrine Tumors

A 2010 case series (Cao, et al.), noted results on outcomes for 58 patients, from 2 different hospitals, with unresectable neuroendocrine liver metastases who were treated with RE from 2003 to 2008. Response was assessed with radiographic evidence before and after RE and measured using RECIST guidelines. Systemic chemotherapy was routinely given at a single institution. Mean patient age at the time of RE was 61 years (range, 29-84 years), and 67% of patients were men. Primary tumor site varied 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 7, and high grade in 7. Forty-three percent of patients had extrahepatic metastatic disease at study entry. Median follow-up was 21 months (range, 1-61 months). Fifty-one patients were evaluable, and 6 achieved complete remission, 14 had a partial response, 14 had stable disease, and 17 experienced disease progression. OS rates at 1, 2, and 3 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 RE, histologic grade of tumor, and whether patients responded to RE.

A 2012 retrospective, nonrandomized control study (Bester, et al.) evaluated the use of SIRT as a salvage treatment for individuals with hepatic metastases. In this study 390 patients, 339 who were treated with SIRT, 51 who either declined SIRT, or were ineligible due to variant hepatic arterial anatomy or extensive hepatopulmonary shunting were subsequently used as controls. Of the SIRT treated patients, 224 had metastatic CRC, and the remainder had an assortment of other metastatic cancers, including neuroendocrine (n=40), breast (n=16), unknown primary (n=10), pancreatic (n=8), gastric (n=8), and others (for example, melanoma; n=33). No significant differences were noted between the treatment and control groups at baseline, including the presence of extra-hepatic disease and hepatic tumor burden. At the time of final follow-up, 59% (201/390) of the SIRT subjects had died, while 76% (39/51) of the control group had died. Overall survival (OS) was reported to be 12 months for the SIRT group and 6.3 months for the control group ($p < 0.001$). In a subgroup analysis, OS was reported as 11.9 months for the CRC group ($p < 0.001$ vs. control) and 12.7 months in the non CRC SIRT group ($p < 0.024$ vs. control). SIRT treatment was a significant predictor of OS ($p < 0.002$), with a 43% reduction in the hazard of death vs. control patients. An important finding is that the site of primary tumor was not a significant predictor of outcomes. No SIRT-related deaths were reported within the 3 month follow-up period. However, several significant complications were noted, including Grade 1 abdominal pain in the immediate postoperative period as well as within 1 month of treatment.

Subsequently, a 2013 case series (Benson, et al.), assessed outcomes for 151 subjects with a variety of liver metastases (CRC, n=61; neuroendocrine, n=43; and other tumor types, n=47) that were refractory to other therapies subsequently treated with TheraSpheres. Disease control rates (DCR) were 59%, 93% and 63% for CRC, neuroendocrine and other primaries, respectively. Median progression-free survival

(PFS) was 2.9 and 2.8 months for CRC and other primaries, respectively. PFS was not achieved in the neuroendocrine group. The median reported survival from SIRT was 8.8 months for CRC and 10.4 months for other primaries. The authors stated that the median survival for subjects with neuroendocrine tumors has not been reached. 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%). The authors concluded that individuals with liver metastases can be safely treated with SIRT.

A 2014 systematic review (Devicic, et al.), analyzed the results of 12 studies that provided RECIST data for hepatic metastatic neuroendocrine tumors treated with RE. For Y90 RE with resin microspheres only, objective radiographic response rates (complete remission or partial response by RECIST) ranged from 12% to 80%, with a random-effects weighted average of 50% (95% CI, 38% to 62%). DCRs (complete remission, partial response, stable disease) ranged from 62% to 100%, with a random-effects weighted average of 86% (95% CI, 78% to 92%).

Unresectable Intrahepatic Metastatic CRC

A 2014 systematic review (Saxena, et al.) evaluated 20 studies comprising of 979 patients on the safety and efficacy of yttrium-90 radioembolization for unresectable, chemorefractory colorectal cancer liver metastases. Patients included in this study had failed a median of 3 lines of chemotherapy. After treatment, the average reported value of patients with complete radiological response, partial response and stable disease was 0%, 31% and 40.5%. The median time to intra-hepatic progression was 9 months, the median overall survival was 12 months, and the median overall acute toxicity rate was 40.5%. Most cases of acute toxicity were mild and resolved without intervention. The number of previous lines of chemotherapy (≥ 3), poor radiological response to treatment, extra-hepatic disease and extensive liver disease ($\geq 25\%$) were the factors most commonly associated with poorer overall survival. The authors concluded that 90Y radioembolization is a safe and effective treatment of chemorefractory colorectal cancer liver metastases in the salvage setting and should be more widely utilized.

A subsequent 2015 multicenter study (Kennedy, et al.) assessed data of the safety and efficacy of radioembolization with yttrium-90-labeled resin microspheres in 606 patients with unresectable colorectal liver metastases. Median tumor-to-liver ratio and -activity administered at first procedure were 15% and 1.17 GBq. Hospital stay was less than 24 hours in 97.8% of cases. Common grade ≥ 3 AEs over 184 days follow-up were: abdominal pain (6.1%), fatigue (5.5%), hyperbilirubinemia (5.4%), ascites (3.6%) and gastrointestinal ulceration (1.7%). Median survivals following radioembolization as a 2nd-line, 3rd-line, or 4th-plus line were 13.0, 9.0, and 8.1 months. The study concluded, radioembolization appears to have a favorable risk/benefit profile, even among mCRC patients who had received ≥ 3 prior lines of chemotherapy.

van Hazel, et al. analyzed 530 patients with previously untreated liver-dominant metastatic disease and compared the difference between modified FOLFOX chemotherapy and FOLFOX chemotherapy plus SIRT, in a 2016 phase 3 RCT. Bevacizumab was permitted as additional treatment at the discretion of the treating physician. About 40% of patients had extrahepatic metastases at randomization and about 28% had metastases with more than 25% liver involvement. The primary end point was overall (any site) 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 (10.6 months for RE vs 10.2 months for control; hazard ratio, 0.93; $p=0.43$). Secondary end points of median PFS in the liver and objective response rate for RE in the liver vs controls were improved in the RE group (liver PFS, 20.5 months vs 12.6 months; liver response rate, 78.7% vs 68.8%), all respectively. OS outcomes were not available at the time of publication. The investigators plan to analyze OS

combination with 2 other studies of chemotherapy with and without RE that have also not been completed. This combined preplanned analysis should provide important data on the efficacy of RE (in combination with current chemotherapy regimens) in first-line treatment of unresectable metastatic CRC.

The Hayes Medical Technology Directory report of 2015 found the evidence is insufficient to draw conclusions, based on a limited number of comparative studies with an inconsistent body of evidence, but noted transarterial radioembolization (TARE) with 90Y has at least comparable clinical outcomes to intra-arterial chemotherapy alone and potentially better outcomes than standard care. The report states that TARE is generally safe, with mild to moderate complications and a low risk of procedure related mortality.

NCCN Guidelines

The National Comprehensive Cancer Network (NCCN) has outlined several recommendations for use of selective internal radiation therapy. Notably it is also silent and does not mention SIRT as a choice in circumstances such as metastatic breast cancer or metastatic cutaneous nor uveal melanoma

For metastatic neuroendocrine tumors, the NCCN gives a category 2B recommendation for hepatic regional therapy (arterial embolization, chemoembolization, RE) in certain clinical situations. In the case of metastatic colon cancer the NCCN states: "...arterial-directed therapies, in particular yttrium-90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases."

As it relates to primary intrahepatic cholangiocarcinoma, the NCCN lists locoregional therapy as an option for unresectable or metastatic disease, or for residual local disease after resection (category 2B recommendation), although primary treatment is fluoropyrimidine-based or gemcitabine-based chemotherapy (category 1 recommendation). The guidelines, however, note that no RCTs of radiofrequency ablation, TACE, or RE exist.

Lastly, primary hepatocellular carcinoma is given a category 2A recommendation for the use of arterially directed therapies, including transarterial bland embolization, transarterial chemoembolization (TACE), and drug-eluting beads TACE, and radioembolization (RE) with yttrium-90 microspheres for specific categories of patients. The guidelines do not distinguish between the different arterially directed therapies.

Applicable Coding

CPT Codes

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
79445	Radiopharmaceutical therapy, by intra-arterial particulate administration

HCPCS Codes

C2616	Brachytherapy source, non-stranded, yttrium-90, per source
S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres

ICD-10 Codes

C18.0	Malignant neoplasm of cecum	C24.0	Malignant neoplasm of extrahepatic bile duct
C18.1	Malignant neoplasm of appendix	C25.0	Malignant neoplasm of head of pancreas
C18.2	Malignant neoplasm of ascending colon	C25.1	Malignant neoplasm of body of pancreas
C18.3	Malignant neoplasm of hepatic flexure	C25.2	Malignant neoplasm of tail of pancreas
C18.4	Malignant neoplasm of transverse colon	C25.3	Malignant neoplasm of pancreatic duct
C18.5	Malignant neoplasm of splenic flexure	C25.4	Malignant neoplasm of endocrine pancreas
C18.6	Malignant neoplasm of descending colon	C25.7	Malignant neoplasm of other parts of pancreas
C18.7	Malignant neoplasm of sigmoid colon	C25.8	Malignant neoplasm of overlapping sites of pancreas
C18.8	Malignant neoplasm of overlapping sites of colon	C25.9	Malignant neoplasm of pancreas, unspecified
C18.9	Malignant neoplasm of colon, unspecified	C69.40	Malignant neoplasm of unspecified ciliary body
C22.0	Liver cell carcinoma	C69.41	Malignant neoplasm of right ciliary body
C22.1	Intrahepatic bile duct carcinoma	C69.42	Malignant neoplasm of left ciliary body
C22.2	Hepatoblastoma	C78.5	Secondary malignant neoplasm of large intestine and rectum
C22.3	Angiosarcoma of liver	C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C22.4	Other sarcomas of liver	C78.89	Secondary malignant neoplasm of other digestive organs
C22.7	Other specified carcinomas of liver	C7A.010	Malignant carcinoid tumor of the duodenum
C22.8	Malignant neoplasm of liver, primary, unspecified as to type		
C22.9	Malignant neoplasm of liver, not specified as primary or secondary		

C7A.011	Malignant carcinoid tumor of the jejunum	C7A.098	Malignant carcinoid tumors of other sites
C7A.012	Malignant carcinoid tumor of the ileum	C7A.1	Malignant poorly differentiated neuroendocrine tumors
C7A.019	Malignant carcinoid tumor of the small intestine, unspecified portion	C7A.8	Other malignant neuroendocrine tumors
C7A.020	Malignant carcinoid tumor of the appendix	C7B.00	Secondary carcinoid tumors, unspecified site
C7A.021	Malignant carcinoid tumor of the cecum	C7B.01	Secondary carcinoid tumors of distant lymph nodes
C7A.022	Malignant carcinoid tumor of the ascending colon	C7B.02	Secondary carcinoid tumors of liver
C7A.023	Malignant carcinoid tumor of the transverse colon	C7B.03	Secondary carcinoid tumors of bone
C7A.024	Malignant carcinoid tumor of the descending colon	C7B.04	Secondary carcinoid tumors of peritoneum
C7A.025	Malignant carcinoid tumor of the sigmoid colon	C7B.09	Secondary carcinoid tumors of other sites
C7A.026	Malignant carcinoid tumor of the rectum	C7B.8	Other secondary neuroendocrine tumors
C7A.029	Malignant carcinoid tumor of the large intestine, unspecified portion	D01.5	Carcinoma in situ of liver, gallbladder and bile ducts
C7A.090	Malignant carcinoid tumor of the bronchus and lung	D13.4	Benign neoplasm of liver
C7A.091	Malignant carcinoid tumor of the thymus	D37.6	Neoplasm of uncertain behavior of liver, gallbladder and bile ducts
C7A.092	Malignant carcinoid tumor of the stomach	D3A.00	Benign carcinoid tumor of unspecified site
C7A.093	Malignant carcinoid tumor of the kidney	D3A.010	Benign carcinoid tumor of the duodenum
C7A.094	Malignant carcinoid tumor of the foregut, unspecified	D3A.011	Benign carcinoid tumor of the jejunum
C7A.095	Malignant carcinoid tumor of the midgut, unspecified	D3A.012	Benign carcinoid tumor of the ileum
C7A.096	Malignant carcinoid tumor of the hindgut, unspecified	D3A.019	Benign carcinoid tumor of the small intestine, unspecified portion
		D3A.020	Benign carcinoid tumor of the appendix

D3A.021	Benign carcinoid tumor of the cecum	D3A.025	Benign carcinoid tumor of the sigmoid colon
D3A.022	Benign carcinoid tumor of the ascending colon	D3A.026	Benign carcinoid tumor of the rectum
D3A.023	Benign carcinoid tumor of the transverse colon	D3A.029	Benign carcinoid tumor of the large intestine, unspecified portion
D3A.024	Benign carcinoid tumor of the descending colon	D49.0	Neoplasm of unspecified behavior of digestive system

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