Radioembolization for Unresectable Neuroendocrine Hepatic Metastases Using Resin ^{90}Y-Microspheres: Early Results in 148 Patients

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Purpose: The use of ^{90}Y-microspheres to treat unresectable liver metastases originating from a variety of neuroendocrine tumors was reviewed.

Materials and Methods: This is a retrospective review from 10 institutions of patients given ^{90}Y-microsphere therapy for neuroendocrine hepatic metastases. Physical, radiographic, biochemical, and clinical factors associated with treatment and response were examined. All patients were followed with laboratory and imaging studies at regular intervals until death, or censured whether other therapy was given after brachytherapy. Toxicities (acute and late) were recorded, and survival of the group determined.

Results: A total of 148 patients were treated with 185 separate procedures. The median age was 58 years (26–95 years) at treatment with median performance status of Eastern Cooperative Oncology Group (0). The median activity delivered was 1.14 GBq (0.33–3.30 GBq) with a median of 99% of the planned activity able to be given (38.1%–147.4%). There were no acute or delayed toxicity of Common Terminology Criteria for Adverse Events v3.0 grade 3 in 67% of patients, with fatigue (6.5%) the most common side effect. Imaging response was stable in 22.7%, partial response in 60.5%, complete in 2.7% and progressive disease in 4.9%. No radiation liver failure occurred. The median survival is 70 months.

Conclusion: Radioembolization with ^{90}Y-microspheres to the whole liver, or lobe with single or multiple fractions are safe and produce high response rates, even with extensive tumor replacement of normal liver and/or heavy pretreatment. The acute and delayed toxicity was very low without a treatment related grade 4 acute event or radiation induced liver disease in this modest-sized cohort. The significant objective response suggests that further investigation of this approach is warranted.

Key Words: liver, carcinoid, microsphere, yttrium-90, neuroendocrine-related liver metastases

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Neuroendocrine tumors (NETs) are uncommon, heterogeneous group of different slow growing, hormone secreting, malignancies. Often the group is referred to as simply "carcinoid" tumors. They derive from enterochromaffin or Kulchitsky cells, resemble adenocarcinomas, and can originate from any anatomic site. A century ago these tumors were viewed as benign, but since the 1950s it has been clear that carcinoids have a more severe pathology and clinical course.[1,2] The overall age-adjusted incidence rate for carcinoids is about 2 to 3 cases per 100,000 population per year, depending on age, gender, and race.[3,4] There are also reports of rising rates among women.[5] Patients tend to be younger than other patients with cancerous tumors; the average age of the patient is 60 years.

Primary NETs vary in location, but most commonly develop in the midgut (small intestine and appendiceal carcinoids) which comprise 40% to 70% of all carcinoids[6,7]; are mostly located in the ileum with liver metastases; secrete excessive vasoactive amines including serotonin; and are, therefore, commonly associated with the carcinoid syndrome: diarrhea, flush, bronchoconstriction (wheezing), and right valvular heart failure.[6–9] Five-year survival rates are less than 20% with metastases to the liver.[10] Conventional therapies have largely been considered palliative supportive care.[8] However, aggressive local treatments in the liver have demonstrated improvements in both symptomatic control and survival.[11]

With the lack of effective chemotherapy for NETs, internal radiotherapy is being used to control, eradicate, or simply debulk hepatic metastases, often to palliate carcinoid syndrome or local pain from liver capsular stretching. There is a long history of successful treatment of metastatic NETs

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with external beam radiotherapy[12–17]; however, the very reason that surgical resection and/or other local ablative therapies are of limited use—ie, diffuse multiple lesions, also prevents the application of even the most advanced radiotherapy approaches such as intensity modulation radiation therapy, 3D-conformal technique radiation therapy, and image-guided radiation therapy. Intra-arterial nonradioactive liver treatments with and without concurrent chemotherapy have shown efficacy and safety in multiple small studies.[18–23] This report was conceived to learn key aspects of the recent experience using radioembolization, which may improve techniques, patient selection, and efficacy. Because NETS are less common than carcinomas a retrospective collaboration of North American and European Union medical centers that perform radioembolization routinely was completed.

MATERIALS AND METHODS

Treatment

All patients in this report received only resin microspheres. The details of treatment have been described elsewhere in detail including a multidisciplinary consensus report providing additional guidelines.[24–28] The best opportunity of successful implantation of microspheres selectively in the multiple hepatic tumors is via a multidisciplinary team with complementary skills in Interventional Radiology, Radiation Oncology, Nuclear Medicine, and Medical Physics, Surgical Oncology, and Medical Oncology. A microcatheter is placed via a femoral approach into the hepatic artery where the release of ^{90}Y-microspheres occurs. In this manner, radioembolization appears very similar to other vascular embolic treatments using either bland (nonradioactive) particle alone, or with chemotherapy—transarterial chemoembolization (TACE). However, the biologic goals are different in radioembolization of microspheres where hypoxia from embolization is not desired. Maximal cell killing by radiation requires normal oxygen tension in the target cells, but also sufficient microsphere coverage of the tumor nodule to avoid gaps in radiation. Despite being suspended in a liquid, ^{90}Y-microspheres are considered by the US Nuclear Regulatory Commission to be a brachytherapy device. Patients undergo a "simulated" treatment via hepatic angiogram to map vessels for treatment delivery and identify any vessels to the gastrointestinal tract as they must be avoided or embolized before treatment. An albumin particle of approximately the same size as a microsphere is labeled with the gamma emitting ^{99m}Technetium (^{99m}Tc) isotope and infused before the conclusion of the angiogram. The ^{99m}Tc allows for SPECT gamma imaging and can identify the proportion of the microparticles that have passed through to the lungs or into the gastrointestinal tract. The actual microsphere treatment occurs a week or two later in eligible patients that have adequate liver function and exclusive hepatic artery access without significant passage of particles to the pulmonary capillary beds.

Radioactive Material

Yttrium-90 (^{90}Y) is a pure-beta emitter that decays to stable zirconium-90 with an average energy of 0.94 MeV via a half-life of 2.67 days (64.2 hours). It is produced by neutron bombardment of ^{89}Y in a commercial reactor, which yields ^{90}Y beta radiation having a tissue penetration of 2.5 mm and a maximum range of 1.1 cm. One GBq (27 mCi) of ^{90}Y delivers a total dose of 50 Gy/kg in tissue. Two radioactive microsphere products are available in North America, Asia, and Europe: a glass (TheraSphere—MDS Nordion, Inc., Ontario, Canada) sphere and a resin (SIR-Spheres—Sirtex Medical Limited, Lane Cove, Australia) sphere, both in which ^{90}Y is permanently embedded within the structure. Only the resin sphere is analyzed for this report. Salem et al have recently published an excellent series of reports as a reference on glass microsphere therapy.[28–30] Resin spheres have a diameter of 32 $\pm$ 10 μm, which causes them to be permanently embolized within the terminal arterioles of the tumor. No clinically significant amount of ^{90}Y escapes from the sphere when in the patient. A standard dose of resin microspheres is 1.5 to 2 GBq, which contain approximately 50 million microspheres (range, 40–80 million), each microsphere containing 50 Bq activity.

Activity Selection

The resin microsphere manufacturer suggests 3 methods to determine the activity for use in a single patient: empiric (EMP) method, body surface area method (BSA), and partition method. Originally proposed by Ho et al,[31,32] the partition method approach is not used for NETs metastases as it can only be applied in special circumstances, ie, for a single well-defined tumor, which is rarely the case in NETs. The patients in this report were treated via the BSA method of activity calculation as the EMP approach is thought to overestimate activity for some patients with disease burdens less than 20% of the total liver volume. The consensus report[24] recommended BSA as the most appropriate method to avoid the rare occurrence of radiation-induced liver disease, a late effect of excessive hepatic radiotherapy.

Patient Selection

All US and European Union institutions using resin microspheres were invited to participate in this retrospective review. The groups elsewhere in the world, ie, Australia, Asia, were not approached simply due to lack of established relationships between investigators. As this work was an unfunded project the overall response to join was modest. All patients had previously completed comprehensive evaluation and treatment of the primary tumor and metastatic disease and were not excluded for treatment based on prior therapy except if they were not eligible based on accepted standards for radioembolization. With few exceptions, all patients were included or excluded by well-established and accepted parameters regarding liver reserve and vascular access. The important clues to adequate liver tolerance for radioembolization were: lack of ascites and synthetic liver dysfunction, and abnormal total bilirubin (>2.0 ng/mL). Vascular issues of import included the ability to isolate the liver arterial tree from gastric and small bowel branches, and excluding patients with arteriovenous fistulas in tumor that allowed for more than 20% of microparticles to pass through the liver capillary bed to the lung vascular bed. All patients completed a written informed

consent before treatment and were not eligible if less than 18-year-old, pregnant, mentally compromised.

Follow-up and Toxicity

The follow-up schedule varied slightly between institutions; however, all patients were evaluated at least during the 6th and 12th weeks postmicrosphere treatment, with some patients needing more frequent evaluations. During follow-up visits laboratory data was obtained including liver function tests, tumor marker(s) if elevated before treatment, abdominal imaging with computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography/OctreoScan and a physical examination with recent history taken for side effects. These data were converted to a toxicity score according to the Common Toxicity Criteria 3.0AE (http://www.fda.gov/cder/cancer/toxicityframe.htm). After 12 weeks, patients resumed a routine schedule of labs and imaging at 3-month intervals.

Response

Imaging criteria for response was graded per World Health Organization or Response Evaluation Criteria in Solid Tumors criteria when possible, however, in patients where this was not possible due to differences in imaging technique or imaging instrument from pre- and post-treatment, a best estimate was given for stable disease, partial response, complete response, and progressive disease. Tumor marker changes were graded as none (less than 20% decrease or increase), partial (>20% but not in normal range), complete (tumor marker in normal range), and progression (>20% elevation over pretreatment). Chromogranin A and serotonin were most commonly employed; however, 24-hour 5-HIAA was occasionally used.

Statistics

Survival was calculated using the Kaplan Meier method starting from the day of first microsphere treatment. Patients lost to follow-up were censured as of the date of last follow-up. Descriptive statistics were derived from the raw data with 95% confidence intervals determined where appropriate.

RESULTS

Patients

A total of 148 patients were treated nearly evenly divided between male and female with a median age at treatment of 58 years; see further details in Table 1. Not surprisingly, midgut tumors and carcinoids were the most common site and histology reported, with pancreas and islet cell next most frequent. The majority of patients and treatments (Table 2) were performed by half of the 10 centers, however, all treatment teams are known as "Centers of Excellence" for radioembolization. The higher number of treatments did not always indicate retreatment; rather, it is the case that some centers prefer sequential treatment of the 1 hepatic lobe and then the other lobe in a month or so later. Patients continued to be followed and there is a median of 42 months follow-up presently. Occasionally specific data could not be found for a patient and therefore all results are provided with the actual number of patients or treatments for which data was available (numerator) over the total number of possible patients or treatments (denominator). Fortunately most data could be reviewed.

TABLE 1. Patient Characteristics

All patients	148	100%
Gender		
Male	72	49%
Female	76	51%
Age (median)	58 yrs	(26–95 yrs)
Performance status (0–4 scale)		
ECOG (median)	0	(0–3)
Site of primary tumor (N = 148)		
Small intestine	100	67%
Pancreas	28	19%
Unknown	7	7%
Lung	6	4%
Colon	2	1%
Ovary	1	<1%
Kidney	1	<1%
Histology (N = 148)		
Carcinoid (NOS)	121	82%
Islet cell	15	10%
Insulinoma	3	2%
Atypical	3	2%
Glucogonoma	3	2%
Gastrinoma	2	1%
VIPoma	1	<1%
Status*		
Alive	115	77.7%
Dead	33	22.3%

ECOG indicates Eastern Cooperative Oncology Group.
*As of September 1, 2007.

TABLE 2. Treatment Centers

Center	Patients	%/Pts	Treatments	%/Tx
Wake Radiology Oncology	31	20.9	42	22.7
Skyridge Medical Center	29	19.6	35	18.9
Mt. Sinai Hospital	22	14.9	22	11.9
St. Vincent's Hosptial	16	10.8	20	10.8
University of Texas SW, Dallas	16	10.8	17	9.2
MD Anderson Cancer Center	11	7.4	11	5.9
University of California, San Diego	7	4.7	15	8.1
Northwestern University Hospital	7	4.7	13	7.0
Banner Good Samaritan	5	3.4	6	3.2
University Hospital of Bonn	4	2.7	4	2.2
Total	148	100	185	100

Radiation Delivery

All patients received resin ^{90}Y-microspheres with the activity of radiation determined by the BSA method in all cases, with other details listed in Table 3. The percentage of microparticles that passes from the liver arterial system

TABLE 3. Treatment Parameters

Liver to lung shunting (^{99m}Tc macro aggregated albumin scan)		
Median (%)	4	
Min/max (%)	0–34.1	
Treatment volume (178/185 procedures; 96.2%)		
Right lobe	77	41.6%
Left lobe	33	17.3%
Whole liver	69	37.3%
Unknown	7	3.8%
Retreatment of volume (33/148 patients; 22.3%)		
2 treatments	29/148	19.6%
3 treatments	4/148	2.7%
Activity (^{90}Y) Delivered (178/185 procedures; 96.2%)		
Median (GBq)	1.14	
Min/max (GBq)	0.33–3.33	
Mean (GBq)	1.31	
Standard deviation	0.53	
95% CI (GBq)	1.23–1.38	
Percent of planned ^{90}Y delivered (132/185 procedures; 71.4%)		
Median (%)	99	
Min/max (%)	38.1–147.4	
Mean (%)	91.2	
Standard deviation	16.9	
95% CI (%)	88.2–94.1	

through to the pulmonary capillary beds was low, with a few patients receiving treatment despite shunt fractions above 20%. The intended treatment volume of the liver was known for most treatments including retreatment of the same lobe later on, with the right lobe was most frequently treated followed by whole liver and left lobe. The total activity delivered per individual treatment was also relatively low compared with non-NET tumors, only a median of 1.14 GBq/procedure. The percentage of the BSA-calculated activity that was fully delivered to the patient was high with a median of 99% but could be as low as 38.1%. The rationale for these reductions was not systematically recorded and so not available for this report, however, typically a lower than calculated activity delivery is due to vascular stasis secondary to the number of microspheres given. Retreatment of the same lobe(s) was completed in 33 patients and no radiation-induced liver disease or liver failure was noted in these or any other patient in this report.

Toxicity

With few exceptions, this was an outpatient procedure without the necessity for inpatient support. The most commonly reported grade 3 side effects are listed in Table 4, which is consistent with reports of radioembolization of non-NETs. The 1 patient with development of ascites had tumor progression in the liver.

Response

Most patients were monitored for response via CT scan at 6 weeks and 12 weeks posttreatment, but others used MRI and q3 month ^{111}In pentetreotide scintigraphy. Because several different cross sectional imaging sources were used in some patients, each investigator reported the 3-month imaging result which was classified as 1 of 4 categories listed previously in Methods, and are detailed in Table 4.

TABLE 4. Toxicity and Hepatic Response After ^{90}Y-Microsphere Treatment

Toxicity (CTCae 3.0 grade 3–4 only) in 161/185 treatments (87%)	
None	124/185 = 67%
Fatigue	12/185 = 6.5%
Nausea	6/185 = 3.2%
Pain	5/185 = 2.7%
Ascites	1/185 = 0.5%
Imaging response (CT/MRI/OctreoScan) in 168/185 treatments (91%)	
Stable disease	42/185 = 22.7%
Partial response	112/185 = 60.5%
Complete response	5/185 = 2.7%
Progressive disease	9/185 = 4.9%

Survival

Metastatic disease in and outside the liver contributed to death in the majority of patients with only 7% lost to follow-up (censured in survival calculation) as shown in Figure 1. Typical response as seen on CT axial images and tumor destruction in tissue is demonstrated in Figures 2A–C.

DISCUSSION

It has become clear over the past 30 years that patients suffering from NETs benefit substantially by receiving aggressive antitumor therapy.[8,27–36] Because of the sometime indolent growth rate and absence of symptoms, patients have been followed without therapy or minimal treatment unless or until tumor growth caused a decrement in quality of life (QOL) or threatened vital organs or weight-bearing bones. Fortunately there are now a variety of treatments to combat NETs with increasing effectiveness and thus implement them much earlier in the course of the disease. It is worthwhile to review the rationale for aggressive hepatic treatments, particu-

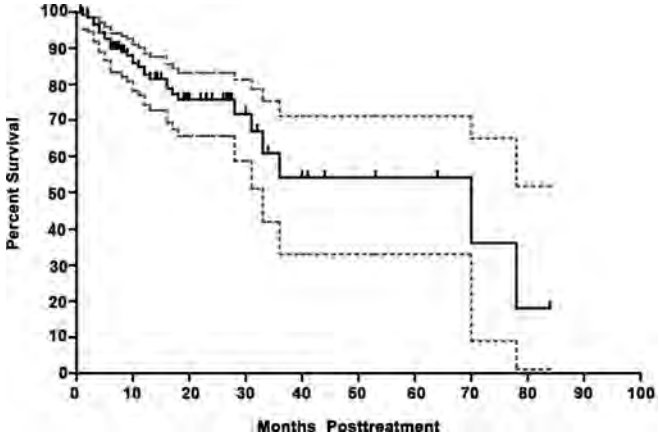

FIGURE 1. Kaplan Meier survival graph of all patients (solid black line) with tic marks for patients censured for lost to follow-up or death. The 95% confidence interval (dashed blue lines) is also plotted but without tic marks.

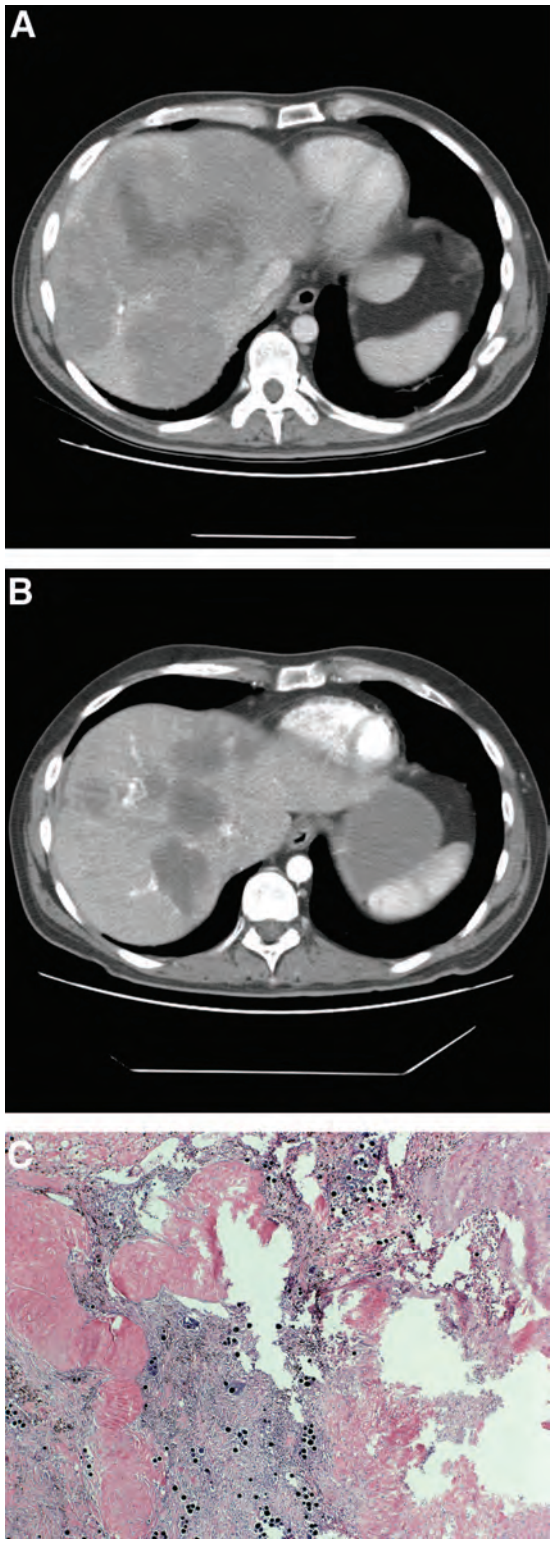

FIGURE 2. A, Axial CT scan image of a 45-year-old man with extensive liver metastases from a primary midgut (jejunum) carcinoid tumor. He received sequential lobar ^{90}Y-microsphere treatments; right lobe (2.15 GBq) then 3 months later left lobe (0.73 GBq). B, Axial CT scan image of the same liver area in this patient at 3 months postmicrosphere treatment showing significant tumor destruction, necrosis, and overall reduced tumor volume. C, Photomicrograph of a portion of the tumor and normal liver of the above patient demonstrating extensive tumor destruction with necrosis in all areas of microsphere implantation (original magnification ×100). Other areas without microspheres contained viable tumor (not shown) without damage. Microspheres appear as dark spheres due to uptake of hematoxylin and eosin staining used on the tissues.

larly given the high frequency of hepatic metastases, the exacerbation of symptoms from those lesions, and ultimately the high mortality associated with hepatic disease. Veenendaal et al[33] pointed out that liver metastases are a negative prognostic indicator with only 40% 5-year survival compared with 75% to 99% in nonhepatic metastatic disease. Soreide et al reviewed a 75-patient cohort of advanced carcinoid patients, 65 of which had midgut primary tumors. The mean survival of those undergoing intra-abdominal and liver tumor debulking had a mean survival of 216 months compared with a mean of only 48 months for those without surgery ($P < 0.001$).[34] Many other investigators have concluded that aggressive local therapies of liver metastases improve not only NETs secretory output, but improvement in overall and disease specific survival and QOL. Indeed survival as an end point is less important to many patients compared with improved QOL for however long their life will last. Surgical[38–48] management (Table 5) of liver metastases have shown the greatest improvement in survival and freedom from symptoms, which may be a reflection of lesser disease burden and earlier disease compared with nonsurgical—embolization ± chemotherapy;[33,44,49–60] external radiotherapy[12–17]; and internal radiotherapy[35–38] approaches (Tables 6–8).

Hepatic transcatheter arterial embolization (both TAE and HAE are used) has consistently provided symptomatic relief and increased survival in selected cases of NET liver metastases. The addition of single or multiagent chemotherapy (hepatic transcatheter chemoembolization—both TACE and HACE are used) to embolization has also been shown to improve QOL and produce sometimes significant tumor reduction although there is not consensus as to whether the addition of chemotherapy is of benefit (Table 6). Ho et al reported long-term follow-up on 46 patients with diffuse bilobar liver metastases from carcinoid and islet cell tumors. They concluded that the benefits of HAE and HACE were significant despite the presence of extra-hepatic disease.[39]

External beam radiotherapy to the liver in particular has been limited by the low tolerance of normal liver to radiation compared with the higher doses of radiation needed to kill tumors. The historical record (Table 7) contains reports of generally effective symptomatic improvement but was performed with large field radiation therapy to treat extensive disease. However, in a few cases small, shaped, conformal treatment to partial liver volumes allowed for dose escalation (57 Gy) with a trend to better tumor control with higher doses. The application of hepatic artery and systemic radionuclides can potentially deliver much higher doses of radiation selectively to hepatic tumors rather than the surrounding normal liver. McStay et al[63] reported the results of ^{90}Y

TABLE 5. Hepatic Surgery for Cure or Palliation of Neuroendocrine Metastases

	Author	*N*	Radiographic Response or Symptomatic Improvement	5 yr Median Survival
1	Sarmiento[51]	170	96% symptoms improved	61%
2	Que[49]	74	Not stated	74% (4 yrs)
3	Osborne[22]	61	86%	Not stated
4	Chen[44]	38	Not stated	73% (curative) 29% (palliative)
5	Chamberlain[43]	34	Not stated	76%
6	Reddy[50]	33	Not stated	Not stated
7	Nave[47]	31	Not stated	86% (curative) 26% (palliative)
8	Hibi[45]	21	92% symptoms improved	41%
9	Yao[52]	16	50% symptoms improved	Not stated
10	Norton[37,48]	16	100% symptoms improved	80%
11	Musunuru[46]	13	Not stated	Not stated
	Total	507	—	—

conjugated via a tetraazacyclododecane tetraacetic acid (DOTA) chealtor to the selective somatostatin analog Lanreotide which can be complexed to ^{111}In for diagnostic imaging or to ^{90}Y for therapy via beta decay. Unique in McStay et al's report is the successful treatment of bulky liver-predominant carcinoid metastases with encouraging results for symptomatic improvement despite modest radiographic response (Table 8). Similarly Safford et al[64] delivered another beta isotope systemically for liver predominant disease with ^{131}I. Chemically, ^{131}I is complexed to meta-iodobenzylguanidine (^{131}I-MIBG) an alkyl-quanidine derivative similar to noradrenaline, is accumulated by tissues arising from neural crest cells, ie, carcinoids, pheochromocytomas, and others. Selective uptake by carcinoid tumors provides the proximity needed for beta radiation cell killing. The use of ^{90}Y-microspheres is a safe and effective treatment for primary or metastatic solid tumors primary in the liver available worldwide, however, most treatments are for metastatic colorectal cancer or hepatocellular tumors.[19,21–24,65–73]

This is the first report dedicated to NETs treated with ^{90}Y-microspheres since Simon and Warner detailed the first 5 patients (7 treatments total) treated with this approach in 1968.[39] Since that time the microparticles have changed in composition somewhat but the sphere size and isotope and total activity delivered are the same as is performed today.[40] As a retrospective review from multiple centers, our data is incomplete and therefore we are continuing our collaboration as a team to examine other factors such as (a) percent of patients that were symptomatic pre and posttreatment, (b) duration of both symptomatic and radiographic response, and (c) tracking of tumor marker response. Another area of additional investigation is standardized the imaging technique (CT and MRI) and application of a single evaluation system—World Health Organization or Response Evaluation Criteria in Solid Tumors and the interval between imaging in the first 6 months after microsphere treatment. Finally, the QOL measures now available from the EORTC and others contain global and liver-related evaluation tools that should be included in future analyses of radioembolization. Currently there has been only 1 QOL study reported for ^{90}Y-microsphere therapy which was limited to hepatocellular carcinoma although it was a positive report in favor of radioembolization compared with TACE.[41]

TABLE 6. Hepatic Trans Arterial Embolization (TAE) and Chemoembolization (TACE) for Neuroendocrine Metastases

	Author	*N* = 661	Radiographic Response or Symptomatic Improvement	5 yr Median Survival
1	Osborne[22]	59 TAE	87% symptoms improved	24 mos mean
2	Moertel[20]	40 TAE; 71 TACE	60% TAE; 80% TACE	Not stated
3	Gupta[19]	74 TAE, 49 TACE	35.2% Islet cell; 66.7% carcinoid	13.7% Islet cell; 28.6% carcinoid
4	Kress[58]	26 TACE	75%	48%
5	Roche[60]	14 TACE	85.7%	83% 5 yrs; 56% 10 yrs
6	Loewe[59]	23 TAE	Not stated	65.4%
7	Dominguez[55]	15 TACE	53%	Not stated
8	Kim[57]	30 TACE	37%	15 mos (2–67 + mo)
9	Eriksson[18]	41 TAE	52%	60%
10	Drougas[56]	15 TACE	65%	Not stated
11	Ruszniewski[65]	24 TACE	33% PR; 11% CR (phase II trial)[1-14]	Not stated
12	Therasse[61]	23 TACE	70% symptomatic improvement	47 mos med survival
13	Clouse[54,66]	30 TACE	90% symptomatic improvement	24 mos med survival
14	Brown[53]	35 TAE	96% symptomatic improvement	54%
	Totals	272 TAE; 297 TACE	—	—

TABLE 7. External Beam Radiotherapy for Hepatic Neuroendocrine Metastases

	Author	*N*	Fractionation (Gy/d)	Total Dose (Gy)	Radiographic Response or Symptomatic Improvement (%)	5 yr Median Survival
1	Abrams[12]	13	1.5–2.25	30–40.5	60	Not stated
2	Gaitan-Gaitan[14]	10	1–2	20–25	50	6 pts lived 5 to 15 yrs
3	Keane[15]	28	1–2	20–25	39	Not stated
4	Samlowski[16]	16	—	—	22	46 mos median responders; 10 mos if no response
5	Schupak[17]	44	2–3	7–42	62	23 mos median
6	Chakravarthy[13]	18	3	12–57	85.7	23 mos median
	Total	129	—	—	—	—

TABLE 8. Intra Arterial Radiotherapy and Systemic Radiotherapy for Hepatic Neuroendocrine Metastases

	Author	*N*	90Y-DOTA-Lanreotide	Dose/Activity	Radiographic Response or Symptomatic Improvement	5 yr Median Survival
1	McStay[63]	23	^{90}Y-DOTA-Lanreotide	1 GBq per treatment	16% PR; 63% SD; 21% PD; 61% symptomatic improvement	15 mos median survival
2	Safford[64]	98	^{131}I-MIBG	14.8 GBq ± 7.47 GBq (2.85–39.81 GBq)	15% radiographic; 37% biochemical; 49% symptomatic improvement	22% (68 mos responders; 25 mos nonresponders)
3	Kennedy[62]	12	^{90}Y-microspheres	142 Gy median (135–162 Gy)	16.3% CR; 83.7% PR, 13.5 mos duration	24 mos median follow-up with median survival not reached
4	Simon[39]	5	^{90}Y-microspheres	1.22 GBq median (0.56–1.85 GBq)	80% symptomatic improvement	Not stated
5	Current study	148	^{90}Y-microspheres	1.14 GBq median (0.33–3.30 GBq)	60.5% PR; 22.7% SD; 2.7% CR; 4.9% PD	70 mos median survival
	Total	286	—	—	—	—

PR indicates partial response; SD, stable disease; CR, complete response; PD, progressive disease.

In comparison to nonradioactive embolic therapy (TACE and TAE), ^{90}Y-microspheres appear to provide a similar level of tumor response by imaging studies and symptomatic improvement. It is unknown for sure but unlikely the patient population treated with liver resection had as advanced hepatic disease as those in this series and yet symptomatic improvement and early survival estimates compare very favorably as well. It is known that the patients (Table 7) that received external beam radiotherapy in older reports had extensive liver tumors and were treated with palliative intent for the most part that likely explains the poorer 5-year median survivals compared with other treatments. The effectiveness of radiotherapy for liver metastases is borne out not only in ^{90}Y-microspheres in this report, but substantiated by the experiences of systemic radiotherapy approaches using ^{90}Y and ^{131}I.

CONCLUSIONS

Radioembolization can deliver high doses of radiation preferentially to hepatic metastases of NETs with a resulting encouraging response rate by imaging and symptomatic improvement. In comparison to published reports of other local treatments in the liver for NETs, radioembolization has a similar safety profile, improvement in debulking of tumor and survival, which warrants further investigation in a controlled prospective manner.

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