

# Radioembolization with yttrium-90 resin microspheres for neuroendocrine tumor liver metastases

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## PURPOSE

We aimed to evaluate the effectiveness and safety of radioembolization with yttrium-90 (<sup>90</sup>Y) microspheres in cases with unresectable neuroendocrine tumor liver metastases (NETLMs).

## METHODS

Thirty patients (mean age, 55 years) underwent resin-based <sup>90</sup>Y radioembolization for unresectable NETLM at a single institution between April 2008 and June 2013. Post-treatment tumor response was assessed by cross-sectional imaging using the Response Evaluation Criteria in Solid Tumors (RECIST). Prognostic variables that affected survival were determined.

## RESULTS

The mean follow-up was 23.0±19.4 months and the median overall survival was 39 months (95% CI, 12.6–65.4 months), with one- and two-year survival rates of 71% and 45%, respectively. Imaging follow-up using RECIST at three-month intervals demonstrated partial response in 43%, complete remission in 3%, stable disease in 37%, and progressive disease in 17% of patients. Extent of tumor involvement was found to have a statistically significant influence on overall survival ( $P = 0.03$ ). The existence of extrahepatic disease at the time of radioembolization, radiographic response, age, and primary neuroendocrine tumor site were not significant prognostic factors.

## CONCLUSION

The current study demonstrates the effectiveness and safety of radioembolization for the treatment of unresectable NETLMs. We identified that the extent of tumor involvement has a significant effect on overall survival. The use of imaging methods reflecting metabolic activity or cellularity such as scintigraphy or diffusion-weighted MRI would be more appropriate, for the response evaluation of liver metastases after radioembolization.

Neuroendocrine tumors (NETs) are a heterogeneous group of slow-growing and hormone-releasing malignant tumors. Even though primary NETs originate from a number of locations, 40%–70% of all carcinoids arise in the small intestine and appendix (1, 2). The most common site for metastasis is the liver. Neuroendocrine tumor liver metastasis (NETLM) results in hormone-secretion-related symptoms leading to carcinoid syndrome, pressure on structures, or liver replacement (1–4). Patients with liver metastasis have a five-year survival rate of less than 20% (5). Over the years, improvements in local treatments yielded better control of the symptoms and survival rates, yet only 10% of the patients have limited illness and are eligible for surgery (6). Patient symptomatology and survival can be improved by transarterial treatments like embolization and chemoembolization (6). Limitations of these techniques include the short duration of the effects and the controversial approaches regarding the optimal timing and sequence of the procedures due to the variability of tumor progression (7, 8). Long-term survival benefit was not achieved with systemic chemotherapy (9–11) and treatment with somatostatin analogues is mostly associated with symptomatic relief; there is no clear knowledge of their effect on survival of patients who have carcinoid tumor and metastasis (12).

Selective internal radiation therapy (SIRT) has been used to treat unresectable primary and secondary liver cancers for over a decade. Yttrium-90 (<sup>90</sup>Y) is a pure high-energy  $\beta$  emitter with a mean tissue penetration of 2.5 mm. The radioactive microspheres prefer tumoral vascular distribution, so that normal liver tissue is relatively spared and high doses are directed to the tumoral tissue (13). Also, radioembolization-related acute and subacute toxicities are seemingly more tolerable than the ones related to other hepatic embolization procedures (14–16). In this study, we aimed to evaluate the effectiveness and safety of <sup>90</sup>Y microspheres in cases with unresectable NETLMs.

## Methods

Thirty patients with histologically proven NETLMs treated by radioembolization using resin <sup>90</sup>Y microspheres (SIR-Spheres®; Sirtex, Sydney, Australia) were identified retrospectively. Inclusion criteria were: unresectable liver metastases; liver-dominant illness (patients diagnosed with extrahepatic disease were included only if severe symptoms were present as a result of the hepatic mass such as abdominal pain or carcinoid syndrome—main goal for these patients was to palliate symptoms by reducing the tumor size in the liver); disease not responding to alternative treatment modalities including local ablation and surgical intervention; a patent portal vein; adequate hematological, hepatic, renal

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function; and arteriovenous shunting <20% to the pulmonary vascular bed. Patients with ascites, portal hypertension, contraindications for angiography and selective visceral catheterization, or expected survival <3 months were excluded from the analysis.

A therapy-planning angiogram (Siemens Artis Zee, Erlangen, Germany) was performed by transfemoral approach. Arteriography for <sup>90</sup>Y microsphere therapy planning is described elsewhere in detail (17). Later, a 150 MBq dose of 99m technetium-labeled macroaggregated albumin (99mTc-MAA) was given through the catheter to detect arteriovenous shunts from the hepatic arteries to the pulmonary vasculature or gastrointestinal tract. Then, planar images of liver, abdomen, and thorax were acquired by a dual-headed gamma camera (Optima, GE healthcare, Buckinghamshire, United Kingdom) and the shunt to the pulmonary vasculature was calculated using regions-of-interest from the lung and the liver.

The <sup>90</sup>Y dose was calculated using body surface area (BSA) method: activity (GBq)=(BSA-0.2)+tumor volume/total liver volume. In cases where extrahepatic deposition of microspheres were suspected, extrahepatic arteries originating from the hepatic arteries were excluded using microcoil embolization (13).

After the initial therapy-planning arteriography, another hepatic arterial catheterization was performed and <sup>90</sup>Y resin microspheres were injected with intermittent fluoroscopic visualization. Antegrade hepatic arterial flow was evaluated with intermittently injected contrast material. Our therapeutic approach for patients with unilobar disease was treating the pathologic hepatic lobe. For patients with bilobar disease we performed whole hepatic treatment in two separate injections. Bremsstrahlung images were obtained within 1–24 hours after treatment, to confirm that <sup>90</sup>Y isotope is accumulated only in the hepatic parenchyma. All patients were hospitalized overnight. Analgesics, H2 receptor antagonists and antiemetics were used, if necessary. Patients were inspected until acute or late toxicities were resolved.

Patients were routinely checked via scheduled laboratory tests and imaging every three-months in the course of follow-up period until death. Targeted lesions were scanned by contrast-enhanced computed tomography (CT), and Response Criteria in Solid Tumors (RECIST) guidelines were used to determine the tumor response (18).

SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. Comparison of rates of radiological response and mortality in two groups was performed using the chi-square test. Survival rates were calculated using the Kaplan-Meier method. Effects of the different factors on survival rates were analyzed by Cox regression model. Statistical significance was accepted as  $P < 0.05$ .

## Results

Between April 2008 and June 2013, 30 patients (11 women and 19 men) with NETLM underwent radioembolization using <sup>90</sup>Y resin microspheres. The mean age at the time of treatment was 55.2±11.8 years (range, 27–75 years). The primary NET site was the pancreas in seven patients (23%), small bowel in six patients (20%), large bowel/rectum in five patients (17%), bronchus in two patients (7%), and unknown in 10 patients (33%). At study entry, nine patients (30%) had pathological or radiological evidence of extrahepatic metastatic disease. Before the intervention, estimated liver involvement was 1%–25% in 11 patients (37%), 26%–50% in eight patients (27%), 51%–75% in nine patients (30%), and 76%–100% in two patients (7%) (Table 1).

Previous treatments included surgery in 17 patients, resection of the primary tumor and hepatic metastasis followed by systemic chemotherapy in 10 patients, chemoembolization in six patients, octreotide therapy in four patients, interferon-alpha treatment in two patients, ablation in two patients and radionuclide therapy (DOTA-TATE) in two patients (Table 1).

A total of 38 therapy sessions were performed, including eight bilobar hepatic, 25 right lobar, and five left lobar treatments. Four patients had two sessions and two patients had three sessions. Estimated mean therapy dose was 1.65±0.14 GBq (range, 1.4–2.0 GBq). Decreasing the estimated dose

or terminating the treatment was not needed, because leakage to the lungs was less than 20% in all patients.

The technical performance was 100% successful. We did not experience any intervention-related complications. Post-radioembolization syndrome (mild abdominal pain, nausea, and subfebrile fever) was seen in all patients and they were given H2 receptor blocker, non-opioid analgesic, and antiemetics to overcome this complication. Symptoms were relieved within one week and totally resolved within 30 days. Bremsstrahlung imaging performed 24 hours after the therapy did not show any activity outside the hepatic parenchyma. Two patients had radiation-induced gastritis confirmed by endoscopy/biopsy at one, two, and six months after therapy. One of these patients died at six months with progressive liver disease. The other patient had persisting ulceration at nine-month follow-up. Screening angiogram/99mTc-MAA scans were reassessed in these two patients, but no aberrant anatomy was detected before <sup>90</sup>Y treatment. We coiled the gastro-duodenal artery to prevent <sup>90</sup>Y reflux to the stomach in these patients.

The mean follow-up was 23.0±19.4 months (range, 2–62 months); 17 of 30 patients (57%) were still alive at the time of analysis. The median overall survival was 39.0 months (95% confidence interval, 12.6–65.4 months) (Fig. 1), with 71% one-year survival and 45% two-year survival.

Contrast-enhanced CT images were available in 29 patients, while one patient was lost to imaging follow-up. Imaging follow-up using RECIST at three-month intervals demonstrated partial response in 43% (Fig. 2), complete remission in 3%, stable disease in 37%, and progressive disease in 17% of patients.

Patients with and without extrahepatic metastasis did not differ significantly in terms of mortality (44% [4/9] vs. 42% [9/21],  $P = 0.936$ ) and radiologic response (33% [3/9] vs. 52% [11/21],  $P = 0.338$ ).

We analysed five clinical factors for their prognostic value on overall survival by Cox regression model ( $P = 0.030$ ). Extent of tumor involvement, evaluated in four groups of 1%–25%, 26%–50%, 51%–75%, and 76%–100%,

**Table 1.** Baseline characteristics of patients

Gender	
Male	19 (63)
Female	11 (37)
Age (years), median (range)	55 (27–75)
Primary tumor site	
Pancreas	7 (23)
Small bowel	6 (20)
Large bowel/rectum	5 (17)
Bronchus	2 (7)
Unknown	10 (33)
Previous treatment	
Surgery	17 (57)
Chemotherapy	10 (33)
Chemoembolization	6 (20)
Octreotide	4 (13)
Interferon $\alpha$	2 (7)
RFA	2 (7)
Radionuclide therapy (DOTA-TATE)	2 (7)
Surgery and TACE	1 (3)
Surgery and systemic therapy	5 (17)
Surgery, TACE, and systemic therapy	3 (10)
Surgery and RFA	1 (3)
Tumor volume	
<25%	11 (37)
26%–50%	8 (27)
51%–75%	9 (30)
76%–100%	2 (7)
Extrahepatic disease	
Present	9 (30)
Absent	21 (70)

Unless otherwise specified, data are given as n (%).

RFA, radiofrequency ablation; DOTA-TATE, tetraazacyclododecane tetraacetic acid-octreotate; TACE, transarterial chemoembolization.

has emerged as a novel treatment option.

Paprottka et al. (29) worked on 42 patients treated with resin microspheres. The mean follow-up for 40 patients was 16.2 months. Three-month follow-up demonstrated partial response (22.5%), stable disease (75%), and progressive disease (2.5%). Hepatic lesions were partially necrotic or hypovascular in 97.5% of patients. King et al. (30) reported that the mean survival rate for 34 patients treated with  $^{90}\text{Y}$  resin microspheres was 27.6 months, and complete or partial response was obtained in 50% of these patients. Another study by Rhee et al. (31) compared the effectiveness of resin-based and glass-based microbeads. Results indicated that the median survival for patients exposed to resin-based microsphere therapy (20 of 42 patients) was 28 months, whereas patients who received glass-based therapy (22 of 42 patients) had a median survival time of 22 months. A recent multicenter retrospective review of 148 patients by Kennedy et al. (32) showed that the median survival of 63.2% of patients having a good radiologic response to treatment with resin-based  $^{90}\text{Y}$  microspheres was 70 months. Their study was the largest to date, with a median follow-up of 42 months and 7% lost to follow-up; however, it did not include information on prognostic factors for a favorable survival. Like previous studies (29–32), our data also shows the effectiveness of this treatment, with 13 patients (43%) obtaining partial response and one patient (3%) obtaining complete remission. The mean follow-up was  $23.0 \pm 19.4$  months, and the median survival in our study was  $39.0 \pm 13.5$  months with a two-year survival of 45%. Our results indicate that radioembolization with  $^{90}\text{Y}$  resin microspheres is an effective treatment modality in patients with treatment-resistant NETLMs. However, patients were not uniform in their previous treatments, since many patients received chemotherapy, surgery, chemoembolization, ablation, or a combination of therapies before radioembolization. Previous treatment might affect the overall result of subsequent radioembolization.

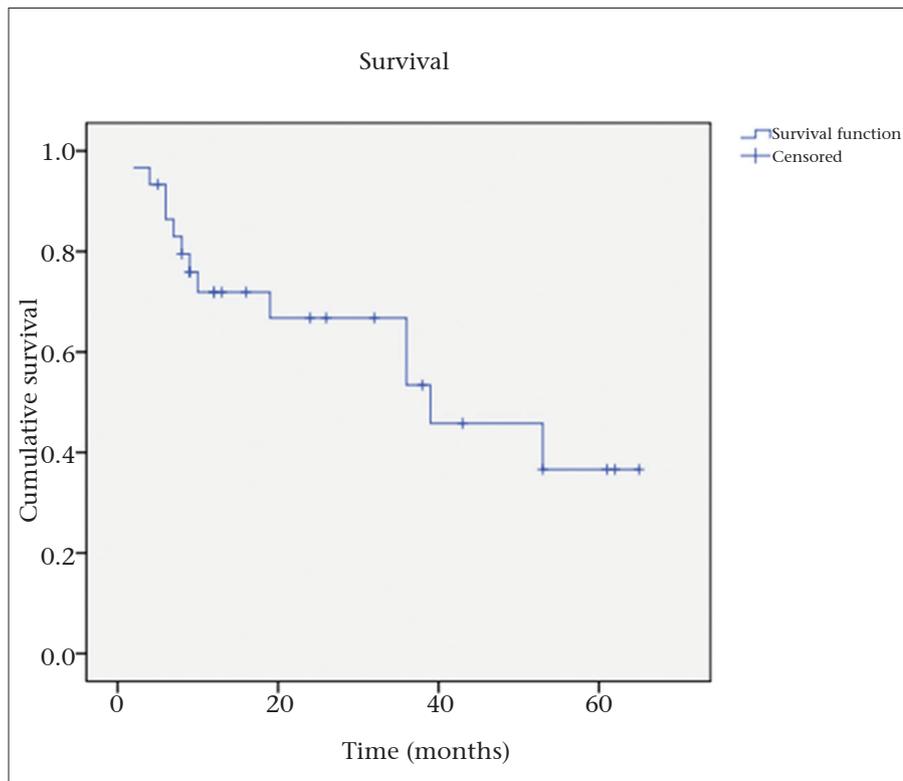
Cao et al. (33) reported that among 51 patients who had evaluable disease, six (12%) showed complete remission,

was found to have a statistically significant influence on overall survival ( $P = 0.033$ ). The existence of extrahepatic disease at the time of radioembolization ( $P = 0.742$ ), radiographic response ( $P = 0.251$ ), age ( $P = 0.653$ ), and primary NET site ( $P = 0.335$ ) were not significant prognostic factors (Table 2).

## Discussion

Patients with NETLMs have a five-year survival rate of 40%, while patients with nonhepatic metastatic

disease have a five-year survival rate of 75%–99% (19). Surgical intervention in selected patients may increase five-year symptom-free survival rate up to 70%. However, options for surgical interventions are limited, and thus, aggressive local therapies such as embolization with or without chemotherapy (20–23) and external beam radiotherapy (24–27) have been used to treat hepatic metastases from NETs (28). For unresectable NETLM, radioembolization with  $^{90}\text{Y}$  microspheres



**Figure 1.** Kaplan Meier cumulative survival curve of the whole patient group.

**Table 2.** Investigation of multiple risk factors for possible predictors of overall survival by multivariate cox proportional hazard regression method

	P	Exp(B)	95% CI for Exp(B)	
			Lower	Upper
Presence of extrahepatic metastases	0.742	1.30	0.26	6.36
Presence of radiological response	0.251	2.28	0.55	9.41
Advanced age	0.653	0.98	0.92	1.04
Tumor volume (1%–25%)*	0.033			
Tumor volume (26%–50%)	0.465	1.85	0.35	9.79
Tumor volume (51%–75%)	0.031	6.33	1.18	33.82
Tumor volume (76%–100%)	0.009	16.56	2.00	136.85
Primary location (unknown)*	0.335			
Primary location (pancreas)	0.579	0.49	0.04	6.05
Primary location (appendix)	0.799	1.45	0.08	26.41
Primary location (ileum)	0.817	0.66	0.02	22.33
Primary location (rectum)	0.975	0.00	0.00	0.00
Primary location (colon)	0.143	9.39	0.46	188.71
Primary location (lung)	0.682	0.51	0.02	11.99

\*Reference category.

14 (27%) showed partial response, 14 (27%) had stable disease, and 17 (33%) showed progressive disease. There was complete remission in six patients with NETLMs; this may be due to lesser tu-

mor burden and earlier disease stages. The median survival was 36 months. The significant prognostic factors for overall survival were radiological response to treatment, extent of tumor

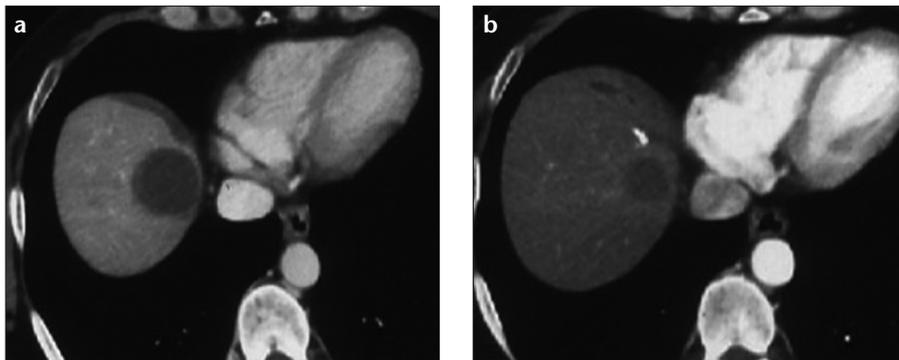
involvement, tumor grade, and extrahepatic disease.

Saxena et al. (34) included 48 patients who received resin-based microspheres. The median survival of the group was 35 months. Imaging results showed that, among the treated patients, seven (15%) had complete remission, 19 (40%) had partial response, 11 (23%) had stable disease, and 11 (23%) had progressive disease. Complete remission/partial response, well-differentiated tumor, female gender, low hepatic tumor burden, and absence of extrahepatic metastasis were found to have a statistically significant impact on overall survival.

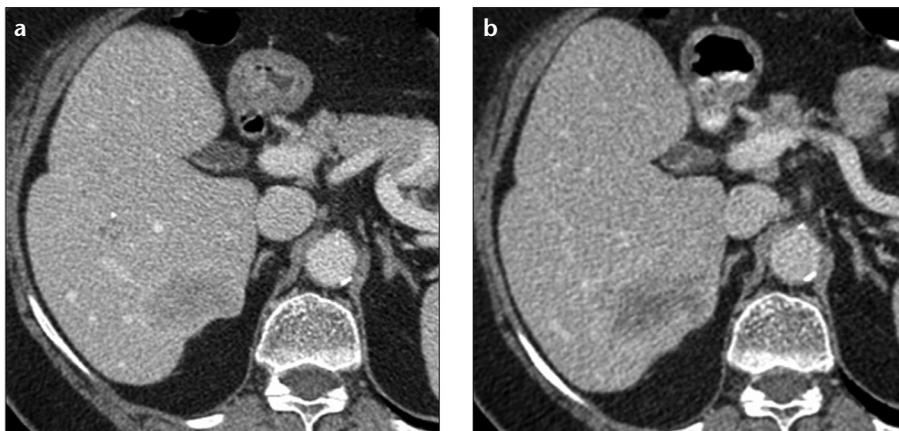
In contrast to the studies of Cao et al. (33) and Saxena et al. (34), existence of extrahepatic disease at the time of radioembolization and radiographic response were not significant prognostic factors in our study. This may be due to smaller number of patients in our study. But in line with their results we found that the extent of tumor involvement had a statistically significant impact on overall survival.

We observed that most of the stable lesions in our patient group appeared hypovascular and partially necrotic after treatment, but they did not meet the criteria for response according to RECIST (Fig. 3). Using <sup>111</sup>In-octreotide scintigraphy, five of 11 patients with stable disease showed metabolic inactivation, which can be regarded as a therapy performance (Fig. 4). Decreasing standardized uptake value in high metabolic lesions, as well as the absence of new lesions are considered to indicate good metabolic response and outcome (35). Therefore, we suggest that, imaging methods reflecting metabolic activity like <sup>111</sup>In-octreotide scintigraphy or cellularity like diffusion-weighted MRI can be preferred for the evaluation of liver metastases after radioembolization.

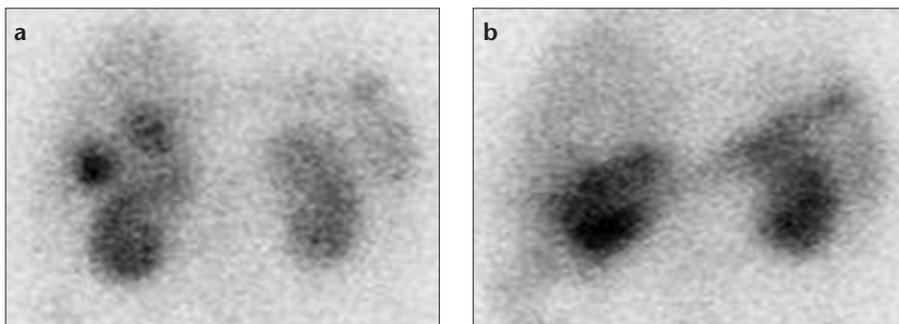
Our study has a number of limitations. The major limitation is that our patients had various kinds of therapies before radioembolization, which might have affected the overall result of subsequent radioembolization. In addition, our study has a retrospective design; the number of patients is less than the previous studies; and it is focused on radiological response, without considering serological markers.



**Figure 2. a, b.** Axial pretreatment (a) and post-treatment (b) CT images show reduction in size which is consistent with partial response.



**Figure 3. a, b.** Axial pretreatment (a) and post-treatment (b) CT images. As there is no significant size reduction, it is accepted as stable disease. However, necrosis has developed at the central portion of the lesion.



**Figure 4. a, b.** Pretreatment (a) and post-treatment (b) planar <sup>111</sup>In-octreotide scintigraphy images of a 65-year-old female patient who received 1.6 GBq selective internal radiation therapy for neuroendocrine tumor liver metastases.

Also, it would have been better to have multiphase CT for determining the response, because NETs are hypervascular, which is another limitation of our study.

In conclusion, our study demonstrates the effectiveness and safety of radioembolization for the treatment of hepatic metastases from NETs. We identified that the extent of tumor involvement has a significant effect

on overall survival. We suggest that it would be better to choose imaging methods like scintigraphy or diffusion weighted MRI, for the evaluation of treatment response of liver metastases after radioembolization. Future studies should focus on significant factors that may influence patient selection process and choosing the right imaging methods for evaluating the post-therapy response.

#### Conflict of interest disclosure

The authors declared no conflicts of interest.

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