^{90}Y Radioembolization in the Treatment of Neuroendocrine Neoplasms: Results of an International Multicenter Retrospective Study

Benedikt M. Schaarschmidt[1], Moritz Wildgruber[2,3], Roman Kloeckner[4], James Nie[5], Verena Steinle[6], Arthur J.A.T. Braat[7], Fabian Lohoefer[8], Hyun S. Kim[5], Harald Lahner[9], Manuel Weber[10], and Jens Theysohn[1]

[1]Department of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, Essen, Germany; [2]Institute of Clinical Radiology, University Hospital of Muenster, Muenster, Germany; [3]Department of Radiology, University Hospital Ludwig Maximilians Universität, Campus Großhadern, Munich, Germany; [4]Department of Diagnostic and Interventional Radiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany; [5]Section of Interventional Radiology, Department of Radiology and Biomedical Imaging, Yale School of Medicine, New Haven, Connecticut; [6]Department of Diagnostic and Interventional Radiology, University Hospital of Heidelberg, Heidelberg, Germany; [7]Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Utrecht, The Netherlands; [8]Department of Radiology, Klinikum Rechts der Isar, Technical University of Munich, Munich, Germany; [9]Department of Endocrinology, Diabetes and Metabolism and Division of Laboratory Research, University Hospital Essen, Essen, Germany; and [10]Clinic of Nuclear Medicine, University Hospital Essen, Essen, Germany

In neuroendocrine neoplasms (NENs), the presence of distant metastases has a severe impact on survival leading to a relevant decrease in the 5-y survival rate. Here, ^{90}Y radioembolization (^{90}Y RE) might be an important treatment option; however, data to support clinical benefits for ^{90}Y RE are scarce. Therefore, the purpose of this study was to analyze the use of ^{90}Y RE in NEN patients with hepatic metastases in an international, multicenter retrospective analysis and assess the potential role of ^{90}Y RE in a multimodal treatment concept. **Methods:** In total, 297 angiographic evaluations in NEN patients before ^{90}Y RE were analyzed. Baseline characteristics and parameters derived from imaging evaluation and ^{90}Y RE were analyzed. Tumor response was assessed using RECIST 1.1, and survival data were collected. Mean overall survival (OS) between different groups was compared using Kaplan–Meier curves and the log rank test. A P value of less than 0.05 indicated statistical significance. **Results:** After ^{90}Y RE, the disease control rate according to RECIST 1.1 was 83.5% after 3 mo and 50.9% after 12 mo. OS in the entire population was 38.9 ± 33.0 mo. High tumor grade ($P < 0.006$) and high tumor burden ($P = 0.001$) were both associated with a significant decrease in OS. The presence of extrahepatic metastases ($P = 0.335$) and the type of metastatic vascularization pattern ($P = 0.460$) had no influence on OS. Patients who received ^{90}Y RE as second-line therapy had a slightly longer but not statistically significant OS than patients who had ^{90}Y RE in a salvage setting (44.8 vs. 30.6 mo, $P = 0.078$). Hepatic and global progression-free survival after ^{90}Y RE was significantly decreased in heavily pretreated patients, compared with patients with second-line therapy ($P = 0.011$ and $P = 0.010$, respectively). **Conclusion:** ^{90}Y RE could be an important alternative to peptide receptor radionuclide therapy as second-line treatment in patients with progressive liver-dominant disease pretreated with somatostatin analogs.

Key Words: radionuclide therapy; neuroendocrine neoplasm; radioembolization; SIRT; neuroendocrine carcinoma; neuroendocrine tumor

Neuroendocrine neoplasms (NENs) are rare, mostly slow-growing malignancies with an age-adjusted incidence rate of 6.98 per 100,000 in the United States (*1*). Because of the slow growth of well-differentiated tumors, overall outcomes are favorable, with a 5-y survival rate of up to 82%, depending on the tumor's primary location, grade according to World Health Organization criteria, and Ki-67 (*1–4*). As symptoms frequently occur in the later stages of the disease, distant metastases are present in up to 29% of all patients at the time of diagnosis (*4*). The presence of distant metastases has a severe impact on survival leading to a decrease in the 5-y survival rate from 82% to 35% in well- and moderately differentiated neuroendocrine tumors (NETs) (*4*). Distant metastases are located predominantly in the liver (*2*), and complete metastatic resection is possible in approximately only 20% of patients (*5*). In most cases, somatostatin analog treatment is considered the first-line treatment because of the favorable safety profile and the available evidence (*6–8*). If hepatic metastases progress during treatment, different therapies including tumor ablation, angiographic procedures such as bland transarterial embolization (TAE) or transarterial chemoembolization (TACE), liver transplantation, and systemic treatments such as chemotherapy or peptide receptor radionuclide therapy (PRRT) are proposed in the guidelines to address different clinical scenarios (*9–11*).

As hepatic metastases are frequently hypervascularized, injection of an embolic agent into a hepatic artery leads to intrametastatic accumulation of the injected material and consequent necrosis. ^{90}Y radioembolization (^{90}Y RE) might be an important adjunct to these procedures. In contrast to TAE or TACE, all patients have to undergo pretherapeutic angiographic evaluation, including local injection of ^{99m}Tc-labeled macroaggregated albumin (^{99m}Tc-MAA), subsequent planar scintigraphy, and SPECT or SPECT/CT to exclude relevant extrahepatic shunting. In a second session, intraarterial injection of a calculated dose of ^{90}Y glass microspheres (TheraSphere; Boston Scientific) or resin

microspheres (SIR-Spheres; Sirtex Medical) is performed on eligible patients for whole-liver, lobar, or segmental treatment. As hepatic metastases of NETs are usually hypervascularized, these microspheres emit a high local radiation dose to each metastasis. In combination with the short range of the β^--radiation emitted by ^{90}Y, effective local tumor control can be ensured with low systemic toxicity (12,13). Moreover, repeated therapies, as in the case of TAE or TACE, are not necessary. However, data to support clinical benefits for ^{90}Y RE are scarce, as previously published, retrospective analyses suffer from the low number of participants (14–17) or a lack of essential baseline characteristics due to a more technical focus (17,18).

Therefore, our study aimed to provide a retrospective analysis on the current use of ^{90}Y RE in different clinical scenarios and to assess why ^{90}Y RE was not performed on eligible patients to provide data missing from current publications.

MATERIALS AND METHODS

Data Collection

A retrospective data collection of patients with NETs who had undergone angiographic evaluations, including local ^{99m}Tc-MAA injection for ^{90}Y RE of hepatic metastases between May 2007 and August 2019, was performed in 6 tertiary-care centers in Europe (Germany and The Netherlands) and 1 in America.

All data were collected using a unified data collection form consisting of these subsections: baseline characteristics; imaging evaluation, including ^{99m}Tc-MAA injection; ^{90}Y RE; follow-up examinations after 3 and 12 mo, including tumor response (complete response, partial response, stable disease, and progressive disease) assessed at the contributing center based on RECIST 1.1 (19); and overall survival (OS). Additionally, hepatic and global progression-free survival (PFS) was assessed according to RECIST 1.1 (Supplement 1; supplemental materials are available at http://jnm.snmjournals.org).

Statistical Analysis

For all patients after undergoing the first ^{90}Y RE, survival characteristics were investigated using Kaplan–Meier curves and the log rank test for tumor grade, hepatic tumor burden, tumor vascularization, the presence of extrahepatic metastases, and the type of microspheres used for ^{90}Y RE. In addition, Kaplan–Meier curves and the log rank test were used to analyze differences in OS, as well as hepatic and global PFS, between patients who had undergone only surgery for the primary tumor or metastases and somatostatin analog treatment before ^{90}Y RE (second-line ^{90}Y RE) and patients with extensive systemic pretreatment (therapy additional to surgery for the primary tumor or metastases and somatostatin analog treatment before ^{90}Y RE [salvage ^{90}Y RE]).

A P value of less than 0.05 was considered statistically significant. SPSS Statistics 27 (IBM) was used for statistical analysis. Because of the exploratory nature of this study, no correction for α-error accumulation was performed (Supplement 2).

RESULTS

Baseline Characteristics

In total, 297 angiographic evaluations including local ^{99m}Tc-MAA injection were performed on 210 patients (91 women and 119 men; mean age ± SD, 59.1 ± 37.3 y) between May 2007 and August 2019 (Fig. 1). Multiple evaluations were performed on 72 patients (2 evaluations in 57 patients, 3 in 7 patients, and 4 in 4 patients). NETs were present in 90.9% (270/297), and neuroendocrine carcinomas in 9.1% (27/297), of all angiographic evaluations. In NET, a tumor grade of 1 was found in 25.6% (76/297), of 2 in 50.5% (150/297), and of 3 in 5.7% (17/297); the grade was unknown in 9.1% (27/297). Hypersecretion symptoms were observed in 32.7%
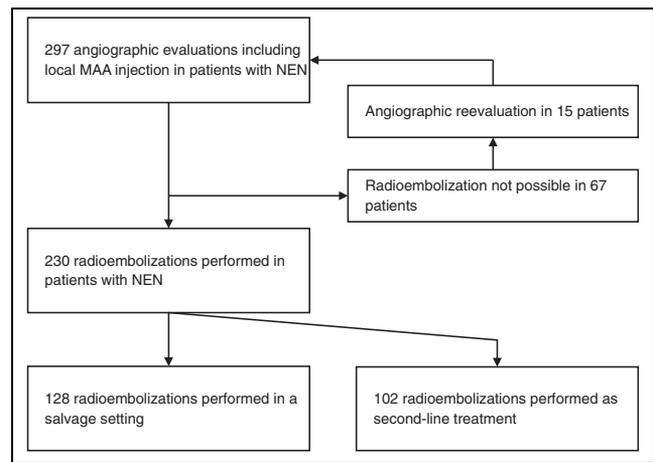

FIGURE 1. Flowchart of analyzed patient cohort.

(97/297), and extrahepatic metastases were observed in 41.4% (122/297) (Table 1; Supplemental Table 1). Before angiographic evaluation including ^{99m}Tc-MAA injection, different treatments were used in 91.6% (272/297), including external-beam radiotherapy in 1.7% (5/297), primary-tumor surgery in 64.3% (191/297), treatment of hepatic metastases by surgery in 18.2% (54/297), local ablation (e.g., radiofrequency ablation or microwave ablation) in 4.0% (12/297), and TACE or TAE in 8.8% (26/297). PRRT was used in 20.2% (60/297), antibody-based therapy in 2.4% (7/297), somatostatin analog therapy in 57.2% (170/297), prior ^{90}Y RE in 9.8% (29/297), liver transplantation in 0.3% (1/297), chemotherapy in 29.3% (87/297), and targeted therapy in 7.7% (23/297).

Imaging Evaluation Including ^{99m}Tc-MAA Injection

Before the angiographic evaluation, a CT scan was performed on 84.2% of patients (250/297) and an MRI scan on 24.2% (72/297). A hepatic tumor burden of 25% or less was present in 50.2% (149/297), 25%–50% in 31.0% (92/297), and 50% or more in 16.2% (48/297); the hepatic tumor burden was unknown in 2.7% (6/297). Metastases were hypervascularized in 63.6% (188/297), hypovascularized in 18.2% (54/297), and of a mixed or atypical appearance in 15.5% (46/297). The vascularization type was unknown in 3.0% (9/287).

Before ^{99m}Tc-MAA injection, vessel occlusion was necessary in 39.1% (116/297). Preexistent vessel occlusion due to prior coiling was found in 6.1% (18/297) (Table 2; Supplemental Table 2).

A central ^{99m}Tc-MAA injection was performed on 17.8% (53/297), a lobar ^{99m}Tc-MAA injection on 71% (211/297), and a segmental ^{99m}Tc-MAA injection on 2.7% (8/297). Other types of ^{99m}Tc-MAA injection were performed on 8.4% (25/297).

Complications occurred in 19 (6.4%) of the 297 patients, with 4 (1.4%) having vascular occlusion, 2 (0.7%) having dissection, and 1 each (0.3%) having the following complications: vasospasm, hypertension, a combination of pain/hypertension and tachycardia, complications associated with contrast medium, and coil dislocation. Complications in 8 additional patients were not specified (2.8%).

A mean lung shunt fraction of 5.7% ± 5.6% was observed in ^{99m}Tc-MAA scintigraphy (261 with a lung shunt fraction of ≤10%, 29 with >10%, and 7 with an unknown fraction).

^{90}Y RE

^{90}Y RE was performed after 77.4% of angiographic evaluations including local ^{99m}Tc-MAA injection (230/297; glass microspheres, 46.8% [139/297]; resin microspheres, 30.6% [91/297]) across a

TABLE 1
Baseline Characteristics of All Performed Imaging Evaluations

Parameter	%	n
Localization of primary tumor		
NET	90.9	270
Lung	3.0	9
Esophagus	0.7	2
Stomach	4.4	13
Pancreas	24.9	75
Small bowel or pancreas	0.7	2
Small bowel	31.1	92
Appendix	1.1	3
Colon	4.4	13
Rectum	5.1	15
Unknown primary	7.4	22
Not specified	8.1	24
Neuroendocrine carcinoma	9.1	27
Grading		
NET		
Grade 1	25.6	76
Grade 2	50.5	150
Grade 3	5.7	17
Unknown	9.1	27
Neuroendocrine carcinoma	9.1	27
Extrahepatic metastases		
Yes	41.1	122
No	58.9	175
Endocrine symptoms		
Yes	28.7	85
Carcinoid syndrome	5.7	17
Diabetes	6.4	19
Flush	9.7	29
Hedinger syndrome	1	3
Hypertonia	0.7	2
Hypoglycemia	1.3	4
Zollinger–Ellison syndrome	0.7	2
Unspecified	2.7	8
No	67.3	200
Unknown	4.0	12
Therapy before ^{90}Y RE		
Yes	91.6	272
No	8.4	25

TABLE 2
Imaging Evaluation Including ^{99m}Tc-MAA Injection

Parameter	%	n
Hepatic tumor burden		
<25%	50.2	149
25%–50%	31	92
>50%	16.2	48
Unknown	2.7	8
Vascularization pattern		
Hypervascularization	63.3	188
Hypovascularization	18.2	54
Mixed/atypical	15.5	46
Unknown	3.0	9
Vessel coiling present	39.1	116
Lateral left hepatic artery	2	0.7
Medial left hepatic artery	2.7	8
Gastroduodenal artery	25.3	75
Left gastric artery	0.7	2
Right gastric artery	14.8	44
Falciforme artery	0.3	1
Accessory vessel	11.0	33
Prior coiling		
Present	6.1	18
Absent	54.8	163
Preexisting portal vein thrombosis		
Partial	2.0	6
Complete	0.0	0
None	96.0	285
Unknown	2.0	6
Complications		
Present	6.4	19
Vasospasm	0.3	1
Dissection	0.7	2
Vascular occlusion	1.4	4
Hypertonia	0.3	1
Pain, hypertonia, or tachycardia	0.3	1
Complication associated with contrast medium	0.3	1
Coil dislocation	0.3	1
Not specified	2.8	8
Absent	92.2	274
Unknown	1.4	4
Lung shunt fraction		
≤10%	87.9	261
10%	9.8	29
Unknown	2.4	7

total of 176 patients (1 treatment, 71.6% [126/176]; 2 treatments, 26.7% [47/176]; 3 treatments, 0.7% [2/176]; 4 treatments, 0.3% [1/176]). For glass microspheres, dosimetry planning was performed using the single-compartment model with a perfused target volume dose of 80–150 Gy. For resin microspheres, the body-surface-area model was used. For resin microspheres, a mean activity of 1.26 ± 0.59 GBq was used for ^{90}Y RE, and for glass microspheres, the mean activity was 3.78 ± 2.24 GBq.

In 44.3% (102/230) of all cases, patients had been treated only by surgery or somatostatin analog therapy before ^{90}Y RE (second-line treatment, Fig. 2). In most other cases (55.7% [128/230]), ^{90}Y RE was performed in a salvage setting after extensive prior therapy.
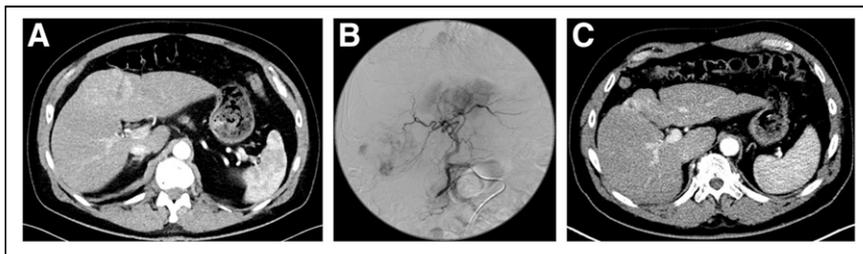
FIGURE 2. A 67-y-old man with grade 2 gastric NET and hepatic metastases. Hepatic tumor progression was observed with somatostatin analog treatment. (A) At time of ^{90}Y RE, hepatic tumor burden was less than 25%. (B) In angiographic evaluation, hypervascularized metastases were detected in both liver lobes; thus, same-session sequential therapy of whole liver with ^{90}Y glass microspheres was performed. (C) At follow-up, partial response was observed, with residual metastases in liver segment 4.

^{90}Y RE of the whole liver was used in 44.9% (108/230), and sequential whole-liver therapies was used in separate sessions in 33.1% (76/230). ^{90}Y RE was performed for a single lobe in 19.6% (45/230) and for a selected liver part in 0.4% (1/230).

Second-line ^{90}Y RE after a minimum of prior therapy (including surgery of the primary tumor or hepatic metastasis and somatostatin analog therapy) was used in 44.3% (102/230), whereas extensive prior therapy was used in 55.7% (128/230).

Procedural complications were observed in 4.8% of all cases (11/230, including 3 with vasospasm; 2 each with liver organ necrosis, pain, or stasis of blood flow; and 1 each with sepsis/pain and hemodynamic instability). No complications were observed in 73.7% (219/230). ^{90}Y RE was not performed on 22.6% (67/297) (Table 3; Supplement 3).

Survival Analysis

Entire Population. At the time of data collection, 59.7% of all patients (105/176) were deceased, 27.3% (48/176) were still alive,

TABLE 3
Reasons for Canceling ^{90}Y RE

Parameter	%	n
^{90}Y RE performed	77.4	230
^{90}Y RE not performed	22.6	67
Reasons for canceling ^{90}Y RE		
Extrahepatic shunting	8.1	24
Lack of ^{99m}Tc-MAA accumulation	3.4	10
Worsening of patient's general condition	2.0	6
Extrahepatic tumor progression	1.3	4
Different therapy	1.1	3
Hepatic tumor burden too high	1.1	3
Unfavorable vessel anatomy	1.1	3
Worsening of hepatic laboratory parameters	0.7	2
Residual primary tumor	0.3	1
Hepatic vessel occlusion	0.3	1
Inhomogeneous ^{99m}Tc-MAA distribution	0.3	1
Technical problems with vial	0.3	1
Contrast agent–associated problem	0.3	1
Patient did not appear	0.3	1
Unknown	2.0	6

0.4% were lost to follow-up, and in 12.5% (22/176) the last follow-up visit was used for survival analysis. Mean OS after ^{90}Y RE was 38.9 ± 33.0 mo.

After ^{90}Y RE, OS was longer in NET patients (40.8 mo; 95% CI, 27.0–54.7 mo) than in NEC patients (19.3 mo; 95% CI, 8.1–35.1 mo) (Fig. 3A). Differences between the 2 groups were found by the log rank test ($\chi^2_{(2)} = 6.88$, $P < 0.009$). In NET patients, patients with a grade 1 tumor had a more prolonged median OS (79.3 mo; 95% CI, 42.6–116.0 mo) than patients with a grade 2 tumor (30.6 mo; 95% CI, 25.2–36.0 mo) or grade 3 tumor (21.4 mo; 95% CI, 10.7–32.1 mo) (Fig. 3B). According to the log rank test, the survival distributions for the 3 different tumor grades were statistically significant ($\chi^2_{(2)} = 10.21$, $P < 0.006$).

An increase in hepatic tumor burden was associated with a reduction in median OS (burden < 25%: 63.2 mo, 95% CI of 36.0–90.4 mo; burden of 25%–50%: 30.3 mo, 95% CI of 25.8–34.8 mo; burden > 50%: 22.5 mo, 95% CI of 16.6–28.4 mo). Significant differences among these 3 survival groups were detected by the log rank test ($\chi^2_{(2)} = 14.10$, $P = 0.001$) (Fig. 3C).

Only slight differences were observed in OS after ^{90}Y RE in patients with different vascularization patterns of hepatic metastases (hypervascularization: 40.5 mo, 95% CI of 17.4–63.6 mo; hypovascularization: 30.3 mo, 95% CI of 20.1–40.5 mo; and mixed appearance: 17.7 mo, 95% CI of 26.5–95.9). The log rank test found no significant differences among the survival distributions for these 3 hepatic vascularization patterns ($\chi^2_{(2)} = 1.6$, $P = 0.460$) (Fig. 3D).

Median OS was similar in patients with extrahepatic metastases (30.6 mo; 95% CI, 19.4–41.8) and without (44.8 mo; 95% CI, 29.8–59.8). No significant differences between the 2 survival groups were observed in the log rank test ($\chi^2_{(2)} = 0.931$, $P = 0.335$) (Fig. 3E; Supplements 4 and 5; Supplemental Fig. 1).

Second-Line Therapy Versus Salvage Setting. Patients who received ^{90}Y RE as second-line therapy had a slightly longer OS (44.8 mo; 95% CI, 24.2–65.4 mo) than patients who had ^{90}Y RE in a salvage setting (30.6 mo; 95% CI, 18.5–42.7) (Fig. 4A). However, the log rank test did not yield a statistically significant result ($\chi^2_{(2)} = 3.109$, $P = 0.078$).

Median hepatic PFS (15.9 mo; 95% CI, 10.6–21.2 mo) and global PFS (14.7 mo; 95% CI, 10.5–18.9 mo) were worse in patients undergoing ^{90}Y RE in a salvage setting than in patients with ^{90}Y RE as second-line therapy (hepatic PFS: 18.6 mo, 95% CI of 14.0–23.2 mo; global PFS: 18.8 mo, 95% CI of 8.3–29.3 mo). The log rank test detected significant differences between the 2 survival groups for hepatic PFS ($\chi^2_{(2)} = 6.44$, $P = 0.011$) and global PFS ($\chi^2_{(2)} = 6.63$, $P = 0.010$) (Figs. 4B and 4C; Supplement 6; Supplemental Fig. 2).

In patients receiving ^{90}Y RE as salvage therapy, OS in patients with prior PRRT (30.3 mo; 95% CI, 26.2–34.3 mo) was comparable to that in patients who did not receive prior PRRT (36.2 mo; 95% CI, 19.8–52.5 mo). No significant differences between the 2 groups were found in the log rank test ($\chi^2_{(2)} = 0.16$, $P = 0.692$) (Fig. 5).

DISCUSSION

^{90}Y RE is a possible alternative to a surgical approach to achieve local tumor control in metastatic liver disease. However, alternatives to ^{90}Y RE are manifold, and systemic approaches such as PRRT or
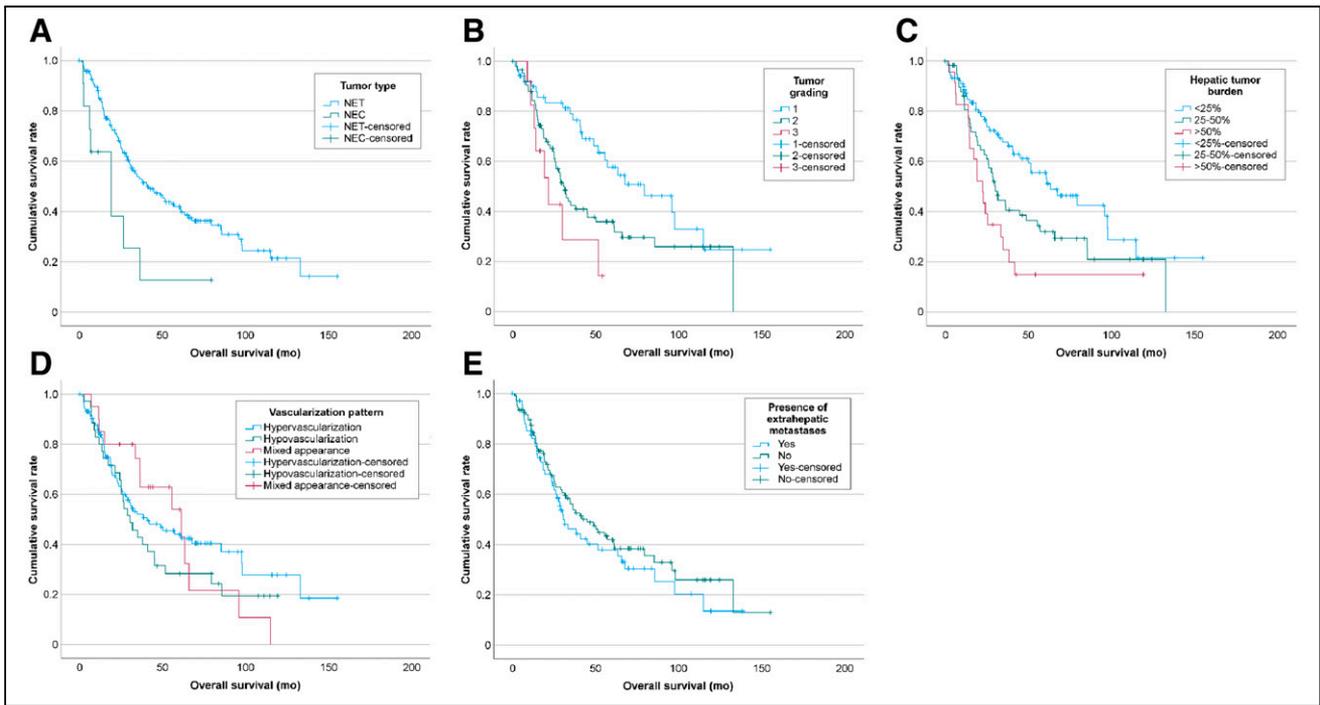
FIGURE 3. Kaplan–Meier survival curves investigating influence of 6 different parameters on survival in entire population: tumor type (A), NET tumor grading (B), hepatic tumor burden (C), metastatic vascularization (D), and extrahepatic metastases (E).

new chemotherapies challenge the concept of local liver ^{90}Y RE in general. Therefore, further data are necessary to balance the advantages and disadvantages of all available therapies in NEN patients with hepatic metastases. In this context, the results of this retrospective international multicenter study hold 3 key messages. First, second-line ^{90}Y RE is associated with increased OS and a significant increase in hepatic and global PFS, with OS slightly superior to that seen in published PRRT data. Second, the vascularization type of hepatic metastases does not significantly affect survival after ^{90}Y RE. Third, the presence of extrahepatic metastases in patients with liver-dominant disease does not significantly affect OS in patients undergoing ^{90}Y RE—neither in the entire population nor in patients receiving ^{90}Y RE as second-line therapy.

Successful surgical removal of hepatic metastases is associated with 5-y survival rates of 64%–100% (5,20), but only a minority of patients is eligible for this procedure (5). In patients with increased somatostatin expression who cannot undergo surgery,

systemic treatment using somatostatin analogs is considered the treatment of choice in the latest guidelines (9–11). In patients with progressive hepatic metastases, angiographic procedures such as TAE, TACE, or ^{90}Y RE or PRRT are possible treatment options. Although comparative studies among these options are not available, PRRT is recommended as the second-line therapy of choice in the most recent guidelines (9–11). Because of the lack of data, the treatment of sole hepatic metastases or liver-dominant disease remains a controversial topic. In a recent recommendation by Frilling et al., TAE, TACE, or ^{90}Y RE is proposed as a possible alternative in these 2 scenarios (21).

Our study results support these recommendations and further raise the question of whether ^{90}Y RE should be primarily performed in specific scenarios as second-line treatment before PRRT.

We found that patients who had undergone ^{90}Y RE as second-line treatment did show a relevant increase in OS and a significant increase in hepatic and global PFS, compared with patients with a
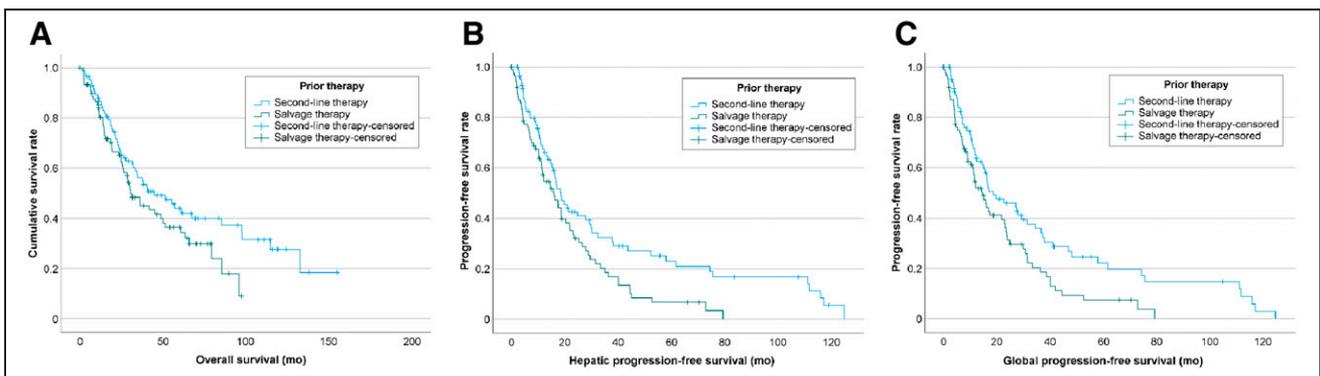

FIGURE 4. Kaplan–Meier survival curves investigating influence of extent of prior therapy (second-line therapy: prior surgery for primary tumor or metastases and somatostatin analog treatment before ^{90}Y RE vs. salvage therapy) on OS (A), hepatic PFS (B), and global PFS (C).
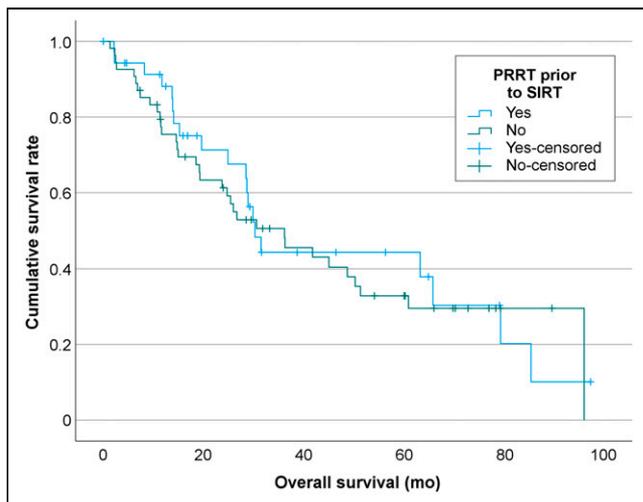
FIGURE 5. Kaplan–Meier survival curve investigating influence of prior PRRT on survival in patients receiving ^{90}Y RE as salvage therapy.

more extensive pretreatment. OS in patients with ^{90}Y RE as second-line treatment was only slightly worse than the results of PRRT in the Rotterdam cohort, with overlapping 95% CIs (44.8 mo, 95% CI of 24.2–65.4 mo, vs. 63 mo, 95% CI of 55–72 mo) (*22*). Furthermore, the presence of extrahepatic metastases does not influence OS after ^{90}Y RE as second-line therapy. In contrast to ^{90}Y RE in a salvage setting, hepatic tumor burden has no significant impact on OS if ^{90}Y RE is performed as a second-line therapy. Additionally, our data indicate that in 22.6% of all cases, ^{90}Y RE could not be performed because of contraindications associated with advanced hepatic disease such as shunting, a high tumor burden, or liver function deterioration. These findings further suggest that early ^{90}Y RE before PRRT could be beneficial in patients with the liver-dominant disease. In this clinical pathway, a successful local, liver-directed therapy using ^{90}Y RE could be ensured independently of hepatic tumor burden, and the risk of contraindications for ^{90}Y RE caused by advanced oncologic disease such as shunting could be avoided.

In certain scenarios, ^{90}Y RE might yield even further benefits. Although PRRT is limited to patients with increased somatostatin receptor expression compared with the background hepatic uptake (*23*), this requirement does not hinder ^{90}Y RE. Even hypovascularization of hepatic metastases in contrast-enhanced cross-sectional imaging does not influence OS after ^{90}Y RE. Additional benefits of ^{90}Y RE as second-line therapy in comparison to PRRT are the possibility of continuing somatostatin analog therapy during ^{90}Y RE, the absence of hematologic and renal toxicity, and the possibility of performing ^{90}Y RE as a 1-stop-shop treatment in contrast to the prolonged treatment duration of PRRT (*12,22*).

Furthermore, the benefits to this therapeutic approach do not seem to be limited to patients without extrahepatic metastases. The presence of extrahepatic metastases in liver-dominant disease did not have a significant impact on OS in our analysis and was not associated with a significant hazard ratio, in contrast to previous studies (*12,24*).

Hence, our findings stress the need for a prospective study comparing PRRT and ^{90}Y RE as second-line treatment in patients with progressive liver-dominant disease treated with somatostatin analogs.

Our study had some limitations. Because of its retrospective nature and the combined analysis of ^{90}Y RE performed with resin and glass microspheres, differences in the procedural technique could be possible. These limitations could be circumvented only by a prospective study. We did not perform a comparison between ^{90}Y RE and TAE or TACE. Because PRRT is recommended as the therapy of choice, TAE and TACE are considered by some authors as advantageous over ^{90}Y RE to avoid radiation-induced liver failure when PRRT and ^{90}Y RE are combined (*25*). However, recent findings by Braat et al., as well as our own findings on ^{90}Y RE as salvage therapy in patients with and without prior PRRT, indicate that ^{90}Y RE can be performed safely after PRRT without an increased risk of radiation-induced liver failure (*26,27*). Furthermore, there are several distinct disadvantages of TAE or TACE compared with ^{90}Y RE, most notably the higher proportion (≤61%) of patients with pain, nausea, or treatment-associated fever (*25,28,29*) and the need to perform multiple therapies (*30*). Especially in the current raging coronavirus disease 2019 pandemic, ^{90}Y RE might be advantageous because of the reduced number of procedures necessary to achieve a favorable result and lower therapy-associated complications. However, a randomized trial between TAE or TACE and ^{90}Y RE might improve the acceptance of interventional procedures in general in NET patients with liver-dominant disease.

CONCLUSION

Our results show that ^{90}Y RE has potential as second-line therapy in patients with NENs with liver-dominant disease and thus could be an important alternative to PRRT in certain scenarios. However, a prospective study is necessary to support these promising data.

DISCLOSURE

KEY POINTS

QUESTION: Is ^{90}Y RE a potential a treatment option in patients with NENs?

PERTINENT FINDINGS: In this retrospective multicenter study, second-line ^{90}Y RE was associated with a significant increase in PFS, with satisfactory OS rates. The presence of extrahepatic metastases in patients with liver-dominant disease undergoing ^{90}Y RE did not affect OS.

IMPLICATIONS FOR PATIENT CARE: This study showed the potential of ^{90}Y RE as a treatment option in patients with NENs with liver-dominant disease and thus could be an important alternative to PRRT.

REFERENCES

1. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol.* 2017;3:1335–1342.

2. Pape U-F, Berndt U, Müller-Nordhorn J, et al. Prognostic factors of long-term outcome in gastroenteropancreatic neuroendocrine tumours. *Endocr Relat Cancer.* 2008;15:1083–1097.

3. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer.* 2003;97:934–959.

4. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol.* 2008;26:3063–3072.

5. Frilling A, Li J, Malamutmann E, Schmid K-W, Bockisch A, Broelsch CE. Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease. *Br J Surg.* 2009;96:175–184.

6. Rinke A, Müller H-H, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. *J Clin Oncol.* 2009;27:4656–4663.

7. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med.* 2014;371:224–233.

8. Caplin ME, Pavel M, Phan AT, et al. Lanreotide autogel/depot in advanced enteropancreatic neuroendocrine tumours: final results of the CLARINET open-label extension study. *Endocrine.* 2021;71:502–513.

9. Pavel M, Baudin E, Couvelard A, et al. ENETS consensus guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology.* 2012;95:157–176.

10. Rinke A, Wiedenmann B, Auernhammer C, et al. Practice guideline neuroendocrine tumors - AWMF-Reg. 021-27 [in German]. *Z Gastroenterol.* 2018;56:583–681.

11. Pavel M, Öberg K, Falconi M, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2020;31:844–860.

12. Braat AJAT, Kappadath SC, Ahmadzadehfar H, et al. Radioembolization with ⁹⁰Y resin microspheres of neuroendocrine liver metastases: international multicenter study on efficacy and toxicity. *Cardiovasc Intervent Radiol.* 2019;42:413–425.

13. D'Souza D, Golzarian J, Young S. Interventional liver-directed therapy for neuroendocrine metastases: current status and future directions. *Curr Treat Options Oncol.* 2020;21:52.

14. Tsang ES, Loree JM, Davies JM, et al. Efficacy and prognostic factors for Y-90 radioembolization (Y-90) in metastatic neuroendocrine tumors with liver metastases. *Can J Gastroenterol Hepatol.* 2020;2020:5104082.

15. Rhee TK, Lewandowski RJ, Liu DM, et al. ⁹⁰Y radioembolization for metastatic neuroendocrine liver tumors: preliminary results from a multi-institutional experience. *Ann Surg.* 2008;247:1029–1035.

16. Cao CQ, Yan TD, Bester L, Liauw W, Morris DL. Radioembolization with yttrium microspheres for neuroendocrine tumour liver metastases. *Br J Surg.* 2010;97:537–543.

17. Paprottka PM, Hoffmann R-T, Haug A, et al. Radioembolization of symptomatic, unresectable neuroendocrine hepatic metastases using yttrium-90 microspheres. *Cardiovasc Intervent Radiol.* 2012;35:334–342.

18. Kennedy AS, Dezarn WA, McNeillie P, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin ⁹⁰Y-microspheres: early results in 148 patients. *Am J Clin Oncol.* 2008;31:271–279.

19. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228–247.

20. Schurr PG, Strate T, Rese K, et al. Aggressive surgery improves long-term survival in neuroendocrine pancreatic tumors: an institutional experience. *Ann Surg.* 2007;245:273–281.

21. Frilling A, Clift AK. Therapeutic strategies for neuroendocrine liver metastases. *Cancer.* 2015;121:1172–1186.

22. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safety of [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. *Clin Cancer Res.* 2017;23:4617–4624.

23. Hope TA, Abbott A, Colucci K, et al. NANETS/SNMMI procedure standard for somatostatin receptor–based peptide receptor radionuclide therapy with ¹⁷⁷Lu-DOTATATE. *J Nucl Med.* 2019;60:937–943.

24. Do Minh D, Chapiro J, Gorodetski B, et al. Intra-arterial therapy of neuroendocrine tumor liver metastases: comparing conventional TACE, drug-eluting beads TACE and ⁹⁰yttrium radioembolization as treatment options using a propensity score analysis model. *Eur Radiol.* 2017;27:4995–5005.

25. Lehrman ED, Fidelman N. Liver-directed therapy for neuroendocrine tumor liver metastases in the era of peptide receptor radionuclide therapy. *Semin Intervent Radiol.* 2020;37:499–507.

26. Braat AJAT, Bruijnen RCG, van Rooij R, et al. Additional holmium-166 radioembolisation after lutetium-177-dotatate in patients with neuroendocrine tumour liver metastases (HEPAR PLuS): a single-centre, single-arm, open-label, phase 2 study. *Lancet Oncol.* 2020;21:561–570.

27. Braat AJAT, Ahmadzadehfar H, Kappadath SC, et al. Radioembolization with ⁹⁰Y resin microspheres of neuroendocrine liver metastases after initial peptide receptor radionuclide therapy. *Cardiovasc Intervent Radiol.* 2020;43:246–253.

28. Fiore F, Del Prete M, Franco R, et al. Transarterial embolization (TAE) is equally effective and slightly safer than transarterial chemoembolization (TACE) to manage liver metastases in neuroendocrine tumors. *Endocrine.* 2014;47:177–182.

29. Pericleous M, Caplin ME, Tsochatzis E, Yu D, Morgan-Rowe L, Toumpanakis C. Hepatic artery embolization in advanced neuroendocrine tumors: efficacy and long-term outcomes. *Asia Pac J Clin Oncol.* 2016;12:61–69.

30. Grozinsky-Glasberg S, Kaltsas G, Kaltsatou M, et al. Hepatic intra-arterial therapies in metastatic neuroendocrine tumors: lessons from clinical practice. *Endocrine.* 2018;60:499–509.