⁹⁰Y radioembolization in the treatment of neuroendocrine neoplasms: Results of an international multicenter retrospective study.

Running Title

⁹⁰Y RE in neuroendocrine neoplasms

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Conflict of Interest

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ABSTRACT

Purpose

In neuroendocrine neoplasms (NEN), the presence of distant metastases has a severe impact on survival leading to a relevant decrease of the 5-year survival rate. Here, 90Y radioembolization (RE) might be an important treatment option, however, data to support clinical benefits for RE are scarce. Therefore, the purpose of this study was to analyze the use of RE in NEN patients with hepatic metastases in an international, multi-center retrospective analysis and assess the potential role of RE in a multimodal treatment concept.

Methods

297 angiographic evaluations in NEN patients prior to RE were analyzed. Baseline characteristics and parameters derived from imaging evaluation and 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. $p < 0.05$ indicated statistical significance.

Results

After RE, disease control rate according to RECIST 1.1 was 83.5% after three and 50.9% after twelve months. OS in the entire population was 38.9 ± 33.0 months. High tumor grade ($p < 0.006$) and high tumor burden ($p = 0.001$) were both associated with a significant decrease of 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 RE as second-line therapy had a slightly longer but not statistically significant OS than patients who had RE in a salvage setting (44.8 vs. 30.6 months, $p = 0.078$). Hepatic and global progression-free survival after RE was significantly decreased in heavily pretreated patients than patients with second-line therapy ($p = 0.011$ and $p = 0.010$, respectively).

Conclusion

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.

INTRODUCTION

Neuroendocrine neoplasms (NEN) are rare, mostly slow-growing malignancies with an age-adjusted incidence rate of 6.98 per 100,000 in the USA(1). Due to the slow growth speed of well-differentiated tumors, overall outcomes are favorable with a 5-year survival rate of up to 82%, depending on the tumors' primary location and tumor grade according to WHO grading 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 time of diagnosis(4). The presence of distant metastases has a severe impact on survival leading to a decrease of the 5-year survival rate from 82% to 35% in well- and moderately differentiated neuroendocrine tumors (NET)(4). Distant metastases are predominantly located in the liver(2), and complete metastatic resection is only possible in approximately 20% of patients(5). In the majority of cases, somatostatin analog treatment is considered the first-line treatment due to 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 radiotherapy (PRRT) are proposed in the guidelines to address different clinical scenarios(9–11).

As hepatic metastases are frequently hypervascularized, the injection of an embolic agent into a hepatic artery leads to intrametastatic accumulation of the injected material and consecutive necrosis. ^{90}Y radioembolization (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 $^{99\text{m}}\text{Tc}$ -labeled macroaggregated albumin (MAA), subsequent planar scintigraphy and SPECT(/CT) to exclude relevant extrahepatic shunting. In a second session, intra-arterial injection of a calculated dose of ^{90}Y glass (TheraSphere®, Boston Scientific, Marlborough, Massachusetts) or resin microspheres (SIR-Spheres®, Sirtex Medical, Sydney, Australia) is performed in eligible patients for whole liver, lobar or segmental treatment. As hepatic metastases of neuroendocrine tumors 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 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 RE in different clinical scenarios and to assess why RE was not performed in eligible patients to provide data missing in current publications.

MATERIAL AND METHODS

Data collection

A retrospective data collection of patients with neuroendocrine tumors that had undergone angiographic evaluations, including local MAA injection for RE of hepatic metastases between May 2007 and August 2019, was performed in six European (including hospitals in Germany and the Netherlands) and one American tertiary care center.

All data were collected using a unified data collection form, consisting of these subsections: baseline characteristics, imaging evaluation including MAA injection, RE, follow-up examinations after three and twelve months including tumor response (complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD)) assessed at the contributing center based on the response evaluation criteria in solid tumours (RECIST) 1.1 (19), and overall survival (OS). Additionally, hepatic and global progression-free survival were assessed according to RECIST 1.1 (PFS, online supplement 1).

Statistical analysis

Survival characteristics were investigated for all patients after undergoing the first RE using Kaplan Meier curves and log rank test for tumor grade, hepatic tumor burden, tumor vascularization, the presence of extrahepatic metastases and the type of microspheres used for 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 only undergone surgery for the primary tumor and/or metastases and somatostatin analog treatment prior to RE (second-line RE) and patients with extensive systemic pretreatment (additional therapy to surgery for the primary tumor and/or metastases and somatostatin analog treatment prior to RE, salvage RE).

A p-value of <0.05 was considered statistically significant. IBM SPSS Statistics 27 (IBM, Armonk, NY, USA) was used for statistical analysis. Due to the exploratory nature of this study, no correction for alpha error accumulation was performed (online supplement 2).

RESULTS

Baseline characteristics

A total of 297 angiographic evaluations including local MAA injection were performed in 210 patients (female: n=91; male: n=119; mean age 59.1±37.3y) between May 2007 and August 2019 (figure 1). Multiple evaluations were performed in 72 patients (two: n=57; three: n=7; four: n=4). Neuroendocrine tumors 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 G1 was found in 25.6%(76/297), of G2 in 50.5%(150/297), and of G3 in 5.7%(17/297) and unknown in 9.1%(27/297). Hypersecretion symptoms were observed in 32.7%(97/297) and extrahepatic metastases in 41.4%(122/297, table 1, see online supplement table 1 for further information). Prior to angiographic evaluation including MAA injection, different treatments were performed in 91.6%(272/297), including external beam radiotherapy in 1.7%(5/297), primary tumor surgery in 64.3%(191/297) and treatment of hepatic metastases by surgery in 18.2%(54/297), local ablation (e.g. radiofrequency ablation (RFA) or microwave ablation (MWA)) in 4.0%(12/297) and TACE/TAE in 8.8%(26/297). PRRT was performed in 20.2%(60/297), antibody based therapy in 2.4%(7/297), somatostatin analog therapy in 57.2%(170/297), prior 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 MAA injection

Prior to the angiographic evaluation, a CT scan was performed in 84.2%(250/297) and a MRI scan in 24.2%(72/297). Hepatic tumor burden ≤25% was present in 50.2%(149/297), 25-50% in 31.0%(92/297), ≥50% in 16.2%(48/297) and unknown in 2.7%(6/297). Metastases were hypervascularized in 63.6%(188/297), hypovascularized in 18.2%(54/297) and a mixed or atypical appearance was observed in 15.5%(46/297). Vascularization type was unknown in 3.0%(9/287).

Prior to 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, see online supplement table 2 for further information).

A central MAA injection was performed in 17.8%(53/297), a lobar MAA injection in 71%(211/297), and a segmental MAA injection in 2.7%(8/297). Other types of MAA injection were performed in 8.4%(25/297).

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

A mean lung shunt fraction of $5.7 \pm 5.6\%$ was observed in MAA scintigraphy (lung shunt fraction $\leq 10\%$: n=261; $>10\%$: n=29; unknown: n=7).

⁹⁰Y radioembolization

RE was performed after 77.4% of angiographic evaluations including local MAA injection (230/297; glass microspheres: 46.8%(139/297), resin microspheres: 30.6%(91/297)) across a total of 176 patients (one treatment: 71.6%(126/176); two treatments: 26.7%(47/176); three treatments: 0.7%(2/176); four 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 and for glass microspheres, a mean activity of 3.78 ± 2.24 Gbq was used for RE.

In 44.3%(102/230) of all cases, patients had only been treated by surgery and/or somatostatin analog therapy prior to RE (second line treatment, figure 2). In most other cases (55.7%; 128/230), RE was performed in salvage setting following extensive prior therapy.

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

Primary RE after a minimum of prior therapy (including surgery of the primary and/or hepatic metastasis, somatostatin analog therapy) was performed in 44.3%(102/230), while extensive prior therapy was performed in 55.7%(128/230).

Procedural complications were observed in 4.8% of all cases (11/230; including vasospasm (n=3); liver organ necrosis/pain/stasis of blood flow (n=2), respectively; sepsis/pain & hemodynamic instability (n=1), respectively). No complications were observed in 73.7%(219/230). RE was not performed in 22.6%(67/297, table 3, online 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, 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 RE was 38.9 ± 33.0 months.

After RE, OS was longer in NET (40.8 months, 95% CI, 27.0 to 54.7) than in NEC patients (19.3 months, 95% CI, 8.1 to 35.1, figure 3a). Differences between both groups were found by the log rank test, $\chi^2(2)=6.88$, $p<0.009$. In NET patients, patients with a G1 tumor had a more prolonged median OS (79.3 months, 95% CI, 42.6 to 116.0) than patients with a G2 (30.6 months, 95% CI, 25.2 to 36.0) or G3 tumor (21.4 months, 95% CI, 10.7 to 32.1, figure 3b). According to the log rank test, the survival distributions for the three different tumor grades were statistically significant, $\chi^2(2)=10.21$, $p<0.006$.

An increase of hepatic tumor burden was associated with a reduction of median OS (hepatic tumor burden <25%: 63.2 months, 95% CI, 36.0 to 90.4; 25-50%: 30.3 months, 95% CI, 25.8 to 34.8; >50%: 22.5 months, 95% CI, 16.6 to 28.4). Significant differences between these three survival groups were detected by the log rank test, $\chi^2(2)=14.10$, $p=0.001$ (figure 3c).

Only slight differences were observed in OS after RE in patients with different vascularization patterns of hepatic metastases (hypervascularization: 40.5 months, 95% CI, 17.4 to 63.6, hypovascularization: 30.3 months, 95% CI, 20.1 to 40.5 and mixed appearance: 17.7 months, 95% CI, 26.5 to 95.9). The log rank test found no significant differences between the survival distributions for these three hepatic vascularization patterns, $\chi^2(2)=1.6$, $p=0.460$ (figure 3d).

Median OS was similar in patients with (30.6 months, 95% CI, 19.4 to 41.8) and without extrahepatic metastases (44.8 months, 95% CI, 29.8 to 59.8). No significant differences in the two survival groups were observed in the log rank test, $\chi^2(2)=0.931$, $p=0.335$ (figure 3e, online supplement 4, 5 and online supplement figure 1 for further analysis).

Second-line therapy versus salvage setting

Patients who received RE as second-line therapy had a slightly longer OS (44.8 months, 95% CI, 24.2 to 65.4) than patients who had RE in a salvage setting (30.6 months, 95% CI, 18.5 to 42.7, figure 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 months, 95% CI, 10.6 to 21.2) as well as global PFS (14.7 months, 95% CI, 10.5 to 18.9) was worse in patients undergoing RE in a salvage setting than in patients with RE as second-line therapy (hepatic PFS: 18.6 months, 95% CI, 14.0 to 23.2; global PFS: 18.8 months, 95% CI, 8.3 to 29.3). The log rank test detected significant differences between both survival groups for hepatic PFS ($\chi^2(2)=6.44$, $p=0.011$) and global PFS ($\chi^2(2)=6.63$, $p=0.010$, figure 4b&c, see supplement 6 and online supplement figure 2 for further analysis).

In patients receiving RE as salvage therapy, OS in patients with prior PRRT (30.3 months, 95% CI, 26.2 to 34.3) was comparable to patients that did not receive prior PRRT (36.2 months, 95% CI, 19.8 to 52.5). No significant differences between both groups were found in the log rank test ($\chi^2(2)=0.16$, $p=0.692$, figure 5).

DISCUSSION

RE is a possible alternative to a surgical approach to achieve local tumor control in metastatic liver disease. However, alternatives to RE are manifold and systemic approaches such as PRRT or new chemotherapies challenge the concept of local liver RE in general. Therefore, further data is 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 three key messages. First, second-line RE is associated with increased OS and a significant increase of hepatic and global progression-free survival with slightly superior OS compared to published PRRT data, Second, The vascularization type of hepatic metastases does not have a significant impact on survival after RE. Third, the presence of extrahepatic metastases in patients with a liver-dominant disease does not significantly affect OS in patients undergoing RE, neither in the entire population nor in patients receiving RE as second-line therapy.

Successful surgical removal of hepatic metastases is associated with 5-year 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 RE or PRRT are possible treatment options. Although comparative studies between these options are not available, PRRT is recommended as the second-line therapy of choice in the most recent guidelines(9–11). Due to 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 RE are proposed as possible alternatives in these two scenarios(21).

Our study results support these recommendations and further raise the question of whether RE should be primarily performed in specific scenarios as second-line treatment prior to PRRT.

We found that patients who had undergone RE as second-line treatment did show a relevant increase of OS and a significant increase of hepatic and global PFS compared to patients with a more extensive pretreatment. OS of patients with RE as second-line treatment was only slightly worse than the results of PRRT in the Rotterdam cohort with overlapping 95% confidence intervals (44.8 months, 95% CI, 24.2 to 65.4 vs. 63 months, 95% CI 55-72)(22). Furthermore, the presence of extrahepatic metastases does not influence OS after RE as second-line therapy. In contrast to RE in a salvage setting, hepatic tumor burden has no significant impact on OS if RE is performed as a second-line therapy. Additionally, our data indicate that in 22.6% of all cases, RE could not be performed due to contraindications associated with advanced hepatic disease such as shunting, a high tumor burden, or liver function deterioration. These findings further suggest that early RE before PRRT could be beneficial in patients with the liver-dominant disease. In this clinical pathway, a successful local, liver-directed therapy using RE could be ensured independent of hepatic tumor burden and the risk of contraindications for RE caused by advanced oncological disease such as shunting could be avoided.

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

Furthermore, this therapeutic approach's benefits 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 our analysis and was not associated with a significant HR in contrast to previous studies(12,24).

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

Our study has some limitations. Due to the retrospective nature of this study and the combined analysis of RE performed with resin and glass microspheres, differences in the procedural technique could be possible. These limitations could only be circumvented by a prospective study. We did not perform a comparison between RE and TAE or TACE. As PRRT is recommended as therapy of choice, TAE and TACE are considered by some authors as advantageous to RE to avoid radiation-induced liver failure when PRRT and RE are combined(25). However, recent findings by Braat et al. as well as our own findings on RE as salvage therapy in patients with and without prior PRRT indicate that 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/TACE compared to RE, most notably the higher proportion of(up to 61%) patients suffering from pain, nausea, treatment associated fever(25,28,29) and the need to perform multiple therapies(30). Especially in the current raging COVID-19 Pandemic, RE might be advantageous due to the reduced number of procedures necessary to achieve a favorable result and lower therapy-associated complications. However, a randomized trial between TAE/TACE and RE might improve the acceptance of interventional procedures in general in NET patients with liver dominant disease.

In conclusion, our study results show the potential of RE as second-line therapy in the treatment of patients suffering from NEN 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.

KEY POINTS

Question:

Is ^{90}Y radioembolization a potential a treatment option in patients suffering from neuroendocrine neoplasms?

Pertinent Finding

In this retrospective multicenter study, second-line ^{90}Y radioembolization was associated with a significant increase of progression-free survival with satisfactory overall survival rates. The presence of extrahepatic metastases in patients with liver-dominant disease undergoing ^{90}Y radioembolization did not affect overall survival.

Implications for Patient Care

This study shows the potential of ^{90}Y radioembolization as a treatment option in patients suffering from neuroendocrine neoplasms with liver-dominant disease and thus could be an important alternative to peptide receptor radionuclide radiotherapy.

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TABLES

Table 1: Baseline characteristics of all performed imaging evaluations:

				%	n
Localization of primary tumor	Neuroendocrine Tumor (NET)			90.9	270
		Lung		3.0	9
		Esophagus		0.7	2
		Stomach		4.4	13
		Pancreas		24.9	75
		Small bowel/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 (NEC)			9.1	27
Grading	NET	G1		25.6	76
		G2		50.5	150
		G3		5.7	17
		unknown		9.1	27
	NEC			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 Elison Syndrome	0.7	2
			unspecified	2.7	8
		No		67.3	200
		Unknown		4.0	12
Therapy prior to RE		Yes		91.6	272
		No		8.4	25

Table 2: Imaging evaluation including MAA injection

			%	n
Hepatic tumor burden		<25%	50.2	149
		25-50%	31	92
		>50%	16.2	48
		Unknown	2.7	8
Vascularization pattern		Hypervascularisation	63.3	188
		Hypovascularization	18.2	54
		Mixed/atypical	15.5	46
		Unknown	3.0	9
Vessel Coiling	Yes		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		6.1	18
	No		54.8	163
Preexisting portal vein thrombosis	Yes	Partial portal vein thrombosis	2.0	6
		Complete portal vein thrombosis	0.0	0
	No		96.0	285
	Unknown		2.0	6
Complications	Yes		6.4	19
		Vasospasm	0.3	1
		Dissection	0.7	2
		Vascular occlusion	1.4	4
		Hypertonia	0.3	1
		Pain/Hypertonia/Tachycardia	0.3	1
		Complication associated with contrast medium	0.3	1
		Coil dislocation	0.3	1
		Not specified	2.8	8
	No		92.2	274
	Unknown		1.4	4
Lung shunt fraction	≤10%		87.9	261

	>10%		9.8	29
	Unknown		2.4	7

Table 3: Reasons for canceling radioembolization

			%	n
Radioembolization performed	Yes		77.4	230
	No		22.6	67
		Extrahepatic shunting	8.1	24
		Lack of MAA accumulation	3.4	10
		Worsening of the patients 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 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

Figures

Figure 1: Flowchart of analyzed patient cohort.

Figure 2: 67y old male patient with gastric NET G2 and hepatic metastases. Hepatic tumor progression was observed with somatostatin analog treatment. At the timepoint of RE, hepatic tumor burden was <25%(A). In angiographic evaluation, hypervascularized metastases were detected in both liver lobes (A, B), thus, same-session sequential therapy of the whole liver with ^{90}Y glass microspheres was performed. At follow-up, partial response was observed with residual metastases in liver segment 4 (C).

A:

B:

C:

Figure 3: Kaplan Meier survival curves investigating the influence of six different parameters on survival in the entire population (A: Tumor type, B: NET tumor grading, C: hepatic tumor burden, D: metastatic vascularization, E: extrahepatic metastases)

A:

B:

C:

D:

E:

Figure 4: Kaplan Meier survival curves investigating the influence of the extent of prior therapy (second-line therapy: prior surgery for the primary tumor and/or metastases and somatostatin analog treatment prior to RE vs. salvage therapy) on OS (A), hepatic PFS (B) and global PFS (C).

A:

B:

C:

Figure 5: Kaplan Meier survival curve investigating the influence of prior PRRT on survival in patients receiving RE as salvage therapy.

⁹⁰Y radioembolization in the treatment of neuroendocrine neoplasms: Results of an international multicenter retrospective study.

Online Supplements

Supplement 1:

Material and Methods

Data collection

All data were collected using a unified data collection form. This form consisted of the following subsections: baseline characteristics, imaging evaluation including MAA injection, ⁹⁰Y RE, follow-up examinations, and outcome variables.

Baseline characteristics comprised gender, age, tumor histology based on a specimen obtained via surgery or biopsy (including tumor differentiation, tumor grade and Ki67 index), the presence of hypersecretion symptoms as well as medical treatment prior to ⁹⁰Y RE. In the second subsection, imaging evaluation including MAA injection, type of imaging performed prior to pretherapeutic angiographic evaluation, extent of hepatic tumor spread and the type of metastatic vascularization were gathered. Furthermore, information on the pretherapeutic angiography was collected, including necessity of vessel occlusion via coiling, catheter position for MAA injection, complications as well as the lung shunt fraction as assessed by scintigraphy. For ⁹⁰Y RE, the type of therapy (glass or resin microspheres), applied activity, catheter position including the treated liver part and complications were analyzed. For patients who could not undergo ⁹⁰Y RE, the reason for not performing this procedure was assessed.

For follow-up examinations after three and twelve months, tumor response (complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD)) based on the response evaluation criteria in solid tumours (RECIST) 1.1 was determined by radiologists in participating centers and provided for central data analysis(1). Here, the disease control rate (DCR) was defined as CR, PR and SD. Information on further medical treatment after ⁹⁰Y RE as well as late complications were compiled.

Supplement 2:

Material and Methods

Statistical analysis

Explorative data analysis was performed to assess baseline characteristics, parameters derived from imaging evaluation including MAA injection, ⁹⁰Y RE procedures, complications, and reasons why ⁹⁰Y RE was not performed. Furthermore, analysis was conducted on treatment response according to RECIST 1.1 criteria after three and twelve months, late complications, and further therapies. Means were calculated for age, lung shunt fraction, and applied activity for ⁹⁰Y RE.

Supplement 3:

Results

Follow-up examinations

The first follow-up took place after a mean of 105.0±58.1 days. In 230 ⁹⁰Y REs, DCR was 83.5% (192/230; CR: 2.2% (5/230); PR: 39.1% (90/230); SD: 42.2% (97/230)). PD was observed in 11.3% (26/230) and in 5.2% (12/230), no follow-up imaging data were available. 35.2% (81/230) received additional therapy between ⁹⁰Y RE and the first follow-up. In 23.5% (54/230) a therapy with somatostatin analogs, additional chemotherapy in 3.5% (8/230), an additional PRRT in 3.0% (7/230) and other therapies in 2.6% (6/230, including primary tumor resection (n=1), TACE (n=1), a second ⁹⁰Y RE (n=2) or liver transplantation (n=2)) was performed. Multiple therapies were performed in 3.0% (7/230). In 10.9% (25/230), no information was available about any further treatment and no further therapy was performed in 53.9% (124/230).

Late complications were observed in 6.1% of all cases (14/230, including pain (n=5),; liver failure/renal failure/hepatomegaly (n=2), and fever/cholestasis/cholangitis (n=1), respectively). No complications were observed in 79.1% (182/230) and the late complication status was unknown in 14.8% (34/230).

The second follow-up was performed after a mean of 340.9 ± 102.2 days. In 230 ⁹⁰Y REs, DCR was 50.9% (117/230; CR: 3.0% (7/230); PR: 12.2% (28/230); SD: 35.7% (82/230)). PD was observed in 25.7% (59/230) and in 23.5% (54/230), no follow-up data were available (figure 1).

In 51.3% (118/230) of cases, an additional therapy was performed at the second follow-up, multiple therapies in 11.3% (26/230). In 27.8% (64/230), no information was available regarding any further treatment and patients did not undergo any further therapy in 20.9% (48/230).

Supplement 4:

Statistical analysis

Additionally, multivariate cox regression analysis was performed for tumor grade, hepatic tumor burden, the presence of extrahepatic metastases and DCR in three months follow-up in the entire population and in patients receiving RE as second line therapy as previously described in the literature(2).

Cox regression analysis

Entire population

In cox regression analysis, higher tumor grading (G2: HR 1.6 (95% CI, 1.0 to 2.6), $p=0.070$; G3: HR 2.6 (95% CI, 1.3 to 5.3), $p=0.009$) and an intrahepatic tumor burden $>50\%$ (25-50%: HR 1.5 (95% CI, 0.9 to 2.4), $p=0.090$; $>50\%$: HR 2.2 (95% CI, 1.2 to 4.0), $p=0.013$) and PD in three month follow-up (HR: 2.4 (95% CI, 1.3 to 4.6) were predictive of a worse OS after RE. The presence of extrahepatic metastases, however, was not predictive of a worse OS (HR: 1.2 (95% CI, 0.8 to 1.8), $p=0.486$).

Second line therapy versus salvage setting

In this subgroup analysis, higher tumor grading was predictive of a worse progression in cox regression analysis (G2: HR 2.1 (95% CI, 1.0 to 4.6), $p=0.057$; G3: HR 14.6 (95% CI, 4.1 to 52.8), $p<0.001$). However, intrahepatic tumor burden (25-50%: HR 1.4 (95% CI, 0.7 to 2.9), $p=0.339$; $>50\%$: HR 1.6 (95% CI, 0.6 to 4.4), $p=0.362$), the presence of extrahepatic metastases (HR: 1.4 (95% CI, 0.7 to 2.8), $p=0.284$) and PD in three month follow-up (HR: 2.6 (95% CI, 1.0 to 7.0) were not predictive of a worse OS after second line RE.

Supplement 5:

Median OS was similar in patients treated with glass (31.5 months, 95% CI 20.5 to 42.5) and resin microspheres (51.3 months, 95% CI 18.2 to 84.3). No significant differences were found by the log rank test ($\chi^2(2)=1.50$, $p=0.221$, see figure 1).

Figure 1: Kaplan Meier survival curve investigating the influence of the microsphere type on survival in the entire population

Until now, most of the available evidence on ^{90}Y RE was based on patients treated with resin microspheres (SIR-Spheres®, Sirtex Medical, Sydney, Australia) that have an additional embolic effect(2–4). Similar treatment results using non-embolic glass microspheres (TheraSphere®, Boston Scientific, Marlborough, Massachusetts) have been hypothesized, but have never been demonstrated. Our study shows that both methods seem to have a similar effect and should therefore be used according to the interventional radiologist's experience and preferences.

Supplement 6

In NET patients who received RE as second-line therapy, G1 tumor patients had a longer median OS (97.4 months, CI 95%, 44.5 to 150.3) than patients with a G2 (32.1 months, 95% CI, 22.2 to 42.1) or G3 tumor (12.8 months, 95% CI, 7.7 to 17.9). The log rank test found significant differences between all groups ($\chi^2(2)=20.244$, $p<0.001$). A higher hepatic tumor burden was associated a decrease in median OS (hepatic tumor burden <25%: 97.4 months, 95% CI, 34.7 to 160.2; 25-50%: 27.8 months, 95% CI, 15.0 to 40.7; >50%: 24.2 months, 95% CI, 8.0 to 40.4). However, these differences were not significant according to the log rank test ($\chi^2(2)=5.354$, $p=0.069$). In this subgroup, a comparable median OS was observed in patients with (38.4 months, 95% CI, 19.9 to 57.0) and without hepatic metastases (51.3 months, 95% CI 28.7 to 73.8). No significant differences were observed in the log rank test ($\chi^2(2)=0.166$, $p=0.684$, see figure 2).

Figure 2: Kaplan Meier survival curves investigating the influence of three different parameters on survival in patients receiving RE as second-line therapy (A: NET tumor grading, B: hepatic tumor burden, C: extrahepatic metastases)

A:

B:

C:

Literature:

1. 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(2):228–247. doi: 10.1016/j.ejca.2008.10.026.
2. 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(3):413–425. doi: 10.1007/s00270-018-2148-0.
3. 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(2):334–342. doi: 10.1007/s00270-011-0248-1.
4. 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(3):271–279. doi: 10.1097/COC.0b013e31815e4557.

Online supplement table 1: Baseline characteristics of all performed imaging evaluations

				%	n
Localization of primary tumor	Neuroendocrine tumor (NET)			90.9	270
		Lung		3.0	9
		Esophagus		0.7	2
		Stomach		4.4	13
		Pancreas		24.9	75
		Small bowel/pancreas		0.7	2
		Small bowel		31.1	92
			Duodenum	1.1	3
			Jejunum	1.1	3
			Ileum	17.1	51
			Meckel's diverticulum	0.3	1
			Ileocecal valve	0.7	2
			Not specified	10.8	32
		Appendix		1.1	3
		Colon		4.4	13
			Caecum	2.4	7
			Colon asc.	1.7	5
			Not specified	0.3	1
		Rectum		5.1	15
		Unknown primary		7.4	22
		Not specified		8.1	24
	Neuroendocrine carcinoma (NEC)			9.1	27
		Lung		1.0	3
		Stomach		0.3	1
		Pancreas		2.0	6
		Small bowel		0.3	1
		Colon		1.0	3
		Rectum		0.3	1
		Unknown primary		3.5	10
		Not specified		0.7	2
Grading	NET	G1		25.6	76
		G2		50.5	150
		G3		5.7	17
		unknown		9.1	27
	NEC			9.1	27
Extrahepatic metastases		Yes		41.1	122
			Brain	5.1	15
			Thyroid	0.3	1
			Lung	2.7	8
			Pleura	0.7	2
			Heart	0.3	1
			Peritoneum	2.0	6
			Mesenterium	2.7	8
			Adrenal gland	0.7	2
			Ovary	0.3	1

			Lymph node	14.5	43
			Bone	9.1	27
			Not specified	12.8	38
		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 Elison Syndrome	0.7	2
			unspecified	2.7	8
		No		67.3	200
		Unknown		4.0	12
Therapy prior to RE		Yes		91.6	272
			External beam radiation	1.7	5
			Surgery (primary tumor)	64.3	191
			Surgery (hepatic metastases)	18.2	54
			Local ablation	4.0	12
			TACE /TAE	8.8	26
			PRRT	20.2	60
			Antibody based therapy	2.4	7
			Somatostatin analog therapy	57.2	170
			Prior RE	9.8	29
			Transplantation	0.3	1
			Chemotherapy	29.3	87
			Targeted therapy	7.7	23
		No		8.4	25

Online supplement table 2: Imaging evaluation including MAA injection

			%	n
Hepatic tumor burden		<25%	50.2	149
		25-50%	31	92
		>50%	16.2	48
		Unknown	2.7	8
Vascularization pattern		Hypervascularisation	63.3	188
		Hypovascularization	18.2	54
		Mixed/atypical	15.5	46
		Unknown	3.0	9
Vessel variant according to the Michels classification		I	72.4	215
		II	3.4	10
		III	9.4	28
		IV	0.7	2
		V	0.7	2
		VI	2.0	6
		VII	0.3	1
		VIII	3.1	9
		IX	2.7	8
		X	0.0	0
		XI	2.4	7
		Postoperative changes (e.g. after hemihepatectomy)	1.3	4
		Unknown	1.7	5
Vessel Coiling	Yes		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	6.1	18
	No		54.8	163
	Preexisting portal vein thrombosis	Partial portal vein thrombosis	2.0	6
		Complete portal vein thrombosis	0.0	0
		No	96.0	285
Complications	Yes	Unknown	2.0	6
		Vasospasm	6.4	19
		Dissection	0.3	1
		Vascular occlusion	0.7	2
		Hypertonia	1.4	4
		Pain/Hypertonia/Tachycardia	0.3	1
		Complication associated with contrast medium	0.3	1
		Coil dislocation	0.3	1
		Not specified	0.3	1
	No		2.8	8
			92.2	274

	Unknown		1.4	4
Lung shunt fraction	≤10%		87.9	261
	>10%		9.8	29
	Unknown		2.4	7