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, ^{90}Y 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 ^{90}Y 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 ^{90}Y 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 ^{90}Y 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 ^{90}Y 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, ^{90}Y RE procedures, complications, and reasons why ^{90}Y 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 ^{90}Y RE.

Supplement 3:

Results

Follow-up examinations

The first follow-up took place after a mean of 105.0±58.1 days. In 230 ^{90}Y 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 ^{90}Y 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 ^{90}Y 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 ^{90}Y 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).

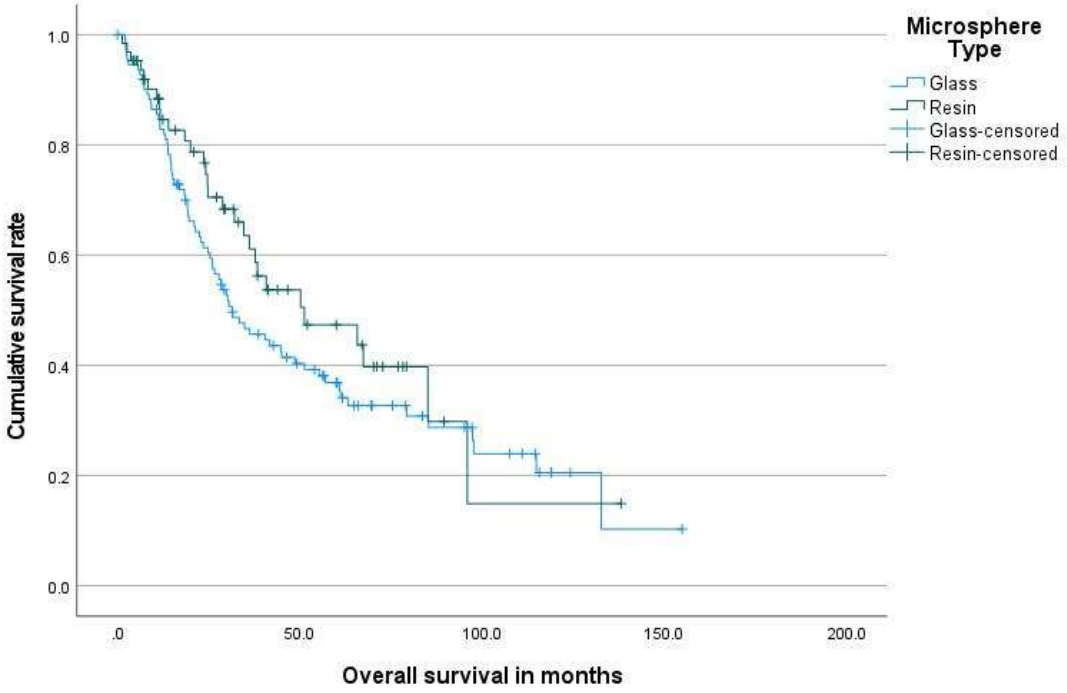
Second line therapy versus salvage setting

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).

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



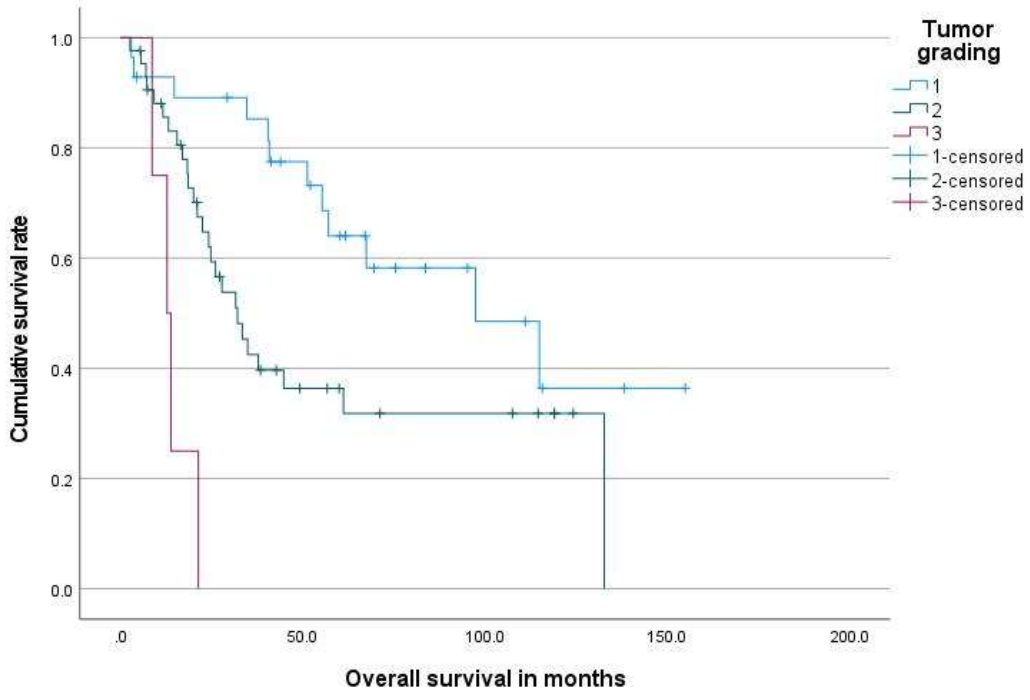
Until now, most of the available evidence on ^{90}Y RE was based on patients treated with resin microspheres (SIR-Spheres©, Sirtex Medical, Sydney, Australia) that have an additional embolic effect(2–4). Similar treatment results using non-embolic glass microspheres (TheraSphere©, Boston Scientific, 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

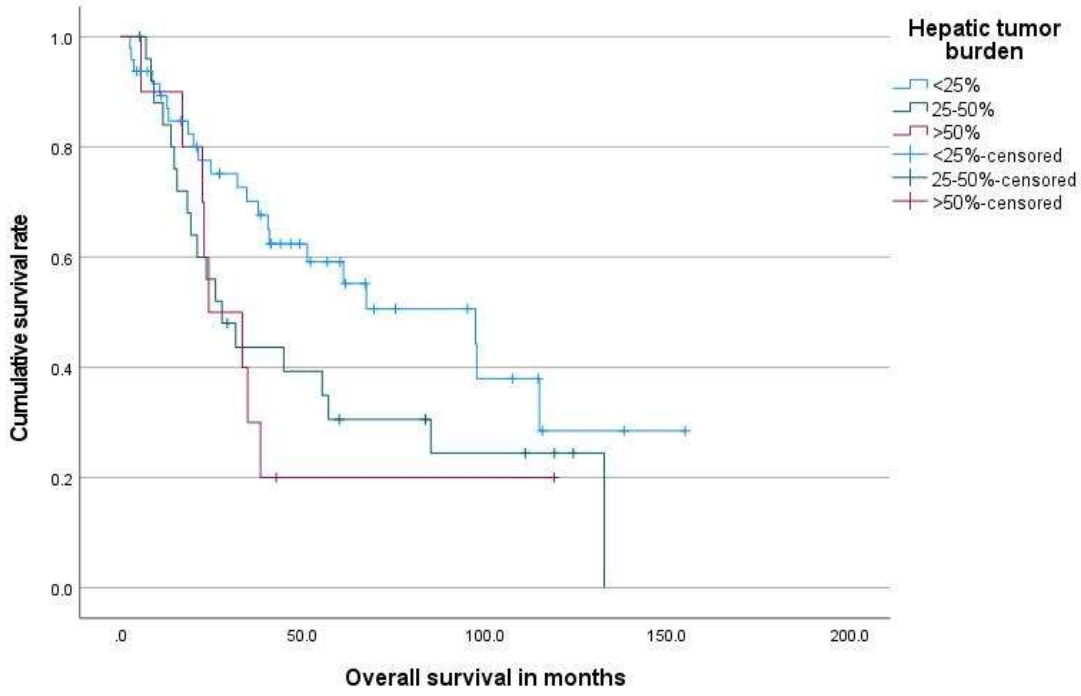
In NET patients who received RE as second-line therapy, G1 tumor patients had a longer median OS (97.4 months, CI 95%, 44.5 to 150.3) than patients with a G2 (32.1 months, 95% CI, 22.2 to 42.1) or G3 tumor (12.8 months, 95% CI, 7.7 to 17.9). The log rank test found significant differences between all 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).

Supplemental 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)

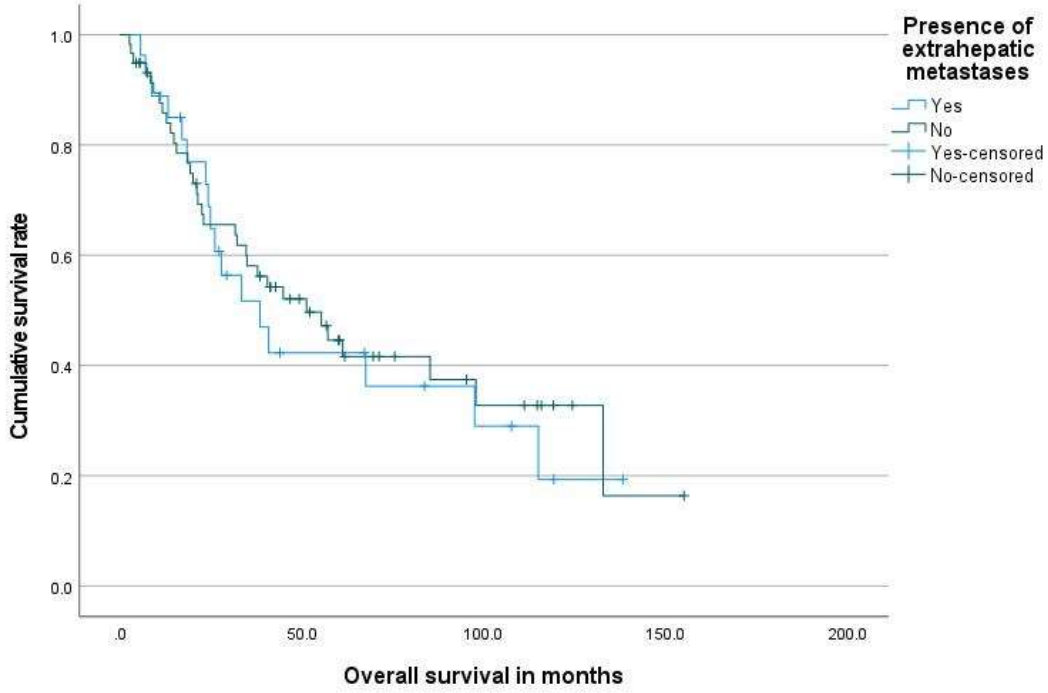
A:



B:


Hepatic tumor burden
<25%
25-50%
>50%
<25%-censored
25-50%-censored
>50%-censored
Cumulative survival rate
1.0
0.8
0.6
0.4
0.2
0.0
.0
50.0
100.0
150.0
200.0
Overall survival in months

C:


Presence of extrahepatic metastases
Yes
No
Yes-censored
No-censored
Cumulative survival rate
1.0
0.8
0.6
0.4
0.2
0.0
.0
50.0
100.0
150.0
200.0
Overall survival in months

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.

Supplemental 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
			Ileocoecal 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

Supplemental 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	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