Radioembolization for neuroendocrine liver metastases is safe and effective prior to major hepatic resection

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Background: Radioembolization (RE) is well established in the treatment of neuroendocrine liver metastases. However surgery is rarely performed after RE, although liver resection is the gold standard in the treatment of localized neuroendocrine liver metastases. Therefore, aim of the present study was to evaluate the safety and feasibility of liver resection after RE in a homogenous cohort.

Methods: From a prospective surgical (n=494) and nuclear medical (n=138) database patients with NELM who underwent liver resection and/or RE were evaluated. Between September 2011 and December 2017 eight patients could be identified who underwent liver resection after RE (mean therapeutic activity of 1,746 Mbq). Overall and progression free survival were evaluated as well as epidemiological and perioperative factors. The surgical specimens were analyzed for necrosis, fibrosis, inflammation, and steatosis.

Results: The mean hepatic tumor load of patients, who had liver surgery after RE, was 31.4% with a mean Ki-67 proliferation index of 5.9%. The majority of these patients (7/8) received whole liver RE prior to liver resection, which did not increase morbidity and mortality compared to a surgical collective. Indications for RE were oncological (6/8) or carcinoid syndrome associated reasons (2/8). Mean overall survival was 25.1 months after RE and subsequent surgery. Tumor necrosis in radioembolized lesions was 29.4% without evidence of fibrosis and inflammation in hepatic tissue.

Conclusions: This is the first study analyzing the multimodal therapeutic approach of liver resection following whole liver RE. This treatment algorithm is safe, does not lead to an increased morbidity and is associated with a favorable oncological outcome. Nonetheless, patient selection remains a key issue.

Keywords: Radioembolization (RE); neuroendocrine tumor; liver surgery

Introduction

Liver metastases of neuroendocrine tumors (NELM) are common and frequently lead to initial diagnosis (1). Even patients with small primary tumors might have a profound hepatic tumor load (2,3). Liver surgery is the gold standard in the treatment of localized liver metastases since resection

provides a chance of cure (4-6). In case of diffuse hepatic metastatic disease surgery might not be feasible. In those patients, the therapeutic approach has to be adapted to the clinical situation.

Liver directed transarterial therapies, such as radioembolization (RE), are established for the treatment of patients with diffuse NELM (7-9). NELM are highly vascularized and with RE a high therapeutic active radiotherapy can be delivered to the liver metastases by the use of yttrium-90. RE prolongs time to progression and survival and can alleviate tumor related symptoms (i.e., carcinoid syndrome, hypoglycemia) (10,11). Additionally, unilateral RE can induce hypertrophy of the contralateral lobe of the liver prior to liver surgery (12,13).

There is only little evidence, if hepatic surgery can safely be performed following RE (14). In particular, no study evaluated the outcome for patients after whole liver SIRT. In this respect, the hepatotoxicity of RE of the future liver remnant (FLR) is not clearly specified since RE was delivered mostly unilaterally in previous studies (14-16). Additionally, no information about the oncological outcome in patients with NELM is given (14,16). In this respect, no previous study analyzed the effect of the multimodal therapeutic approach of liver resection after RE. Therefore, aim of the present study was to evaluate the oncological outcome, safety and feasibility of the multimodal therapeutic approach of liver resection after RE including whole liver RE in a homogenous cohort of patients with NELM.

Methods

From a prospective surgical database (n=494) and from a prospective nuclear medical database (n=138) patients with NELM were identified who received RE for NELM and/or liver resection between September 2011 to December 2017. Out of these databases eight patients had hepatic surgery after RE, 17 patients underwent only liver surgery and 12 patients received RE without liver surgery. Therapeutic activity was determined according to the modified body surface area (mBSA) method as previously published (17). At the day of RE patients received routinely anti-emetics, corticosteroids and antibiotics (ciprofloxacin). Patients did not get somatostatin analogs prior to RE routinely, but somatostatin analogs were continued in pretreated patients. The pre-treatment tumor burden was assessed according to previously published studies (18-20). In the present manuscript the hepatic tumor load was visually assessed on the basis of CT, MRI and PET/CT scans. In

cases where MRI and ^{68}Ga-DOTA-TATE PET/CT were performed, tumor volume was assessed in both modalities. More than 25 variables were collected for every patient and subsequently analyzed. The medical history of each patient is complete and almost every parameter analyzed was available; only the values of serological markers [chromogranin A (CgA), serotonin, neuron-specific enolase (NSE)] and 5-hydroxyindoleacetic acid (5-HIAA) are not complete for every patient. Therefore the analyzed numbers of patients regarding tumor markers differ. The therapeutic approach in every case was discussed in a multidisciplinary tumor board.

Postoperative complications were graded according to the classification by Dindo *et al.* and severe complications were graded as greater or equal than grade 3a (21). Posthepatectomy liver failure (PHLF) was assessed according to the International Study Group of Liver Surgery (22).

To monitor the oncological outcome serological markers (CgA, serotonin, NSE), 5-HIAA, and postoperative cross-sectional imaging were evaluated. Postoperative stating was performed 3, 6, 9, and 12 months after RE or surgery, respectively.

Every resected NELM underwent routine processing at the Institute of Pathology. Additionally, the pathological specimens from patients who received RE prior to liver surgery were further analyzed by a blinded and experienced gastrointestinal pathologist (T Knösel) to assess the hepatic injury induced by RE. To assess the response to RE, T Knösel determined the amount of necrosis, fibrosis, inflammation, and steatosis as described recently (23).

Statistical analyses were performed using SPSS v 20.0 for Mac (IBM Corp., Armonk, NY) and Prism 6.0 for Mac (GraphPad Software, Inc., La Jolla, CA). Chi-squared test for categorical parameters was used for univariate analysis (e.g., Ki-67 proliferation index, hepatic tumor load). Mean survival times along with their 95% confidence intervals (95% CI) and Kaplan-Meier survival statistics were calculated for the entire sample using Log-Rank tests. P values lower than 0.05 were considered significant.

Results

Liver resection after RE

Characteristics of the patients (n=8) included are displayed in *Table 1*. There were four male and four female patients with a mean age of 60.7 (53.8–75.0) years. The analyzed cohort was preoperatively classified as American Society of

Table 1 Patient characteristics (mean values are displayed)

Number	Age (years)	Gender	ASA score	MELD score	Primary tumor	Ki-67 primary tumor	Treatment prior to RE	Hepatic tumor load	Ki-67 liver metastasis	Radioembolization	RE dose (MBq)	Time from RE to surgery (months)
1	53.8	M	2	6	pNET	20	PRRT, SSA, TACE	60	50	Whole liver	2,200	26.3
2	55.2	M	3	6	pNET	5	SSA	1	4	Whole liver	2,069	95.2
3	59.5	M	2	6	siNET	3	SSA	10	3	Whole liver	1,406	4.7
4	63.9	F	3	12	siNET	5	SSA	60	12	Whole liver	1,708	20.9
5	59.3	F	3	8	siNET	1	SSA	30	1	Whole liver	1,696	10.9
6	60.2	F	3	6	Rectum	5	none	30	6	Right lobe, S. IV	1,828	3.1
7	59.0	M	3	6	siNET	5	SSA	30	5	Whole liver	1,754	3.3
8	75.0	F	3	9	siNET	3	PRRT	30	8	Whole liver	1,310	52.3

ASA, American Society of Anesthesiologists; F, female; M, male; MELD, Model of End Stage Liver Disease; n/a, not applicable; pNET, pancreatic neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy; RE, radioembolization; SSA, somatostatin analogs; siNET, small intestine neuroendocrine tumor; TACE, transarterial chemoembolization.

Anesthesiologists (ASA) score of 3 in seven cases and had a mean hepatic tumor load of 31.4% (1–60%). The primary site of NELM was a gastrointestinal NET in six cases (75%) and a pancreas NET in two patients (25%). Most commonly patients had a G2 primary tumor with a mean proliferation Ki-67 index of 5.9% (1–20%). The mean Ki-67 index of the liver metastases was higher and reached 11.4% (2–50%). Moreover, the liver metastasis of one patient was classified postoperatively as G3 with a Ki-67 index of 50%.

The mean RE therapeutic activity was 1,746 MBq (1,310–2,200 MBq). Indication for RE was hepatic tumor progress in six patients and tumor related symptoms (hypoglycemia, carcinoid syndrome) in two patients. Seven patients received whole liver RE. In one patient RE was applied to the segments IV to VIII to achieve tumor control and hypertrophy of the segments II and III.

The mean time interval between RE and liver surgery was 27.1 months (3.1–95.2 months). Hepatic resection after RE resulted in complete hepatic tumor clearance in three patients. In the other patients (n=5) tumor debulking with a reduction of the tumor burden to less than 10 % was achieved.

There was no death within 30 days after surgery. Two patients (25%), of which one patient was already discharged at the time of diagnosis, had a grade 3a complication and required percutaneous drainage of a fluid collection. PHLF (grade A) was seen in only one patient and liver function tests had normalized at the time of discharge. The mean hospital stay was 15.3 days (10–26 days).

Evaluation of the pathologic specimens revealed a mean tumor necrosis of 29.4% (0–60%) (*Figure 1*). Within the liver parenchyma treated with RE almost no inflammation or fibrosis was seen. A correlation between RE therapeutic activity and/or time interval between RE and surgical resection and pathological changes in the tumor or liver tissue was not evident (*Table 2*).

Following RE CgA levels initially decreased but increased again after 9 to 12 months (fold change after 3 months 0.7, 6 months 0.4, 9 months 0.6, 12 months 1.6). Similarly, serotonin (fold change after 12 months 1.4) and NSE (fold change after 12 months 1.7) serum levels increased following RE. In contrast, liver surgery resulted in long-term decreased CgA (fold change after 12 months 0.4), serotonin (fold change after 12 months 0.4) and 5-HIAA (fold change after 12 months 0.3) levels (*Figure 2A,B,C,D*).

Oncological outcome

Patients with liver resection after RE (group A) were compared to patients who underwent major hepatectomy (group B) and to patients who received RE alone as treatment for their liver metastases (group C) within the same time period. Patients of the three groups (A-C) did not differ significantly regarding their age, hepatic tumor load, Ki-67 index, ASA score, MELD score, blood loss (A and B), duration of the operation (A and B), postoperative
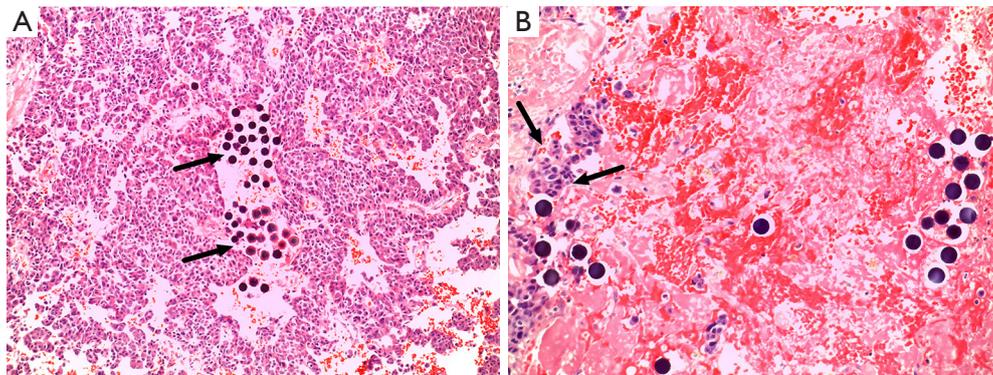
Figure 1 Hematoxylin and eosin (H&E) stain of liver sections. (A) H&E stain, 10× magnification; the picture shows microspheres (arrows) in vascular spaces in metastatic parenchyma. (B) H&E stain, 40× magnification; picture shows microspheres surrounded by necrosis with small amount of viable tumor cells (arrows).

Table 2 Information about surgery and the postoperative course; mean values are displayed. Morbidity is scored according to the classification by Dindo *et al.*

Subject	Procedure	Duration (min)	Estimated blood loss (mL)	30-day-morbidity	PHLF	30-day-mortality	Tumor necrosis (%)	Inflammation grade (0–4)	Fibrosis stage (0–4)	Steatosis (%)
1	SM	110	1,500	3	N/A	N/A	20	1	0	15
2	SM	320	550	0	N/A	N/A	40	2	1	15
3	ERH, AR	142	600	2	A	N/A	0	1	0	5
4	ERH, AR	363	2,200	0	N/A	N/A	60	1	1	10
5	ERH	204	1,500	3	N/A	N/A	30	1	1	10
6	ERH	184	480	0	N/A	N/A	20	1	1	0
7	SM	144	100	0	N/A	N/A	5	1	0	10
8	SM	188	1,600	1	N/A	N/A	60	1	0	5

AR, atypical resection; ERH, extended right hepatectomy; N/A, not applicable; PHLF, posthepatectomy liver failure; SM, segmentectomy ≥2 segments.

complications (A and B), and the length of their hospital stay (A and B) (*Table 3*).

After hepatic tumor clearance a hepatic recurrence was uncommon and not obvious in group A, but seen in one patient of group B. Taken together, the calculated mean time to hepatic progression was 15.8 months (95% CI: 8.2–23.5 months) in group A and 32.5 months (95% CI: 21–44 months) in group B (P>0.05) (*Figure 3*).

Univariate survival analyses were conducted from the date of liver resection and from the date of the first liver directed therapy. If patients were classified regarding the date of liver resection (*Figure 4*), the calculated mean overall survival for group A was 25.1 months (95% CI: 13.1–37.1 months) and for group B 71.3 months (95% CI: 60.4–82.2 months)

(P<0.05). If patients were classified regarding the date of the first liver directed therapy, the calculated mean overall survival for group A was 60.2 months (95% CI: 37.1–83.4 months), for group B 71.3 months (95% CI: 60.4–82.2 months) and for group C 37.7 months (P>0.05) (95% CI: 28.5–46.9 months) (*Figure 5*).

Discussion

Liver resection is the gold standard in the treatment of localized NELM. However in the case of diffuse hepatic metastases surgery might not be feasible. Nonetheless, tumor debulking might be indicated due to oncological reasons or to alleviate tumor related symptoms (i.e.,
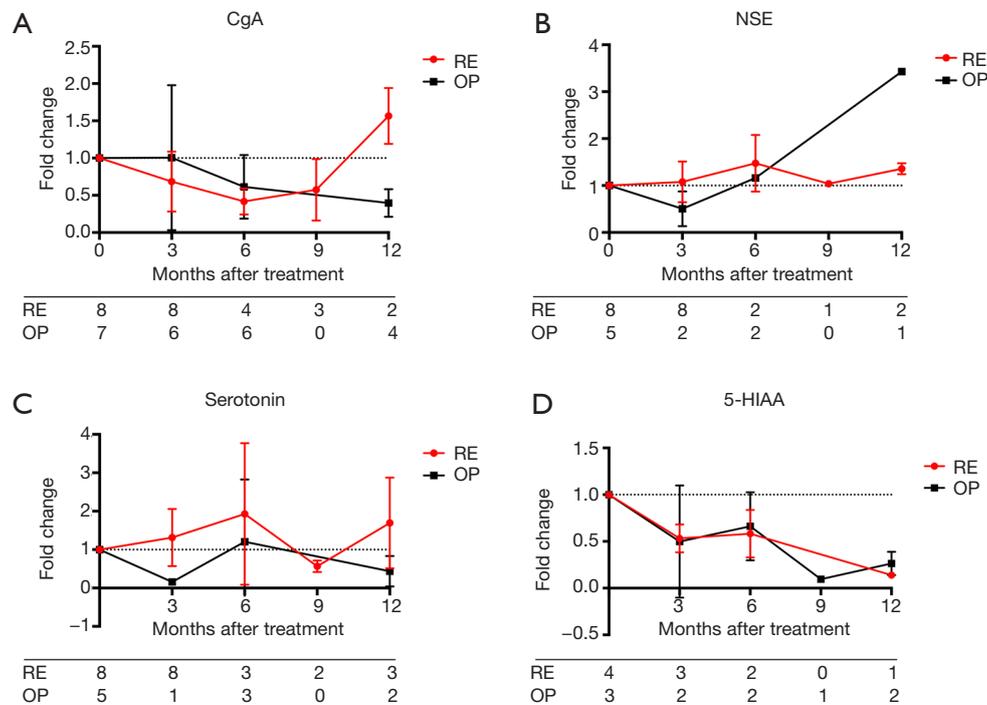
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Figure 2 Time course of tumor markers of group A after treatment. The numbers of included values are given below for each marker. 5-HIAA, 5-hydroxyindoleacetic acid; CgA, chromogranin A; NSE, neuron-specific enolase; OP, patients after operation; RE, patients after radioembolization.

Table 3 Patient characteristics of group A (liver resection after radioembolization), group B (liver surgery) and group C (radioembolization); mean values are displayed

Variable	Group A	Group B	Group C	P value
Mean age (years)	60.7 (53.8–75)	58.4 (32.7–87.5)	65.3 (52.3–72.6)	N/S
Mean postoperative hospital stay (days)	15.3 [10–26]	17.5 [7–49]	N/A	N/S
Mean Ki-67 index primary tumor	5.9% (1–20%)	6.1% (1–20%)	6.9% (2–10%)	N/S
Mean Ki-67 index liver metastasis	11.4% (2–50%)	9.7% (1–30%)	8.7% (2–15%)	N/S
Mean hepatic tumor load	31.4% (1–60%)	25.8% (1–80%)	30% (5–85%)	N/S
Mean RE dose (MBq)	1,746 [1,310–2,200]	N/A	1,483 [583–2,249]	N/S
Mean ASA score	2.8 [2–3]	3	N/A	N/S
Mean MELD score	7.4 [6–12]	7.7 [6–13]	7.2 [6–11]	N/S
Mean blood loss (mL)	1,066.3 [100–2,200]	1,274.3 [300–3,000]	N/A	N/S
Mean duration of operation (min)	206.9 [110–363]	230.7 [108–564]	N/A	N/S
Severe complications	25%	29.4%	N/A	N/S

ASA, American Society of Anesthesiologists; MELD, Model of End Stage Liver Disease; min, minutes; mL, milliliter; N/A, not applicable; N/S, not significant.
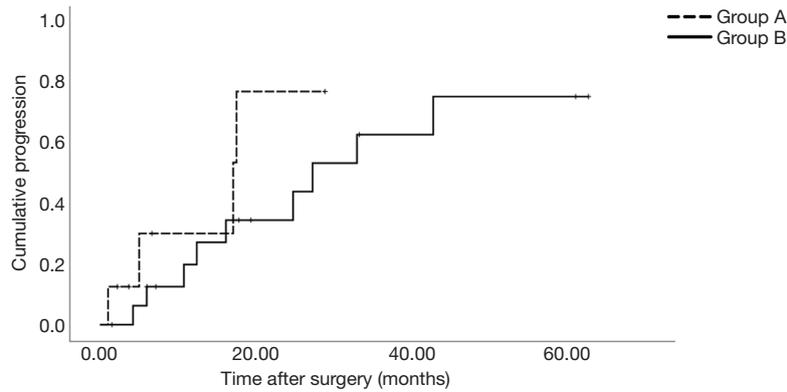
Figure 3 Kaplan-Meier survival analysis displaying the progression free survival (P>0.05). Group A: liver resection after radioembolization. Group B: liver resection.
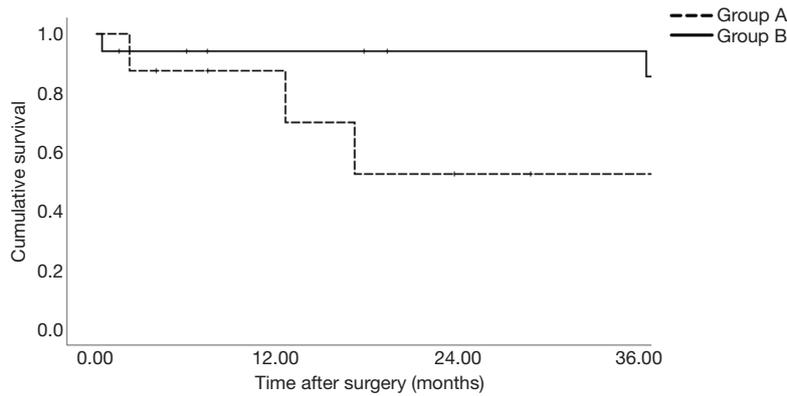

Figure 4 Kaplan-Meier survival analysis displaying the overall survival after surgery (P<0.05). Group A: liver resection after radioembolization. Group B: liver resection.
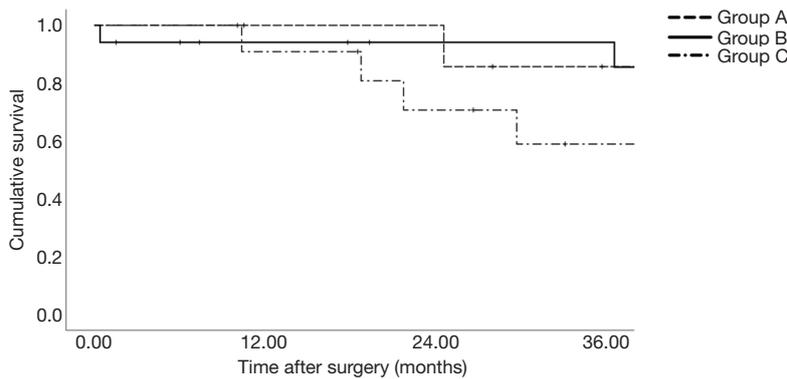

Figure 5 Kaplan-Meier survival analysis displaying the overall survival (P>0.05). Survival analysis is calculated from the first liver directed therapy. Group A: liver resection after radioembolization. Group B: liver resection. Group C: radioembolization.

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carcinoid syndrome, hypoglycemia) (5,6). Additionally, patients with an extensive hepatic tumor burden might receive liver directed therapy such as RE (9). There are no reports available which evaluated the safety and efficiency regarding survival for liver surgery after RE. In this respect, this is the first study in which this specific treatment algorithm is analyzed and compared to liver surgery and RE alone.

RE represents an established therapeutic tool for partial and whole liver treatment in patients with NELM (7-9). Indication for RE is given to achieve oncological tumor control and/or palliate carcinoid syndrome associated symptoms. Patients with diffuse NELM are not considered a priori for hepatic surgery (24), but RE can induce hypertrophy to the FLR (12). Thus, RE may serve as bridging therapy prior to surgery.

In particular in patients with whole organ RE potential detrimental effects to the liver compromising subsequent liver surgery are unclear. In this respect, long-term morphological alterations of hepatic tissue after RE have been demonstrated (15,25). Nonetheless, the results of the present study indicate that major hepatic surgery can be safely performed after whole liver RE. Only one transient PHLF (grade A) and only two severe postoperative complications (both grade 3a) were detected in the eight patients analyzed. Previous studies investigating surgery after RE reported postoperative complication rates of 25–63% (14,16). In these studies, however, whole liver RE was uncommon. Moreover, various tumor entities (hepatocellular carcinoma, intrahepatic cholangiocarcinoma, liver metastases) and patients extensively pretreated with chemotherapy were included which limits the clinical validity of those results.

Pathological examination of the livers revealed only little changes to the liver parenchyma following RE. These findings are in accordance to Wang *et al.* who also have seen only little changes after RE (23). Nonetheless, a mean therapeutic activity of 1,746 MBq was delivered to the livers, which indicates a sufficient treatment of the liver metastases. In this respect, a mean tumor necrosis of 29.4% was seen. The observed tumor necrosis is in part achieved by RE as well due to an embolic effects of the spheres, occluding tumor vessels. The spheres can be detected on histopathological slides and are surrounded by tumor necrosis. However, no pronounced inflammation of the tumor free parenchyma was seen. Since only patients were included who did not receive chemotherapy the changes within the analyzed liver specimens are directly associated

to RE. Therefore, the present study with a highly selected patient collective indicates that major liver surgery can safely be done even after whole liver RE.

The oncological outcome after liver surgery in NELM depends on multiple factors such as grading, hepatic tumor burden, surgical approach (hepatic tumor clearance *vs.* debulking) and progressive *vs.* stable disease (6,24). Although not significant, the RE and surgery group had the highest tumor burden and the highest Ki-67 index. Moreover, 75% had progressive disease at indication for RE. Despite this negative selection the time interval until hepatic progression was not diverging between the surgical patient cohorts. The reported outcome for the RE prior to surgery and the surgery alone group is comparable to the cohorts reported in the literature (24,26). These findings suggest that RE and surgery may have additive therapeutic effects for a selective patient collective. Therefore, RE can be considered as a bridging therapy and downstaging of the metastases can lead to subsequent liver resection. In this respect, RE facilitates to consider patients with diffuse NELM as potential candidates for liver resection. Thus, the multimodal treatment for patients with diffuse progressive NELM seems to be a promising approach and may help to determine tumor biology prior to liver surgery.

Several tumor markers, such as CgA, from patients of group A were analyzed. CgA blood levels correlate with the tumor load and decrease after therapy (27,28). Whereas RE resulted in intermittent amelioration of CgA, surgery led to a long-lasting reduction of CgA blood levels. This suggests that RE is an effective therapeutic bridging therapy and should be performed within six months. However, in the case of unexpected contraindications for surgery (i.e., heart failure, restricted lung function) whole liver RE still represents antitumor therapy.

Despite the valuable findings there are several limitations of the present study that have to be considered when interpreting the results. In particular the study group RE followed by surgery is small. Nonetheless, this collective is highly selected including only patients with liver surgery for NELM following RE. Due to the low incidence of NETs with often diffuse NELM, studies about hepatic resection for NELM included small collectives previously (29,30). Thus, the analyzed group of the present manuscript is in line with the literature. The largest previously published study investigating hepatic surgery after RE included 71 patients treated in 16 centers with a wide variety of different tumor entities, which limits clinical relevance of those results (14). Additionally, this is the only study investigating the effect

of the multimodal therapeutic approach of liver surgery after RE reporting complete information about pre- and postoperative data including pathological examination of the resected livers. Treatment response to RE was evaluated histologically, but radiographic response assessment by MRI or PET/CT has not been performed. Nonetheless, it might be of additional value to evaluate treatment response with ^{68}Ga-DOTA-TATE PET/CT or MRI. Recently, Braat *et al.* demonstrated that response to RE in NET patients can reliably be evaluated with cross-sectional imaging modalities (i.e., CT, MRI) (18). Thus, follow-up of these patients is feasible with widely available imaging modalities. Furthermore, the authors revealed that NELM respond to RE independently of grading and that diffuse hepatic involvement (>75% hepatic tumor load) is associated with a worse outcome, which is in accordance to previous results (6,24,31). Moreover, it was shown that ^{68}Ga-DOTA-TATE PET/CT enables molecular response assessment of NELM to RE (19). Molecular response correlated with survival rates, thus this might be a promising approach identifying patients who will benefit from multimodal treatment, such as liver surgery after RE. Nonetheless, this issue has to be addressed in future studies. Another limitation of our study is that no dosimetric calculation has been performed after RE. The mBSA method has been applied to estimate the delivered activity. This method is feasible and easy to apply and provides the most data in literature (e.g., SIRFLOX and SORAMIC trials) (17,32). Nonetheless, a previsional dose calculation as defined by the Partition Model might have delivered more insight into the therapy and activity concept, but was not performed prior to RE. Thus, one of the limitations of this study is the lack of quantitative dosimetry data after RE, particularly with respect to healthy liver tissue. In the present analysis patients SIR-Spheres distribution after RE was assessed by Bremsstrahlung SPECT/low dose CT and post-therapeutic dosimetry was not performed due to the low diagnostic accuracy of Bremsstrahlung SPECT/CT. In this respect, ^{90}Y-PET/CT might be of high value in NET patients with the possibility of surgical liver resection after RE. This issue should be addressed in future multicenter studies on this subject. Treatment algorithms were different regarding the time interval between RE and liver resection. Nonetheless, the time range between RE and liver surgery might serve as an indicator to safely perform surgery. In this respect, an interval of three months is suggested by the Post-SIR-Spheres Surgery Study group [12], which is supported by the present results. Although baseline characteristics (*Table 3*) were not different in the analyzed groups, patients who underwent only liver surgery or only RE represent independent collectives. To define the best treatment algorithm for each patient, the distribution of the metastases (uni- *vs.* bilobar) is more important than the hepatic tumor load. This has to be considered when a tailor made therapeutic approach is established for a patient with NELM. Survival analyses revealed the most favorable outcome for resected patients. Nonetheless, RE can be used in NELM as bridging therapy and for downstaging.

Despite the numerically limited patients included, this report represents the largest and first study addressing the effect of the multimodal therapeutic approach of liver surgery after RE. Moreover, the feasibility and safety of liver surgery in NELM patients following whole liver RE, which was accompanied by a low morbidity, is analyzed. Within this uniform cohort of NELM the oncological outcome is favorable for patients with complete hepatic tumor clearance. Nonetheless, the role of RE prior to hepatic resection for NELM has to be clarified in prospective multicenter studies.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn.2019.07.11/coif). HI reports speaker honoraria from SIRTEX Medical. CJA has received research contracts (Novartis, Ipsen, ITM Solucin), lecture honorarium (Novartis, Ipsen, Falk Foundation) and advisory board honorarium (Novartis). CS reports personal fees from Ipsen, personal fees from Novartis, personal fees from Shire, personal fees from Blueprint Medicine, personal fees from Bayer, personal fees from Eisai, outside the submitted work. MS reports grants and personal fees from SIRTEX Medical, grants and personal fees from BAYER, personal fees from Siemens, personal fees from Cook, personal fees from Boston Scientific, outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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