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Radiosensitizing Favors Response to Peptide Receptor Radionuclide Therapy in Patients With Highly Proliferative Neuroendocrine Malignancies

Preliminary Evidence From a Clinical Pilot Study

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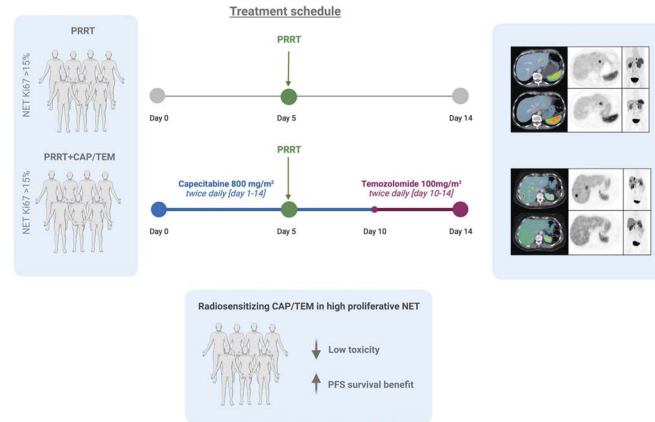
Abstract: Aim/Introduction: Peptide receptor radionuclide therapy (PRRT) represents a cornerstone of treatment regimens for patients with low proliferative neuroendocrine tumors (NETs). However, in patients experiencing somatostatin receptor–positive NET with higher proliferation rates, a value and potential therapeutic benefit of PRRT as part of multimodal treatment approaches and potentially with addition of radiosensitizing agents has not yet been established.

Patients and Methods: In this study, 20 patients with histologically confirmed gastroenteropancreatic (GEP) NET with proliferation rates (Ki67) between 15% and 55% were treated either with PRRT only (n = 10) or with a combination therapy (n = 10) comprising PRRT and capecitabine/temozolomide (CAP/TEM) for at least 2 consecutive cycles.

Results: Disease control rate in patients treated with PRRT alone was 60% (40% stable disease and 20% partial response). Strikingly, in patients treated with PRRT in combination with radiosensitization (CAP/TEM), the disease control rate was 90% (20% stable disease and 70% partial response). The median progression-free survival in the PRRT only group was 12 months, whereas the median progression-free survival in the PRRT + CAP/TEM group was 26 months and has not been yet reached for all patients in the group during the observation period. The median disease-specific survival for patients with PRRT alone was 51 months, whereas this end point was not yet reached in the PRRT + CAP/TEM group. Moreover, the PRRT + CAP/TEM group showed a significantly higher reduction of SSTR-PET–based metabolic tumor volume and chromogranin A levels compared with the PRRT only group. Importantly, adverse events of all grades did not differ between both groups.

Conclusions: PRRT + CAP/TEM represents a highly promising and well-tolerated therapeutic regimen for patients experiencing somatostatin receptor–positive NET with higher (Ki67 ≥ 15%) proliferation rate. Prospective randomized clinical trials are warranted.



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Informed consent statement: All patients agreed to the broad consent of University Hospital Tuebingen, which is fully compatible with standard informed consent statements.

Data availability: The data presented in this study are available from the corresponding author upon reasonable request.

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For more than 2 decades, radiolabeled somatostatin receptor treatment (peptide receptor radionuclide therapy [PRRT]) has been used as a well-established treatment option for patients with low-grade neuroendocrine tumors (NETs).[1] Over time, the radionuclide was changed iteratively, with ^{177}Lu currently being the preferential radionuclide for PRRT in patients with NET.[1–6] The prospective phase 3 NETTER1 trial had crucial impact on the therapy stratification for patients with metastasized G1 (Ki67 <3%) and G2 (Ki67 3% to 20%) midgut NETs. In this study, patients receiving ^{177}Lu-DOTATATE showed significantly better progression-free survival (PFS) and overall survival (OS) rates compared with patients in the octreotide-treated control group.[7]

In contrast to NET G1-2, neuroendocrine neoplasms G3 (Ki67 > 20%) are quite heterogenous, ranging from well-differentiated NETs G3 to poorly differentiated neuroendocrine carcinomas G3.[8] Neuroendocrine tumors G3 can be defined by a well-differentiated morphology and Ki67 index ranging from 20% up to 55%, whereas neuroendocrine carcinomas G3 often show a poorly differentiated morphology (large-cell or small-cell type) and Ki67 index above 55%.[8–11] In advanced NET G3, considering the paucity of prospective trials, a "standard" therapy regimen has not yet been established so far.[8,12] Patients with NET and Ki67 index above 15% are frequently regarded as high grade in clinical practice and are taken into consideration as potential candidates for chemotherapy including platinum-based therapies as well as chemotherapeutic regimens used in NET G2, particularly capecitabine combined with temozolomide (CAP/TEM).[8,9,12–14] According to the high expression of somatostatin receptor (SSTR) observed even in NET G3, treatment with somatostatin analogs and PRRT seems reasonable, although SSTR-PET imaging upfront and short-term interval imaging to assess disease control are needed.[12,15–19] Currently, prospective randomized phase 3 trials, such as NETTER-2 (NCT03972488) and COMPOSE (NCT04919226), are in progress to evaluate the efficacy and safety of PRRT in gastroenteropancreatic (GEP) NET patients with Ki67 between 10% and 55%.[20,21] To maximize the effects of PRRT, several radiosensitizing agents have been tested in different clinical trials.[22] Whereas the combination of PRRT with CAP/5-FU was first used in 2008, nowadays various agents such as CAP/TEM to increase DNA damage, PARP inhibitors, HSP90 inhibitors, or topotecan to inhibit DNA repair, mTOR inhibitors, hedgehog pathway inhibitors, checkpoint inhibitors, and others are implemented in clinical trials to increase the benefit of PPRT.[22–24] Moreover, previous studies have already shown evidence that safe and successful PRRT in combination with CAP alone or with CAP/TEM in neuroendocrine neoplasms is possible.[25–27]

We here present a clinical observation study, in which the combination of CAP/TEM and PRRT was administered for the treatment of NET patients with higher proliferation indices between 15% and 55% in head-to-head comparison with PRRT alone to evaluate efficacy and safety of the combinational treatment. Notably, patients receiving PRRT combined with CAP/TEM showed a significantly higher disease control rate and treatment response without increased treatment-related toxicities.

PATIENTS AND METHODS

Study Design and Selection of Patients

Between January 2013 and October 2021, a total of 214 NET patients received PRRT at our university hospital. Twenty-seven of these patients showed a Ki67 index in the range of 15% to 55%. Within this cohort, PRRT-naive GEP-NET patients were identified (n = 20). To compare the role of PRRT alone versus its combination with radiosensitizing, we randomized 10 GEP-NET patients treated with PRRT alone and 10 GEP-NET patients receiving PRRT in combination with CAP/TEM. Figure 1 demonstrates the patient selection procedure. All patients showed the following characteristics before PRRT:

- Histopathological diagnosis of an inoperable GEP-NET G2/G3 (Ki67 index 15% to 55%).
- Blood parameters: hemoglobin level >8 g/dL, white blood cell count >2000/μL, platelet count >75,000/μL, and creatinine level <2 mg/dL.
- Age >18 years.
- Positive ^{68}Ga-HA-DOTATATE PET/CT.

No further PRRT cycles were administered, if blood levels decreased below the aforementioned limits.

Only patients with a PET-based Krenning score of ≥3 were included.[28,29]

The observational study was approved by the ethics committee of the faculty of medicine of our university and of the university hospital (433/2022BO2) and was conducted in accordance with the Declaration of Helsinki.

Radiosensitizing Treatment

Neuroendocrine tumor patients in the combinational therapy group were treated with CAP 800 mg/m^2 body surface area (BSA) orally twice daily from day 1 to day 14. Temozolomide was administered orally from day 10 to day 14 at a dose of 100 mg/m^2 BSA twice daily. Peptide receptor radionuclide therapy was performed using ^{177}Lu-HA-DOTATATE on day 5. Furthermore, patients received oral antiemetic treatment with ondansetron 4 mg twice daily from day 10 to day 14. The radiosensitizing treatment scheme is shown in Table 1. The treatment regimen was chosen analogous to the prospective phase 2 single-center study of Claringbold and Turner.[27]

Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy was performed according to the practical guidelines of the joint International Atomic Energy Agency, the European Association of Nuclear Medicine, and the Society of Nuclear Medicine and Molecular Imaging in accordance with

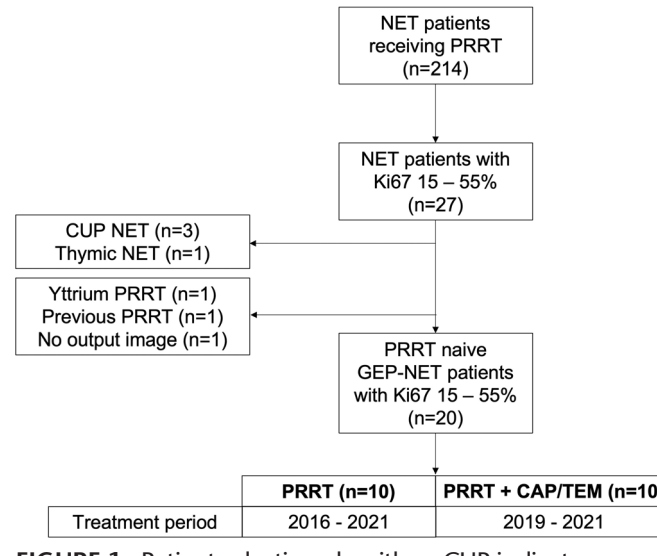

FIGURE 1. Patient selection algorithm. CUP indicates cancer of unknown primary.

TABLE 1. Radiosensitizing Treatment Scheme

Radiosensitizing Treatment Scheme			
Day	**Capecitabine**	**Temozolomide**	**PRRT**
1	800 mg/m^2 BSA twice daily		
2	800 mg/m^2 BSA twice daily		
3	800 mg/m^2 BSA twice daily		
4	800 mg/m^2 BSA twice daily		
5	800 mg/m^2 BSA twice daily		^{177}Lu-HA-DOTATATE
6	800 mg/m^2 BSA twice daily		
7	800 mg/m^2 BSA twice daily		
8	800 mg/m^2 BSA twice daily		
9	800 mg/m^2 BSA twice daily		
10	800 mg/m^2 BSA twice daily	100 mg/m^2 BSA twice daily	
11	800 mg/m^2 BSA twice daily	100 mg/m^2 BSA twice daily	
12	800 mg/m^2 BSA twice daily	100 mg/m^2 BSA twice daily	
13	800 mg/m^2 BSA twice daily	100 mg/m^2 BSA twice daily	
14	800 mg/m^2 BSA twice daily	100 mg/m^2 BSA twice daily	

the Rotterdam protocol.[30] Patients received an IV administration of 7249 ± 354 MBq ^{177}Lu-HA-DOTATATE per cycle, which was accompanied by an amino acid solution for renal protection. ^{68}Ga-HA-DOTATATE and ^{177}Lu-HA-DOTATATE were prepared according to good manufacturing practice and the German Medicinal Products Act (AMG § 13 2b).

Safety

Blood parameters (hemoglobin, leukocytes, neutrophil granulocytes, lymphocytes, platelets, creatinine, alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, and tumor markers chromogranin A [CgA] and neuron-specific enolase) were evaluated before ^{177}Lu-HA-DOTATATE administration. Adverse effects were graded according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0).[31] In the follow-up period, blood parameters were evaluated quarterly in our NET outpatient clinic. After 2 cycles of PRRT ^{68}Ga-HA-DOTATATE PET/CT or PET/MRI interim scans were performed. Also, a PET/CT or PET/MRI restaging was performed 1.5–3 months after the last cycle of PRRT. In case of stable disease (SD) or remission, restaging was performed every 3 to 6 months until diseases progression.

PET Image Acquisition

A baseline ^{68}Ga-HA-DOTATATE PET/CT or PET/MRI scan was performed, on average, a median of 7.5 weeks before PRRT and repeated at a median of 9.7 weeks after the final cycle of PRRT. Scans were conducted either on a state-of-the-art PET/CT scanner (Biograph mCT; Siemens Healthineers) or on a PET/MRI scanner (Biograph mMRL Siemens Healthineers, Germany) 20 minutes after IV injection of 3 MBq kg/BW ^{68}Ga-HA-DOTATATE.[32] Data were corrected for attenuation as well as scatter and reconstructed iteratively with OSEM3D (2 iterations, 21 subsets; Gaussian filter, 2 mm).

Imaging Analysis

The treatment response was assessed by using RECIST 1.1 criteria on CT or MRI scans. The image analysis was performed in joint consensus of a nuclear medicine physician and a board-certified radiologist. The baseline PET/CT or PET/MRI scan was performed 7.5 weeks (range, 2–22) before the first cycle of PRRT. The disease control rate was defined as complete response (CR), partial response (PR), or SD. The molecular tumor volume (MTV) was performed by a threshold-based semiautomatic volumetric segmentation using the software tool Affinity Hybrid Viewer (Hermes Medical Solution, Sweden), as previously described.[33] Pathologic SSTR expression was defined as SUVs, which were higher than 1.5 times mean SUV of the liver plus 2 times the standard deviation (SD_{liver}):

$$MTV = SUV_{tumor} > 1.5 \times SUVmean_{liver} + 2 \times SD_{liver}$$

First, a semiautomatic "single click segmentation" was performed to identify all volumes of interest with an SUV higher than the reference SUV. These areas were afterward selected and reviewed by a trained nuclear

TABLE 2. Patients Characteristics of the 2 Treatment Groups

Characteristics	PRRT	PRRT + CAP/TEM	*P*
Patient count, n	10	10	
Age, y	62.7 ± 12.7	52.2 ± 18.6	0.15
Sex, n (%)			
Male	5 (50)	5 (50)	
Female	5 (50)	5 (50)	>0.99
Primary tumor site, n (%)			
Midgut	5 (50)	3 (30)	
Pancreas	3 (30)	6 (60)	
Hindgut	2 (10)	1 (10)	0.40
Grading, n (%)			
G2	4 (40)	1 (10)	
G3	6 (60)	9 (90)	0.30
Ki67, mean ± SD, %	26 ± 11	31 ± 8	0.12
MTV, mean ± SD, mL	357 ± 502	358 ± 553	0.74
Previous therapy, n (%)			
Surgery	2 (20)	2 (20)	
Somatostatin analogs	8 (80)	8 (80)	
Chemotherapy	3 (30)	5 (50)	0.84

The second column shows the characteristics of patients treated with PRRT alone. The third column shows the characteristics of patients, who received a combination of PRRT and CAP/TEM.

G, grading.

TABLE 3. Imaging Response to Final PRRT According to RECIST 1.1

Response to PRRT	PRRT	PRRT + CAP/TEM
CR	0	0
PR	2	7
SD	4	2
PD	4	1

The middle column represents for patients treated with PRRT alone. The right column shows imaging response of patients, who received a combination of PRRT and CAP/TEM.

PD, progressive disease.

medicine physician, who excluded physiological SSTR-expressing areas (eg, kidney and pituitary gland) as well as non–disease-related lesions.

Statistical Analysis

Progression-free survival and disease-specific survival (DSS) were determined in months and were evaluated using the Kaplan-Meier technique. Before performing each statistical test, we tested for normal distribution using the D'Agostino and Pearson test. Two distinct groups were compared using a log-rank test. Student *t* test or Mann-Whitney *U* test was used for continuous variables, χ^2 test, or Fisher exact test for categorical variables. The statistical analysis was performed using GraphPad Prism 9.4.

RESULTS

Patients

Between January 2013 and October 2021, 214 patients were treated with PRRT at our University Hospital. For our study, we first selected all patients with the histologically confirmed diagnosis of a NET with a Ki67 index between 15% and 55% (n = 27). Then, we excluded all patients with previous PRRT (n = 1), mixed therapy protocols (n = 1), no available output images (n = 1), and other primary tumor sites than the GEP system (n = 4) (Fig. 1). Most patients who received PRRT alone (n = 10) were treated at an earlier time point, whereas combination therapy PRRT with CAP/TEM was introduced more recently for highly proliferative NET (n = 10). Patients in both groups were treated at least with 2 consecutive cycles of ^{177}Lu-HA-DOTATATE PRRT. The median follow-up time was 30 months (range, 15–71 months). Patient characteristics are summarized in Table 2. Whereas sex, Ki67 index, baseline MTV, and previous therapies were equally distributed in both groups, patients in the PRRT alone group were on average 10 years older and had more often a primary tumor localization in the midgut, but these findings were not statistically significant.

Response Analysis

Imaging response evaluation was assessed for all 20 patients. According to RECIST 1.1, the overall disease control rate in all patients among both groups was 75%, including 30% of patients with an SD and 45% of patients with a PR (Table 3). In the group of patients treated with PRRT alone, disease control rate was 60% (40% of patients with SD and 20% of patients with PR). Progressive disease was found in this group in 2 patients already after the first 2 cycles of PRRT. As a consequence, no further PRRT cycles were administered, and an alternative therapy (selective internal radiotherapy and chemotherapy with CAP/TEM) was implemented instead. However, in the combinational group (PRRT + CAP/TEM), disease control rate was found to be even 90% with 20% of patients showing SD and 70% of patients showing PR (Table 3).

The median PFS of all patients was 16 months (Fig. 2A), whereas the median DSS of all patients in both groups has not been reached yet. The 3-year DSS for all patients in both groups was 61% (Fig. 2B). In the group of patients with PRRT alone, the median PFS was found to be only 12 months, whereas the median PFS in the PRRT + CAP/TEM group was 26 months and is not reached for all patients in this group ($P = 0.04$) (Fig. 2C). Furthermore, the median DSS for patients with PRRT alone was 51 months and has not been reached yet for all patients in the group, whereas the median DSS for the PRRT + CAP/TEM group is also not reached yet (Fig. 2D).

In all patients, MTV was evaluated in the pretherapeutic PET/CT or PET/MRI and in the PET images after the last PRRT cycle. There was no significant difference for baseline MTV (Fig. 3A) as well as baseline Ki67 values (Fig. 3B) in both treatment groups. The PRRT + CAP/TEM group showed a significantly higher posttherapeutic relative MTV

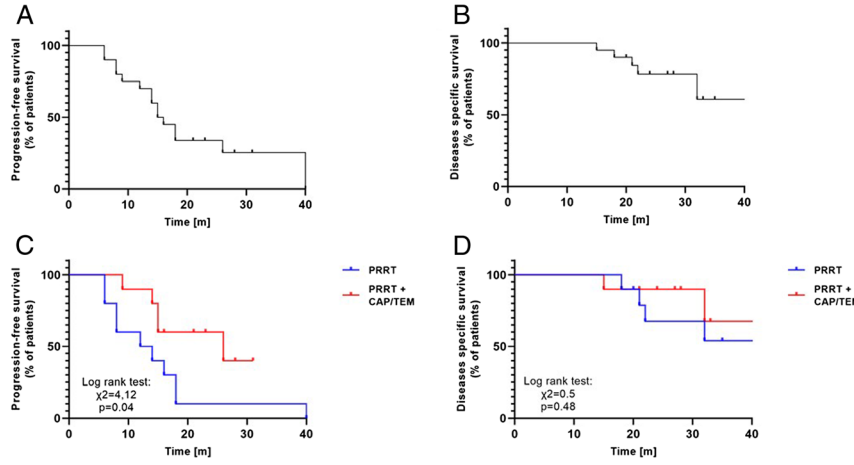

FIGURE 2. Response analysis. **A**, PFS for all patients in both groups undergoing PRRT with a median PFS of 16 months. **B**, The 3-year DSS for all patients in both groups was 61%. The median DSS of all patients in both groups was not reached yet. **C**, PFS presented separately for both groups. The median PFS for PRRT alone (blue line) was 14 months and for the PRRT + CAP/TEM group (red line) 26 months. **D**, DSS presented separately for both groups. The median DSS for PRRT alone (blue line) was 14 months; the median DSS for the PRRT + CAP/TEM (red line) was not reached yet. m indicates months.

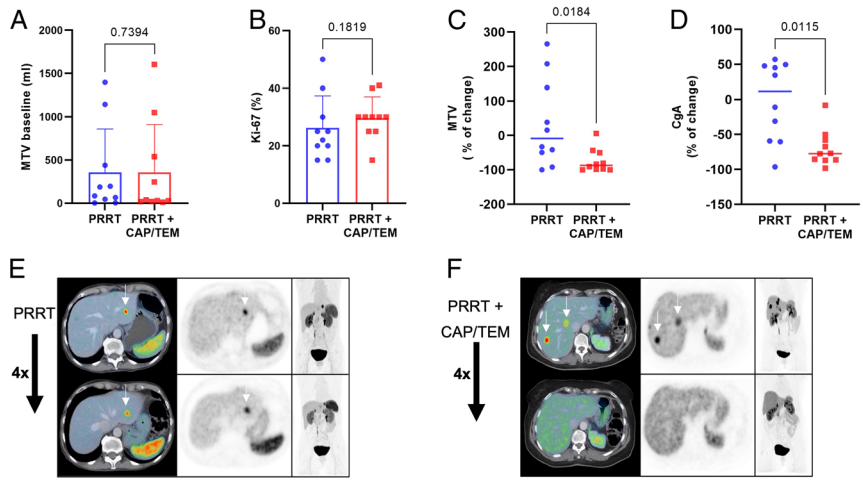

FIGURE 3. **A**, Baseline MTV in both groups showed no significant difference ($P = 0.7394$). **B**, There is also no significant difference for Ki67 values in both groups ($P = 0.1819$). **C**, The PRRT + CAP/TEM group showed a significant higher relative decrease of the MTV in the posttherapeutic PET than the PRRT only group ($P = 0.0184$). **D**, The PRRT + CAP/TEM group showed also a significant higher relative decrease of the CgA in the posttherapeutic blood control than the group with PRRT alone ($P = 0.0115$). **E**, Illustration of exemplary PET images of a patient from the PRRT only group, showing no clear difference between the baseline imaging and the imaging after 4 cycles of PRRT. The shown hepatic tumor lesion is marked by a white arrow. **F**, Illustration of exemplary PET images of a patient from the PRRT + CAP/TEM group, demonstrating a significant treatment response after 4 cycles of PRRT with barely definable hepatic lesions. Exemplary hepatic tumor lesions are marked by white arrows.

reduction compared with the PRRT only group ($P = 0.0184$) (Fig. 3C). Moreover, the PRRT + CAP/TEM group showed also a significantly higher relative decrease of CgA after the final PRRT than the PRRT only group ($P = 0.0115$) (Fig. 3D). Figures 3E and 3F illustrate exemplary PET images of a patient from the PRRT only group as well as the combinational group, respectively. The images of the patient in the PRRT only group show no clear difference in tracer uptake and tumor size between the baseline imaging and the follow-up imaging after 4 cycles of PRRT (Fig. 3E). In the patient who received PRRT in combination with CAP/TEM, a significant response after 4 cycles of PRRT with barely definable hepatic lesions was observed (Fig. 3F).

Potential Role of PRRT + CAP/TEM as a Neoadjuvant Therapeutic Regimen

To highlight the effects of the combinational treatment, the treatment course of a female patient of the study group, diagnosed with a pancreatic NET G3 and liver metastases, is described hereafter. The initial liver biopsy showed a NET G3 with Ki67 index of 25% (Figs. 4A–C). This patient received 4 cycles of PRRT + CAP/TEM as a first-line therapy due to intensive SSTR expression in the baseline PET imaging (Fig. 4G). PET imaging after 4 cycles of PRRT + CAP/TEM no longer showed any detectable tumor in the liver, but still in the pancreas (Fig. 4H). Thus, the interdisciplinary tumor board of our institution recommended surgery as a potentially curative therapeutic option. The patient underwent distal pancreatectomy, splenectomy, atypical gastrectomy, and atypical hepatectomy SIV a/b. PET imaging after surgery demonstrated no residual SSTR-positive tumor in the whole body (Fig. 4I). However, histopathological examination of the liver resection specimen displayed still but only interspersed NET cells (Figs. 4D–F). Ki67 proliferation rate in the liver resection specimen was only 1% (Fig. 4F), and the tissue demonstrated extensive regressive alterations (Fig. 4D). Approximately 1 year after surgery, there is still no evidence of tumor on consecutive PET scans.

Adverse Events and Follow-up

Treatment-related adverse events according to CTCAE v5.0 are displayed in Table 4. In the group of patients receiving PRRT alone, grade 3 or 4 anemia occurred in 20%, grade 3 or 4 leukocytopenia was observed in 10%, and grade 3 or 4 thrombocytopenia was detected in 10% of all cases. On the other hand, patients receiving PRRT + CAP/TEM showed no case of grade 3 or 4 anemia, grade 3 or 4 leukocytopenia was observed in 20%, and grade 3 or 4 thrombocytopenia only occurred in 10% of patients. There were also no significant differences in grade 1 and 2 adverse events between the 2 groups.

For long-term follow-up, the available blood parameters were documented once per quartal. The mean relative changes of the blood parameters from baseline for all patients of both treatment groups are shown in Figure 5. Each time point corresponds to a quarter year. The first time point corresponds to the administration of the first cycle of PRRT. In 2 patients per group, blood values were measured after the third cycle, which resulted in the fact that a fourth cycle could not be administered. For hemoglobin level (Fig. 5A), leukocyte count (Fig. 5B), platelet count (Fig. 5C), and creatinine level (Fig. 5D), no significant differences in mean relative changes after PRRT (time point 4) could be observed in both groups.

DISCUSSION

To further enhance the treatment efficacy of PRRT in NET G3, several combinatorial treatment regimens of PRRT and radiosensitizing agents are currently under clinical investigation.[22]

In our clinical study, a head-to-head comparison of PRRT alone versus PRRT in combination with CAP/TEM was performed in patients with GEP-NETs with Ki67 rates between 15% and 55%. Each treatment group contained 10 patients, treated with the same treatment protocol per group. In a study published in 2019 by Yordanova et al,[34] the authors presented data of 15 patients with higher proliferative NETs (G2 and G3), who were treated with PRRT in combination with radiosensitization. Of note, a respective control group with PRRT mono treatment was missing. In addition, this heterogeneous cohort

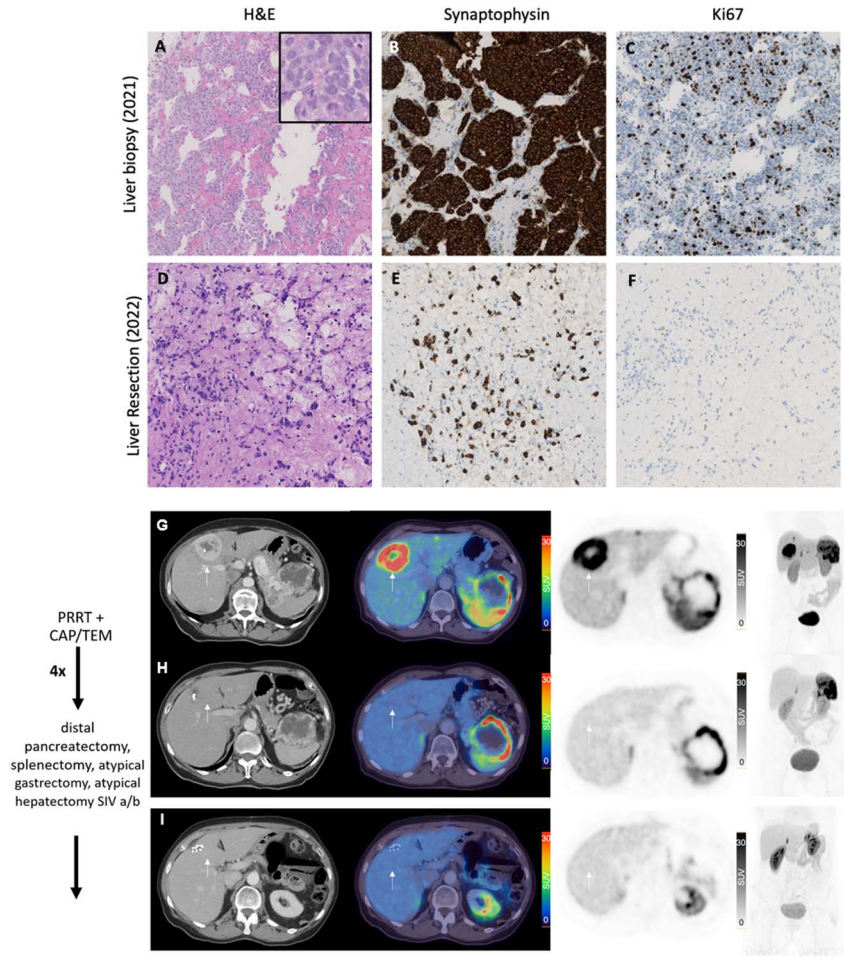

FIGURE 4. Representative case of CR achieved by a neoadjuvant PRRT in combination with CAP/TEM and following surgical resection. **A**–**C**, The liver biopsy specimen shows an epithelial neoplasia with nested growth pattern (HE, **A**) and salt-and-pepper–like chromatin appearance (inset, **A**). The tumor cells are characterized by a strong immunoreactivity for synaptophysin (**B**) and a Ki67 (MIB1) proliferation rate of 25% (**C**), leading to the diagnosis of a NET, G3. **D**–**F**, The liver resection specimen obtained 1 year after the initial biopsy demonstrates extensive regressive alterations of the tumor with myxoid stroma (HE, **D**). In the synaptophysin staining, only interspersed tumor cells can be identified (**E**). The Ki67 proliferation rate upon treatment is <1%. Magnification: 200× (main), inset 800×. **G**, PET imaging before treatment. **H**, PET imaging after 4 cycles of PRRT + CAP/TEM showing no detectable tumor in the liver. **I**, PET imaging after surgery (distal pancreatectomy, splenectomy, atypical gastrectomy, atypical hepatectomy SIV a/b) demonstrating no residual SSTR-positive tumor in the whole body. One exemplary hepatic tumor lesion, which was resected in the course of treatment, is marked by white arrows. HE indicates hematoxylin-eosin staining.

was treated with 2 different radiosensitizing protocols (temozolomide alone vs CAP/TEM).[34] In contrast to this study sex, Ki67 index, baseline MTV, and previous therapies are equally distributed among both groups in our study, resulting in a much better comparability. However, patients in the group with PRRT alone were older (10 years on average), had slightly more a primary tumor localization in the midgut, and presented more often a histological G2 grading. This might indicate that more intensive treatment with the addition of radiosensitizing

TABLE 4. Adverse Events According to CTCAE v5.0 Compared for Both Groups

Adverse Events	PRRT Occurrence of Grade 1/2 (%)	PRRT + CAP/TEM Occurrence of Grade 1/2 (%)	*P*	PRRT Occurrence of Grade 3/4 (%)	PRRT + CAP/TEM Occurrence of Grade 3/4 (%)	*P*
Anemia	8 (80)	8 (80)	>0.99	2 (20)	0 (0)	0.47
Leukocytopenia	6 (60)	3 (30)	0.37	1 (10)	2 (20)	>0.99
Thrombocytopenia	3 (30)	5 (50)	0.65	1 (10)	1 (10)	>0.99

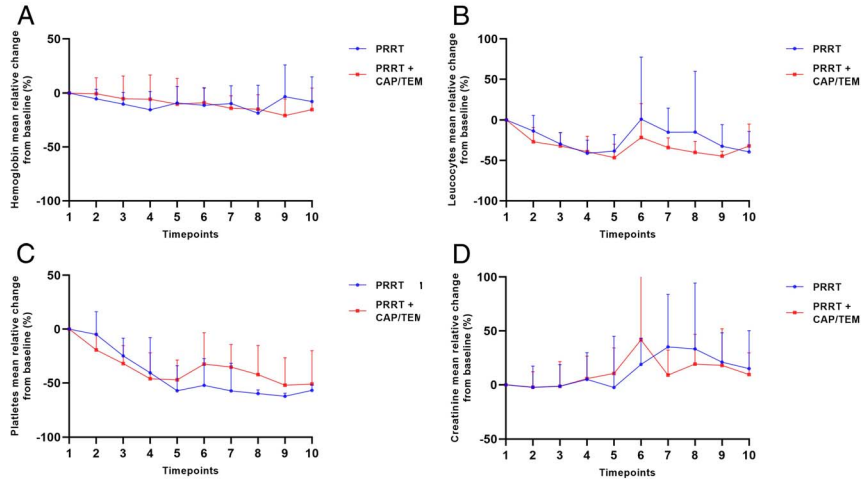

FIGURE 5. Comparison of mean relative changes in blood parameters for each treatment group after PRRT. Each time point corresponds to a quarter year. The first time point corresponds to the administration of the first PRRT cycle. The treatment group with PRRT only is indicated in blue; the treatment group with PRRT + CAP/TEM is indicated in red. **A**, Comparison of mean relative changes in hemoglobin. **B**, Comparison of mean relative changes in leukocyte count. **C**, Comparison of mean relative changes in platelet count. **D**, Comparison of mean relative changes in creatinine.

was considered more feasible in younger patients and necessary in patients with primary sites at the pancreas and higher proliferation rates.

In our study, the disease control rate as well as PFS and DSS were found to be superior in the combinational group (PRRT + CAP/TEM), compared with the patient subgroup receiving only PRRT. This is in line with data from 2 other studies combining PRRT and radiosensitizing agents. Here, patients in the combinational group also showed improved response rates, PFS, and DSS.[34,35] Moreover, in our study, posttherapeutic relative decrease of MTV and CgA was significantly higher in the PRRT + CAP/TEM group compared with the PRRT only group.

Remarkably, the more intense treatment regimen in the combinational group (PRRT + CAP/TEM) showed no increase in the observed toxicities compared with the PRRT alone regimen. In neither in the acute treatment setting nor in the long-term follow-up, we observed significant differences regarding hematotoxicity or nephrotoxicity between the 2 treatment groups. Whereas 2 studies combining PRRT and radiosensitizing agents showed particularly higher toxicity rates, even resulting in a liver failure in 1 patient,[34,35] studies by van Essen et al[23] and Zhang et al[24] did not observe differences in toxicity with or without radiosensitizing.

Of note, due to the very good treatment response in patients in the combinational group (PRRT + CAP/TEM), even a surgical resection leading to CR could be achieved in 2 patients, who were initially classified as inoperable. Taking this into account, PRRT with radiosensitizing might even be used as a novel neoadjuvant concept to open up a curative perspective for patients with NET G3.

LIMITATIONS

An important limitation of this study is the still relatively small cohort size. Neuroendocrine neoplasms are a rare tumor entity with a low prevalence in general, but especially the highly proliferative tumors (NET G2 and NET G3) represent a small subgroup. This may explain the low patient number of our study, but of course the small cohort is an important limitation, which narrows the statistical power of this study. Both therapy groups (PRRT alone and PRRT with CAP/TEM) were treated with a strictly uniform study protocol, which is in accordance with the specifications of a prospective study. However, there was no randomization in the true sense and no blinding of the patients in the therapy groups. Randomization of the patients into the 2 therapy groups was based on historical circumstances. Although patients in the PRRT group were treated from 2016 to 2021, patients in the combinational group received treatment between 2019 and 2021. Therefore, a randomized blinded prospective multicentric study is needed in the future. Another limitation is that, due to the PET-based Krenning score ≥3 in all patients, no supplementary ^{18}F-FDG PET was performed. However, this would be desirable, especially in this aggressive cohort.

CONCLUSIONS

To our knowledge, this is the first comparative study evaluating the benefits and safety of radiosensitizing with CAP/TEM for PRRT in patients with higher proliferative GEP-NET (Ki67 ≥15% and <55%). This study demonstrates that the addition of radiosensitizing to PRRT in patients with higher proliferative GEP-NET (Ki67 ≥15%) results in significantly improved disease control and treatment response with concurrently low toxicity. Of note, additional prospective multicenter studies are warranted to further investigate the use of PRRT in combination with CAP/TEM in patients with GEP-NET and higher proliferation rates.

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