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Peptide Receptor Radionuclide Therapy in Grade 3 Neuroendocrine Neoplasms: Safety and Survival Analysis in 69 Patients

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Running title: PRRT in G3 Neuroendocrine Neoplasms

ABSTRACT

To date, limited data are available concerning peptide receptor radionuclide therapy (PRRT) of grade 3 (G3) neuroendocrine neoplasms (NENs) with a Ki-67 proliferation index of >20%. The purpose of this study was to analyze the long-term outcome, efficacy and safety of PRRT in patients with SSTR-expressing G3 NEN. **Methods:** A total of 69 patients (M=41 males; age 28-81 years) received PRRT with lutetium-177 (^{177}Lu) and/or yttium-90 (^{90}Y) labeled somatostatin analogs (DOTATATE or DOTATOC). Twenty-two patients had radiosensitising chemotherapy. Kaplan–Meier analysis was performed to calculate progression-free survival (PFS) and overall survival (OS), defined from start of PRRT, including a subgroup analysis for patients with a Ki-67 of ≤55% and >55%. Treatment response was evaluated according to RECIST 1.1 as well as by molecular imaging criteria (EORTC). Short and long-term toxicity was documented (CTCAE v.5.0) using a structured database (comprising over 250 items per patient) and retrospectively analyzed. **Results:** Forty-six patients had pancreatic, 11 CUP, 6 midgut, 3 gastric, and 3 rectal NEN. Median follow-up was 94.3 months. The median PFS was 9.6 months and median OS was 19.9 months. For G3 NEN with a Ki-67 ≤55% (n=53), the median PFS was 11 months and median OS 22 months. Patients with a Ki-67 >55% (n=11), had a median PFS of 4 months and a median OS of 7 months. For those patients with positive SSTR imaging, but no FDG uptake, the median PFS was 24 months and median OS was 42 months. A significant difference was found for both, PFS and OS, with a median PFS of 16 vs 5 months and a median OS of 27 vs 9 months for a SUVmax >15.0 and a SUVmax ≤15.0 on SSTR-PET, respectively. In the group with FDG scored as 3-4, the median PFS was 7.1 months and the median OS 17.2 months. For FDG scored as 0-2, the median PFS was 24.3 months and the median OS 41.6 months. PRRT was well-tolerated by all patients; no grade 3 or grade 4 hematotoxicity occurred and no clinically

significant decline in renal function was observed. There was no hepatotoxicity. **Conclusion:** PRRT was tolerated well without significant adverse effects and is efficacious in G3 NEN with promising clinical outcome, especially in patients with a Ki-67 index of ≤55% and even in patients who have failed chemotherapy. Baseline FDG along with SSTR molecular imaging is useful to stratify those G3-NEN patients with high uptake on SSTR PET/CT and no or minor FDG-avidity, a mismatch pattern which is associated with a better long term prognosis.

Keywords: peptide receptor radionuclide therapy (PRRT), lutetium-177(^{177}Lu), yttrium-90(^{90}Y), neuroendocrine neoplasms (NENs), G3

INTRODUCTION

Neuroendocrine neoplasms (NENs) are a heterogeneous group of neoplasms arising from the diffuse neuroendocrine system cells *(1)*. They are classified as grade 1 (G1), G2 and G3 according to the World Health Organization (WHO) classification based on the mitotic activity and Ki-67 immunostaining with a Ki-67 index ≤2%, 3-20%, and >20%, respectively. High-grade (G3) NENs were previously referred to as neuroendocrine carcinomas (NECs), with aggressive malignant character and poor prognosis, which were mainly treated with chemotherapy *(2-3)*. However, substantial heterogeneity of high-grade NENs has been observed based on the clinical behavior, genetic profiling, and proliferation rate. According to the WHO 2017 and European Neuroendocrine Tumour Society (ENETS) classification, a new NEN G3 category for the distinction of well-differentiated NENs G3 from NECs has been introduced. Recent genetic studies also report that G3 NENs express p53 and rb1, which are usually negative in neuroendocrine tumors (NETs), providing a novel basis for prognostic and therapeutic stratification *(4-5)*.

During the last decade, substantial progress has been made in the treatment of G1 and G2 NENs. On the other hand, systemic cytotoxic chemotherapy, typically using platinum compounds, is largely applied for highly malignant G3 NECs.

NENs are characterized by high expression of somatostatin receptors (SSTRs), allowing the use of radiolabeled somatostatin analogs for receptor-mediated imaging and peptide receptor radionuclide therapy (PRRT) using therapeutic radioisotopes such as ^{90}Y and/or ^{177}Lu, which has become an established treatment for patients with unresectable or metastatic, progressive, well differentiated, SSTR positive NETs *(6-10)*. Recently, Lutathera (^{177}Lu-DOTATATE) has been approved by both, the European Commission (EMA) and the U.S. Food and Drug Administration

(FDA) for the treatment of metastatic, progressive, well differentiated (G1/G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults. However, data on PRRT in G3 NENs is very limited.

The aim of this study was to assess the safety and efficacy in terms of survival analysis of PRRT in patients with SSTR-expressing G3 NENs with a Ki-67 proliferation index of >20%. The prognosis of patients with distinctly different Ki-67 proliferation indices having baseline SSTR and FDG PET/CT imaging was also evaluated.

MATERIALS AND METHODS

Patients

Eligible patients were adults with histopathologically confirmed metastatic G3 NEN (Ki-67 index >20%) with confirmed high SSTR expression, i.e., tumor uptake > normal liver parenchyma on ^{68}Ga-SSTR PET imaging. Disease progression was documented within 3 to 6 months before the start of PRRT.

From January 2003 to January 2017, a total of 69 patients with G3 NEN (M 41, F 28; age range 28–81 y, mean age 58.1 ± 12.9 y) who underwent PRRT were retrospectively reviewed. The study was approved by the internal review board and written informed consent was obtained from each patient. The baseline demographics of the patients are listed in Table 1.

Forty-six patients (66.7%) presented with pancreatic NEN, 11 (15.9%) with CUP (cancer of unknown primary), whereas the primary tumor was present in the midgut in 6, in the stomach in 3, and in the rectum in 3 patients. Of the 69 patients, 53 (76.8%) had a Ki-67 ≤55%, 11 (15.9%) had

a Ki-67 ≤55%, while Ki-67 was unknown at their initial assessment and no samples could be obtained for re-analysis in 5 (7.2%) patients. The Ki-67 index for each patient according to the primary tumor site is shown in Figure 1.

PRRT was applied as first-line treatment in 8 patients (11.6%), as second-line in 25/69 (36.2%) and as third-line therapy in 28/69 (40.5%) patients. The time span between biopsy for the assessment of Ki67 and the first treatment cycle was 27.1 ± 36.8 months. Treatment parameters and the number of PRRT cycles are presented in Table 2. The median administered activity for ^{177}Lu-PRRT per cycle was 4.5 ± 13.2 GBq (range 2.5-9.5 GBq). The median administered activity per cycle for ^{90}Y-PRRT was 3.2 ± 1.0 GBq (range 1.3-4.8 GBq). The maximum cumulative administered activity was 38.0 GBq.

Radiopharmaceutical Preparation

The DOTA-conjugated somatostatin analogues DOTATOC, DOTANOC and DOTATATE were labeled with ^{68}Ga, ^{177}Lu and ^{90}Y, respectively in our institutional radiopharmacy according to GMP regulations. The radionuclide ^{68}Ga was obtained in house from a ^{68}Ge/^{68}Ga generator. A highly efficient NaCl-based labeling ^{68}Ga procedure has been developed in our hospital *(11,12)*. ^{177}Lu and ^{90}Y were obtained from different manufacturers. The labeling of DOTA-conjugated peptides with ^{177}Lu and ^{90}Y was performed as previously published *(13)*. High-performance liquid chromatography (HPLC) was used for quality control. The radiochemical purity was always greater than 99%.

Treatment regimen

Nephroprotection was performed by amino-acid infusion (1600 mL of 5% lysine HCl and 10% L-arginine HCl) (*14*). In patients with impaired renal function (GFR < 60 ml/min) and in

case of application of ^{90}Y, 4% Gelofusine was infused according to patients' weight for additional nephroprotection. The infusion was started at least 30 min prior to administration of the radiotherapeutic compound and continued for 4 h thereafter. The radiopharmaceutical was co-administered over 10-15 min by using a second infusion pump system. The activity to administer was individually chosen based on the Bad Berka Score (BBS) (*15*), i.e. the uptake in the tumor lesions as shown by ^{68}Ga-SSTR PET/CT *(performed before each treatment cycle),* renal function, hematological reserve, *liver involvement, extra-hepatic tumor burden, Ki67 index, tumor grade, FDG PET/CT status, tumor dynamics (doubling time, new lesions), weight loss, time since first diagnosis, functional activity of tumor,* previous treatments and general status of the patient (Karnofsky Performance Scale) *(16-18).* Decision to use ^{90}Y and/or ^{177}Lu depended upon the tumor mass, renal and hematological function, previous therapy (especially chemotherapy), SUV, and other factors as described by the BBS *(15, 19-21).* Both radionuclides were used in subsets of patients sequentially (DUO-PRRT) or in combination on the same day (TANDEM-PRRT) *(15).* The interval between the treatment cycles was 10-12 weeks. Depending on the general and hematological status as well as tolerability, 22 patients with high uptake on FDG-PET/CT underwent peptide receptor chemo-radionuclide therapy (PRCRT), i.e. PRRT in combination with low-dose of capecitabine (CAP, 1500 mg/sq. m/day in two daily divided doses) for 2 weeks starting from the day of PRRT. Additionally, temozolomide (CAPTEM) was administered in 4/22 patients *(5).*

Safety

Laboratory parameters (erythrocytes, hemoglobin, platelets, leucocytes, creatinine, BUN, SGOT, SGPT, bilirubin, SAP, TSH, Gamma-GT and respective tumor markers) were evaluated prior to each cycle and at restaging. Renal function was monitored by tubular extraction rate

(TER) using ^{99m}Tc-mercaptoacetyltriglycine (MAG3) renography; in addition the glomerular filtration rate (GFR) was determined using ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) in patients with elevated serum creatinine. Treatment-related adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE v.5.0). Restaging was performed with SSTR PET/CT every 3-4 months after PRRT. In case of stable disease or remission (complete or partial), the patient was restaged with SSTR PET/CT every 6 months until disease progression was evident on imaging. SSTR and FDG PET/CT were performed, until January 2014 with a Siemens Biograph Duo and since then with the Biograph mCT Flow 64; Siemens Medical Solutions AG, Erlangen, Germany. Maximum standardized uptake values (SUVmax) were obtained by drawing circular regions of interest (ROIs), which were automatically adapted (40% isocontour) to a 3D volume of interest using commercial software provided by the vendor. Contrast-enhanced CT (ceCT, spiral CT using Biograph mCT Flow 64) was acquired after intravenous administration of 60-100 mL nonionic iodinated contrast. Images were evaluated by two experienced nuclear medicine specialists. MRI was performed in selected cases (allergy to iodinated contrast or poor detectability of liver metastases on CT scan) and abdominal ultrasound obtained at each visit. PRRT was resumed if progression occurred after a therapy interval of more than 6 months (so-called next "treatment phase" of PRRT).

Response assessment

Treatment response was assessed on CT and/or MRI images according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) *(22).* Imaging was performed prior to each PRRT cycle and at restaging. Disease Control Rate (DCR) was defined as complete remission (CR), partial remission (PR) and stable disease (SD). Best objective response rate (ORR) was defined as patients achieving CR and PR at follow-up according to the RECIST criteria.

Molecular response was evaluated according to the European Organization Research and Treatment of Cancer (EORTC) criteria *(23)*.

Statistical analysis

Kaplan-Meier survival analysis was performed to calculate the progression-free survival (PFS) and overall survival (OS) defined from start of PRRT. Log-rank test and the Cox proportional hazards model were used to analyze the survival distribution of subgroups. Continuous variables were denoted as means ± standard deviation. Differences between two independent groups were determined by Student's t-tests. Differences among groups were compared with one-way analysis of variance. All statistical tests were 2-tailed, and a P-value of <0.05 was considered statistically significant.

RESULTS

Safety

No CTCAE grade 4 hematotoxicity was observed, and except for one (1.4%) patient with grade 3 leukocytopenia, there was no significant toxicity. No grade 3 or 4 anemia was observed after PRRT, although 2 (2.9%) patients had grade 3 anemia prior to PRRT. No myelodysplastic syndrome (MDS) or leukemia occurred during follow-up until death or study cut-off date.

No CTCAE grade 3-4 nephrotoxicity was observed in any patient. At baseline, creatinine was normal in 57/69 (82.6%) of subjects, while 14.5% (10/69) had grade 1, and 2.9% (2/69) had grade 2 renal dysfunction. On follow-up, 84.6% (44/52) had normal creatinine, 13.5% (7/52) had grade 1 and 1.9% (1/52) had grade 2 elevation of creatinine, respectively. However, there was no

correlation with the number of cycles or the cumulative administered radioactivity administered. No patients with grade 2 renal impairment at baseline demonstrated a further decline in renal function. GFR did not demonstrate any significant change after PRRT, despite subjects with grade 2 renal impairment at baseline (GFR 35 - 60 ml/min/1.73 m^2). No liver function dysfunction was observed after therapy.

Treatment Response

Response evaluation was possible in 55 patients. Five patients died shortly after the first PRRT and in 9 patients the clinical condition severely deteriorated, preventing repeated further imaging. According to RECIST 1.1, DCR at 3 months post-PRRT was 78.2%, including 30.9% of patients with PR and 47.3% with SD. Molecular imaging response at 3 months post-PRRT was 49.1% with PR, 21.8% with SD, 27.3% with PD and 5.5% with mixed response, respectively. Treatment responses are presented in Table 3.

Survival

Until the study cut-off date in January 2018, 56 out of 69 (81%) patients with G3 NEN died. The median follow-up time was 94.3 months (interquartile range (IQR) 56.2-104.9). For the entire group of 69 patients, the median PFS was 9.6 months and the median OS was 19.9 months. Among the 64 patients with G3 NEN (excluding 5 patients in whom the Ki-67 index was not exactly known), the median PFS was 11 months for a Ki-67 ≤55% (N=53), and 4 months for a Ki-67 >55% (N=11) ($P<0.05$, Figure. 2). The median OS was 22 months for a Ki-67 ≤55%, and 7 months for a Ki-67 >55% ($P<0.05$, Figure 3).

PRCRT was performed in 22 patients. 18 patients received CAP and 4 patients CAPTEM. In this group, the median PFS was 9.8 months and the median OS was 21.6 months, respectively.

PET imaging related to Response and Survival

Of the 55 patients, in whom response assessment was performed, 86.0% (37/43) demonstrating an objective response had a SUVmax >15.0 on baseline ^{68}Ga-SSTR PET/CT. All 6 patients with a SUVmax >50, had an objective response to PRRT (4 achieving PR and 2 SD), see Figure 4 A). PFS and OS based on the study-specified ^{68}Ga-SSTR PET/CT SUVmax cutoff of 15.0 are shown in Figure 4 B. A significant difference was found for both, PFS and OS, with a median PFS of 16 vs 5 months ($p<0.05$) and a median OS of 27 vs 9 months ($p<0.05$) for a SUVmax >15.0 and a SUVmax ≤15.0, respectively.

In 48/59 patients having baseline ^{18}F-FDG PET/CT, response were also evaluated. All 9 patients with grade 0-2 imaging results (no or very mild FDG uptake, less than the liver, mismatch between SSTR and FDG imaging) had an objective response to PRRT at 3 months (PR n=7 and SD n=2). On the other hand, out of the 39 patients with grade 3-4 status (higher uptake than the liver), 6 had PR, 23 had SD, and 10 had PD. In the group with FDG scored as 3-4 (n=45), the median PFS was 7.1 months and the median OS 17.2 months. For FDG scored as 0-2 (N=14), the median PFS was 24.3 months and the median OS 41.6 months (Figure 5).

DISCUSSION

Most PRRT studies have focused on G1 and G2 NEN *(6-8,24-27).* The NETTER 1 study, a prospective randomized controlled phase III clinical trial using tandem treatment of ^{177}Lu-DOTA-TATE and octreotide LAR 30mg in patients with advanced midgut neuroendocrine tumors also focused on well-differentiated NEN and reported a markedly improved PFS and a significantly higher response rate than high-dose octreotide LAR *(6).* Clinical experience with PRRT in

patients with G3 NEN is limited, even though SSTR expression in principle enables to use ^{177}Lu and/or ^{90}Y coupled somatostatin analog as a therapy option. Only a small number of PRRT studies have included patients with G3 NEN or NEN with a high proliferation index *(5,28-30).*

Till date, this is the largest reported cohort of SSTR-expressing G3 NEN treated with PRRT. Although the patient group is heterogeneous, including PRRT combined with radiosensitizing chemotherapy in some patients, the majority of G3 NEN patients received only PRRT after failing prior chemotherapy. The follow-up (median 94.3 months) in our patient cohort is the longest among all studies published.

Median PFS and OS of patients with G3 NEN were significantly shorter when compared to well-differentiated G1 and G2 NEN *(6, 31).* However, compared to the results and the PFS/survival obtained with other treatment modalities in G3 NEN patients, our results are very encouraging. The NORDIC study reported a median PFS of just 4 months and a median OS of only 11 months for WHO G3 patients who received first-line chemotherapy *(32).* With a median PFS of 9.6 months and a median OS of 19.9 months, PRRT in our patient cohort demonstrated twice longer PFS and a relatively longer survival, which is even more promising, since 76.7% of our patients had already received at least one line of treatment prior to PRRT. Our results match well with a single-center study in 28 patients from Australia, where a PFS of 9 months and a median OS of 19 months was reported.

The median OS obtained for patients with a Ki-67 ≤55% was markedly longer (22 vs 14 months) than the one reported from the NORDIC group. These results suggest that PRRT may be a superior first-line therapeutic option in selected patients with high SSTR-expression and a Ki-67 ≤55% as compared to platinum-based chemotherapy. On the contrary, in the Ki-67 >55% group, the median OS was shorter for chemotherapy (7 vs 10 months). Therefore, platinum-based

chemotherapy may be better as first-line therapy for patients with a Ki-67 >55%. The median OS obtained in our patients with a Ki-67 ≤55% was markedly shorter (22 vs 46 months) than in the Australian study, whereby the patient number was significantly higher in our group (53 vs 22), contributing to an even greater heterogeneity amongst the patient population. Indeed, our results for Ki-67 >55% matched (7 months in both studies) to the Australian study.

We also found a significant difference between the PFS of the two groups – 11 months for a Ki-67 ≤55% (N=53), and 4 months for a Ki-67 >55% (N=11) - a trend similar to a recent Italian study, which compared patients with a Ki-67 index of >35% and with a Ki-67 index of <35%, demonstrating that the latter had a significantly longer PFS (6.8 and 26.3 months, respectively, p = 0.005). The difference in the absolute PFS in our study could be attributed to the lower cut-off for Ki-67 (of 35%) in the Italian study.In addition, the authors included patients with a Ki-67 >15%, i.e., including patients in the 'gray zone' (Ki-67 15-20%), defined by ENETS as G2 tumors *(29)*.

Indeed, Ki-67 alone may not be truly representative of the tumor grade, mainly due to the heterogeneity amongst the different metastases, thereby yielding different values from biopsy of different lesions. ^{18}F-FDG PET/CT plays an important role in the prognosis of NETs, with FDG-positive tumor denoting a more aggressive phenotype *(33)*. We characterized the FDG imaging phenotypes according to the grade of uptake. Patients with no or very faint FDG uptake responded well to PRRT at 3 months, i.e. a mismatch pattern between SSTR and FDG imaging is of prognostic relevance. For none to mild FDG uptake, the median PFS was significantly longer as compared to the highly FDG-avid group. These results are concordant with a previous study examining the role of FDG PET/CT in advanced well-differentiated grade 1/2 NETs *(34)*.

^{68}Ga-SSTR PET/CT might also play an important role in predicting response to PRRT in G3 NEN. Those patients with good response and a favorable outcome after PRRT had relatively

higher SUVmax on SSTR PET/CT imaging. This finding is in line with another study, in which all grades of NEN were included *(35)*. When using a cutoff of 15.0 for ^{68}Ga-SSTR PET SUVmax, a significant association with both PFS and OS were observed.

A limitation of our study is that it is a retrospective analysis. There was variation in somatostatin receptor affinities by using different radiopharmaceuticals. Also, the number of patients with a Ki-67>55% is limited, probably due to lack of SSTR expression in this group. Thirteen patients have received only one PRRT cycle, which might influence the prognosis. Another limitation is the lack of availability of the exact Ki-67 index in 5 patients, however, these were referred from other centers as histopathologically confirmed G3 NEN. Furthermore, almost a third (31.9%) of the patients with high-grade FDG PET/CT phenotype and a more aggressive tumor type received PRCRT, and the potential additional value of the concomitant radiosensitizing chemotherapy is unclear. Further randomized and controlled studies certainly remain warranted.

CONCLUSION

PRRT is efficacious in G3 neuroendocrine neoplasms, even in patients who have previously failed chemotherapy, resulting in promising clinical outcome, especially in those patients with a Ki-67 ≤55%. High SUV on SSTR PET/CT and no or minor FDG-avidity were associated with a better prognosis, i.e. FDG PET/CT along with SSTR PET/CT helps to stratify those patients with G3-NEN. PRRT was well tolerated without significant adverse effects.

DISCLOSURE

No potential conflicts of interest relevant to this article exist.

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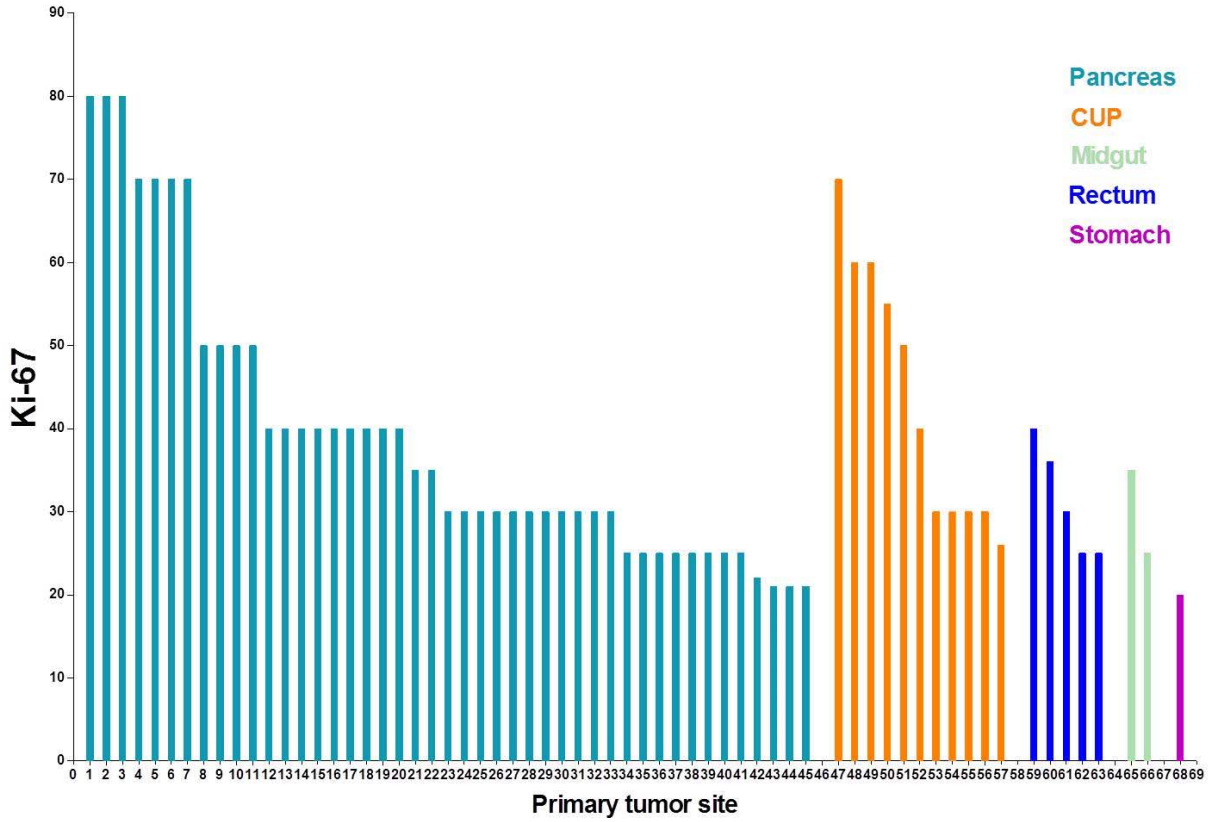

FIGURE 1. Ki-67 proliferation index of G3 NEN patients according to the primary tumor site.

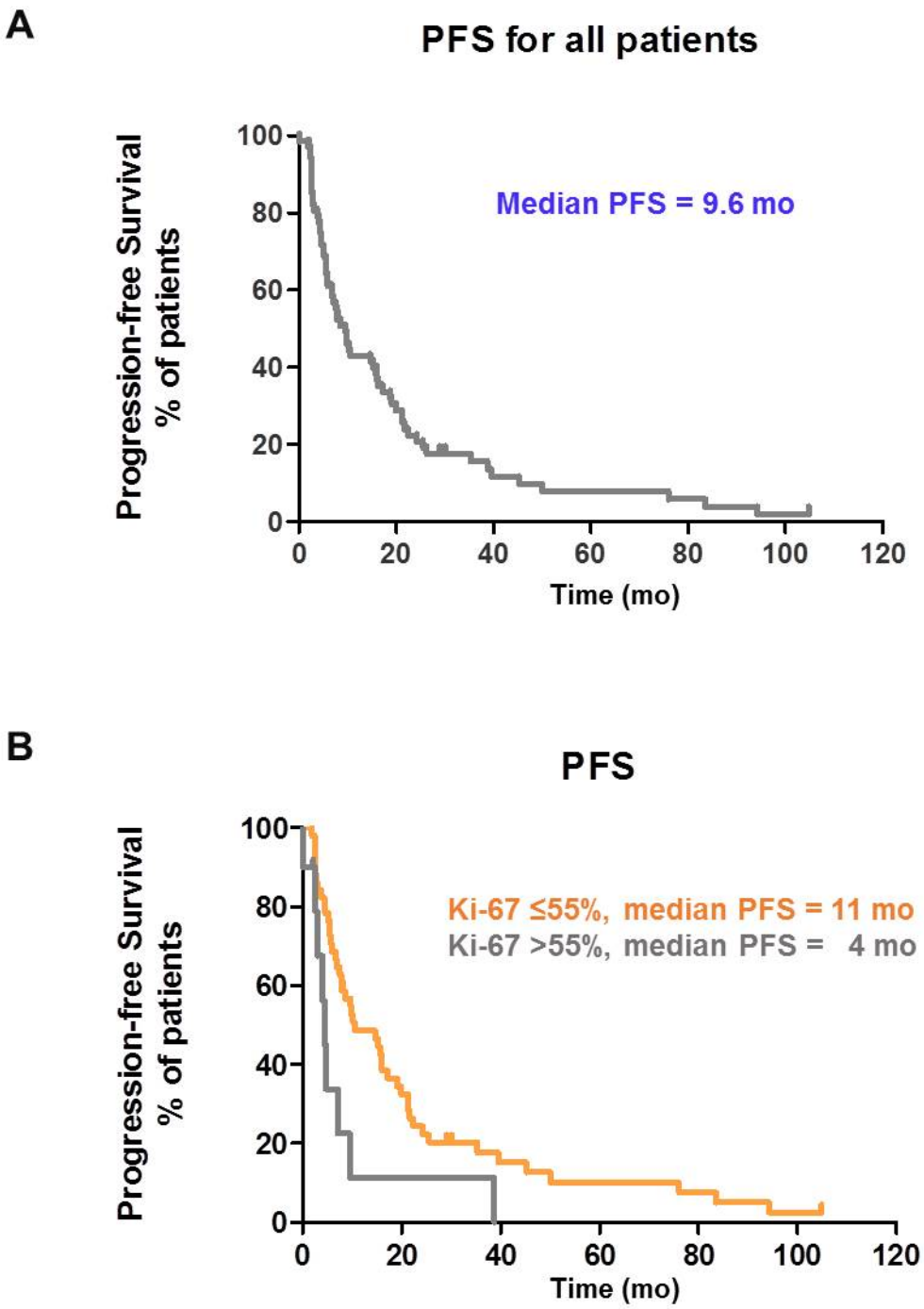

FIGURE 2. Kaplan-Meier curves for progression-free survival (PFS) months in all patients (A) from start of PRRT, and for subgroups (B) with 20%< Ki-67 ≤55% and >55%.

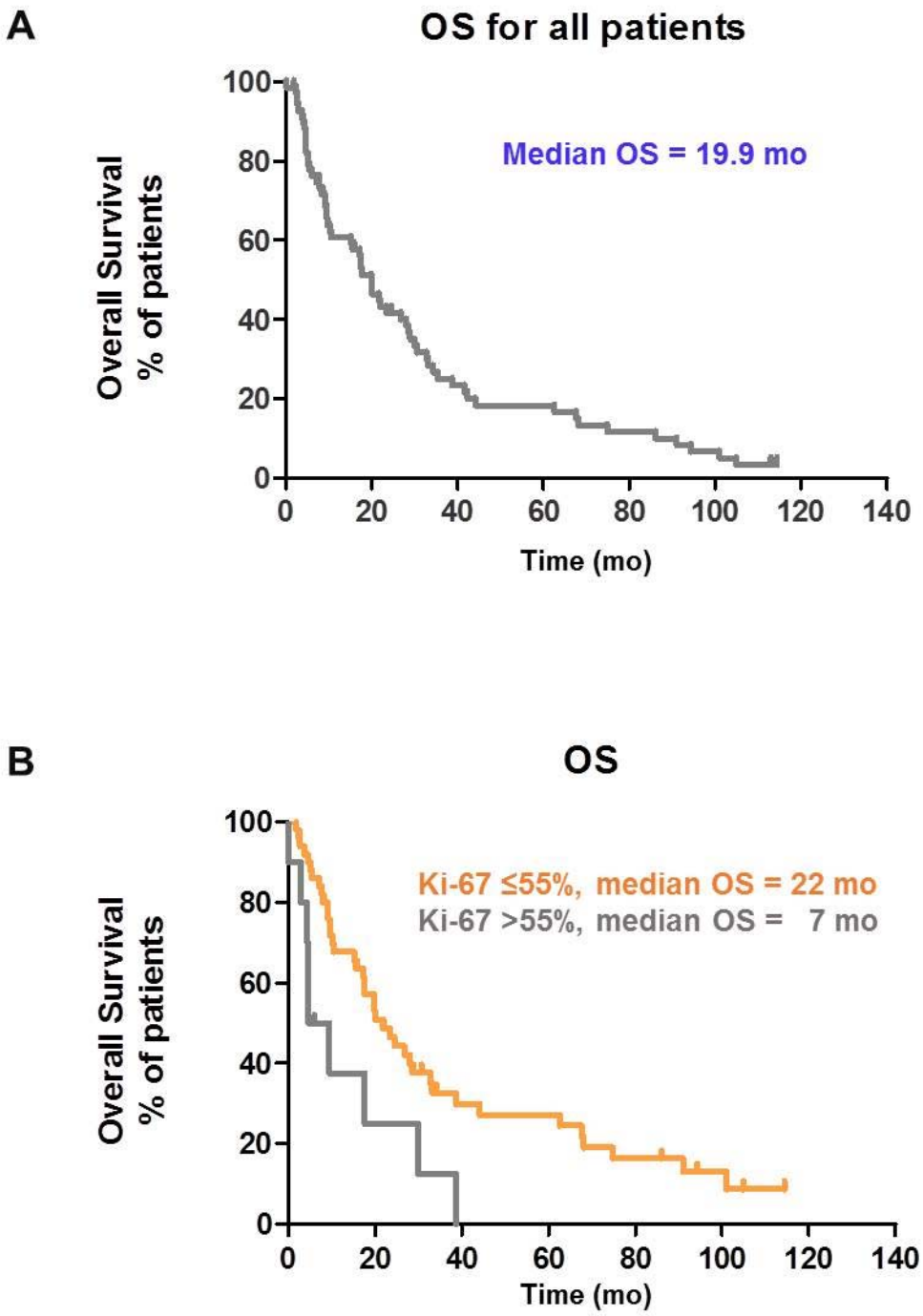

FIGURE 3. Kaplan-Meier curves for overall survival (OS) months for all the patients (A) from start of PRRT, and for subgroups (B) with 20%< Ki-67 ≤ 55% and >55%.

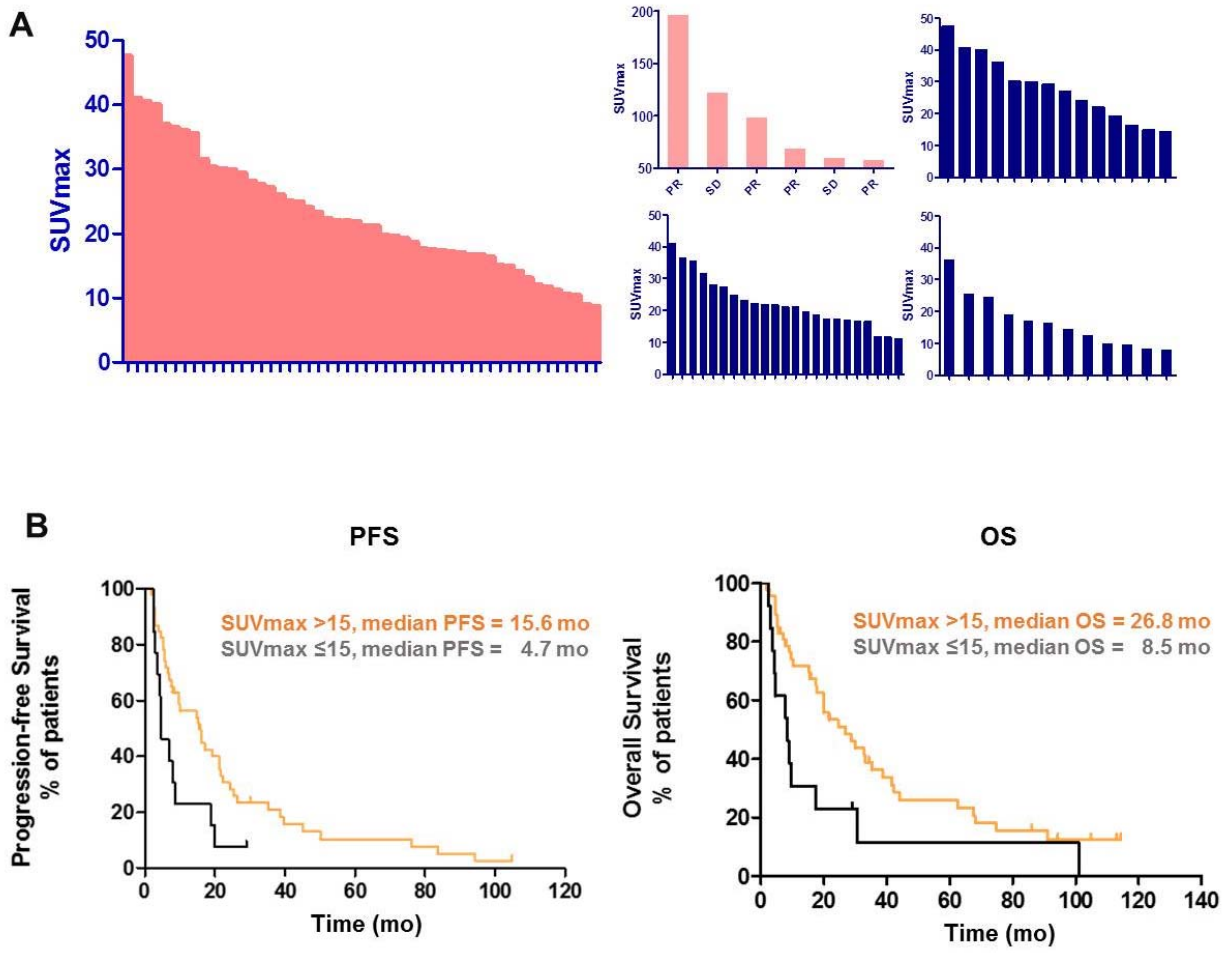

FIGURE 4. (A) Distribution of the SUVmax on ^{68}Ga-SSTR PET prior to PRRT (A, red). Distribution of SUVmax in subgroups (A, blue) at baseline that had response to PRRT as partial response (Top right), stable disease (Bottom left) and progressive disease (Bottom right) at 3 months after PRRT. (B) Kaplan-Meier curves for PFS and OS for subgroups with cutoff value as SUVmax >15 (orange line) and SUVmax ≤15 (black line) on baseline ^{68}Ga-SSTR PET imaging.

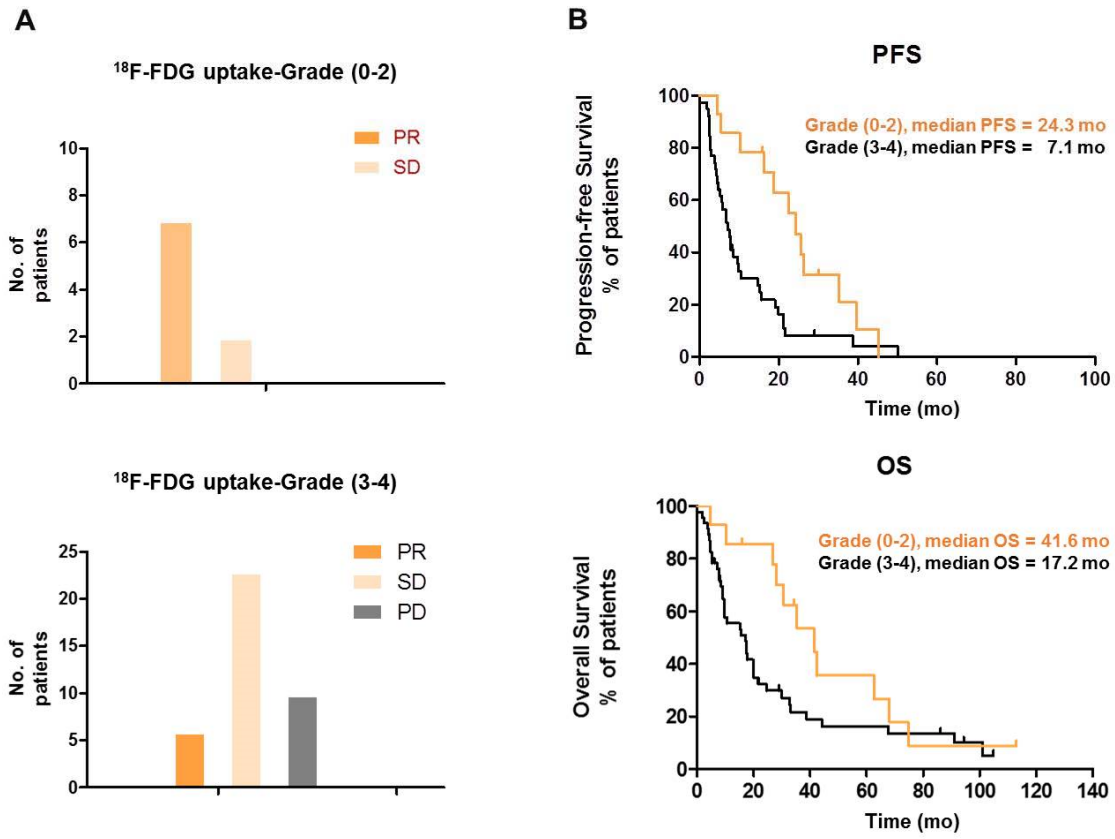

FIGURE 5. (A) Response at 3 months post-PRRT in subgroups with FDG PET at baseline for patients with grade 0-2 and the patients with grade 3-4. (B) Kaplan-Meier curves for PFS and OS for subgroups with grade 0-2 (orange line) and grade 3-4 (black line) on baseline ^{18}F-FDG PET.

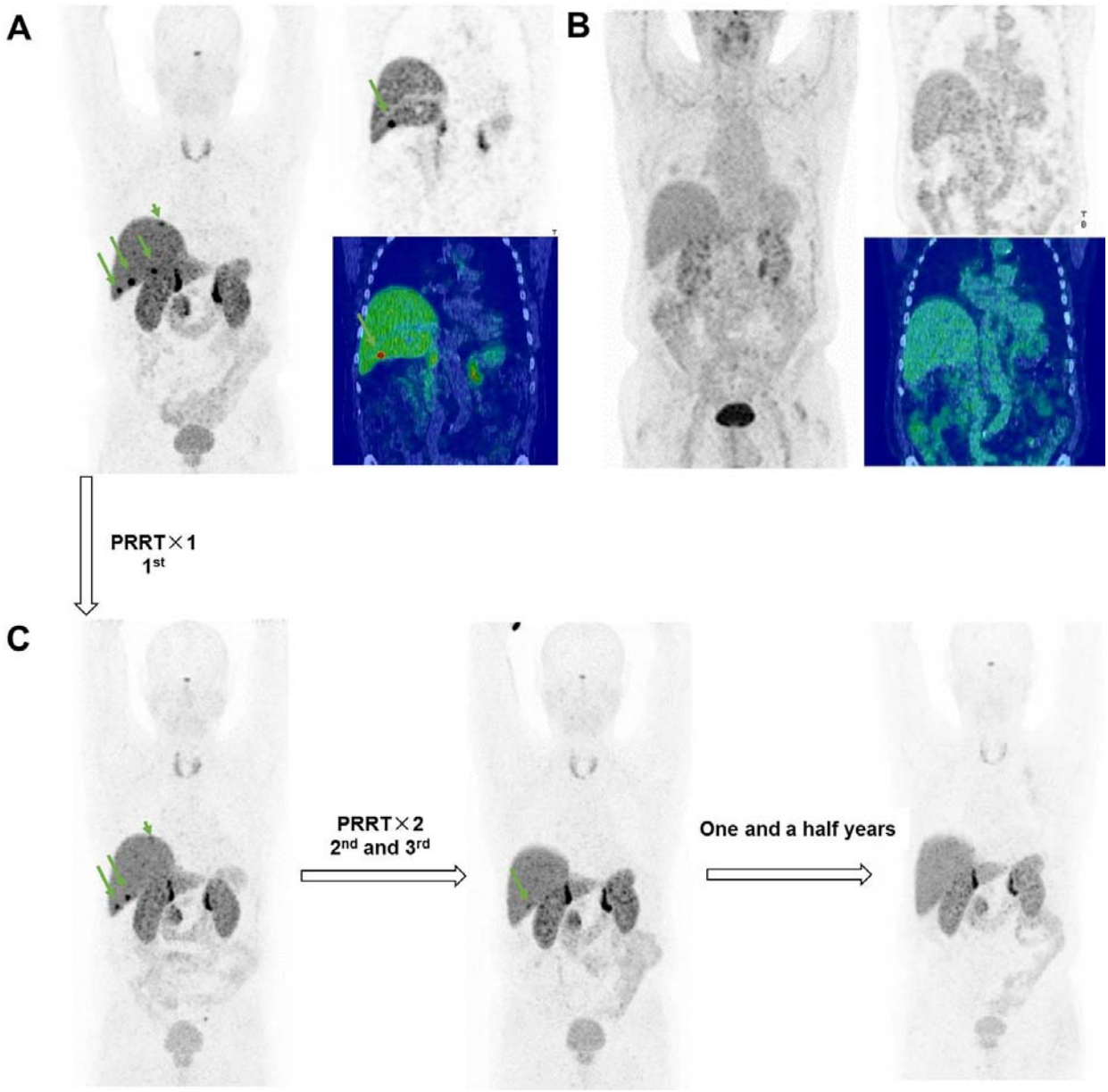

FIGURE 6. A 71-year-old woman with a metastatic pancreatic NEN and Ki-67 of 25% had undergone pancreatic tail resection with splenectomy and adhesiolysis, and progressed after eight cycles of chemotherapy with cisplatin and etoposide within a 6-month period. MIP (A, left) and coronal (A, right) ^{68}Ga-SSTR PET/CT showed somatostatin receptor expression in liver metastases with maximum SUV of 40.0. MIP (B, left) and coronal (B, right) ^{18}F-FDG PET/CT showed no significant FDG hypermetabolism in the liver metastases, and a complete mismatch

between ^{68}Ga-SSTR and ^{18}F-FDG at baseline. She was treated with three cycles of ^{177}Lu-DOTATOC PRRT with a cumulative administered radioactivity of 21.8 GBq. A restaging scan at 3 months showed a significant response (partial remission) (C, left) in the liver metastasis and complete remission on a longer follow-up (C, middle-right), with a progression-free interval of 32 months from first cycle of PRRT.

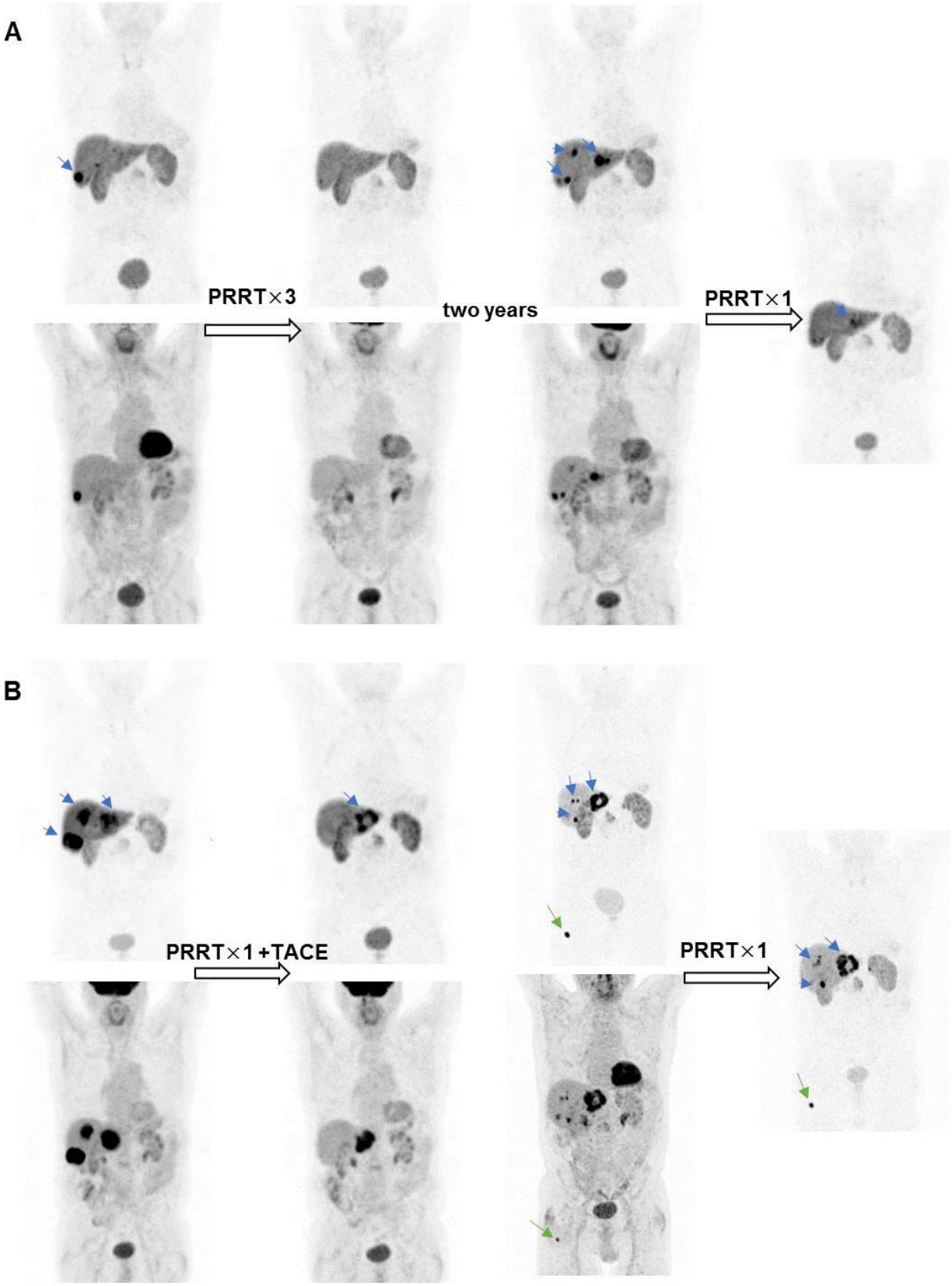
A
PRRT×3
two years
PRRT×1
B
PRRT×1+TACE
PRRT×1

FIGURE 7. Serial ^{68}Ga-SSTR PET/CT and ^{18}F-FDG PET/CT MIP images of a 77-year-old man with pancreatic NEN and liver metastasis, and Ki-67 proliferation index of 30% for the primary tumor. Previous treatments were left pancreatectomy, splenectomy, atypical partial gastrectomy, resection of the left colonic flexure, liver metastasis resection and cholecystectomy, gastric fundus resection, radiofrequency ablation (RFA) of liver metastasis and peritoneal adhesiolysis from 2006 to 2008. (A) Baseline (left) ^{68}Ga-SSTR PET/CT showed somatostatin receptor expression in liver metastases with a maximum SUV of 26.0, and significant hypermetabolism was noted on ^{18}F-FDG PET/CT. After 3 cycles of PRRT, there was a good response (partial remission) with a significant reduction of the hepatic tumor burden on both ^{68}Ga-SSTR and ^{18}F-FDG PET/CT. This disease was stable with a progression-free interval of 32 months. He progressed in 2011 with multiple liver metastases (arrows, blue), and was further treated with one cycle of ^{177}Lu-DOTATATE PRRT, which again revealed a significant regression of the hepatic metastases (right). (B) After a PFS of 19 months, the patient progressed in 2013 with multiple liver metastases (left), which was apparent as a match between the ^{68}Ga-SSTR and the ^{18}F-FDG PET/CT. He then underwent a combined treatment with ^{177}Lu-DOTATATE PRRT and TACE. A restaging scan showed marked partial response in the hepatic metastases. After a short PFS of 10 months, new bone metastases in the right femur was detected on both ^{18}F-FDG and ^{68}Ga-DOTATATE PET/CT (arrows, green), and he was treated with the another cycle of PRRT in 2015. In all, this patient received 6 cycles of PRRT with a cumulative administered radioactivity of total 24.5 GBq of ^{177}Lu-DOTATATE/TOC and 7.5 GBq of ^{90}Y-DOTATATE before he died of disease progression seven and a half years from first cycle of PRRT.

TABLE 1. Demographic and baseline clinical characteristics of patients with grade 3 (G3) NEN (n=69)

Characteristic	N=69	
	Number	%
Sex		
Male	41	59.4
Female	28	40.6
Age - yr	58.1±12.9	
Primary tumor site		
CUP	11	15.9
Pancreas	46	66.7
Stomach	3	4.3
Midgut	6	8.7
Rectum	3	4.3
Differentiation		
Well	11	15.9
Moderately	3	4.3
Poorly	28	40.6
NA	27	39.1
Primary tumor resected		
Yes	25	36.2
No	44	63.8
Ki-67%		
≤55	54	78.3
>55	11	15.9
NA(>20)	5	5.8
Primary treatment before PRRT		
SSA	17	40.2
Chemotherapy	35	50.7
-Temozolomide	4	5.8
-Capecitabine/5FU	13	18.8
-Streptozotocin	5	7.2
-Doxorubicin	4	5.8
-Cisplatin	14	20.3
-Carboplatin	8	11.6
-Etoposide	16	23.2
-Oxaliplatin	3	4.3
-Gemcitabine	3	4.3
-ACO (Adriamycin, Cyclophosphamid, Vincristin)	2	2.9
-Adriamycine, Vincristine, Actinomycine	1	1.2
Interferon	2	2.9

Surgery	34	49.3
Liver-directed therapy	11	15.9
-RFA	2	2.9
-TACE	7	10.1
-Embolization	2	2.9
-SIRT(Radioembosization)	5	7.2
External beam radiotherapy	5	7.2
PET imaging (baseline)		
SSTR imaging	69	100.0
^{68}Ga-SSTR PET	61	88.4
Octreoscan	8	11.6
SSTR imaging uptake		
Grade 1 (=liver)	0	0.0
Grade 2 (liver<SUVmax≤15)	13	18.8
Grade 3 (15<SUVmax<20)	10	14.5
Grade 4 (SUVmax>20)	38	55.1
Octreoscan (Krenning score >/=3)	8	11.6
FDG avidity		
Grade 0 (none-minor uptake)	9	13.0
Grade 1 (<liver)	4	5.8
Grade 2 (=liver)	1	1.4
Grade 3 (liver<SUVmax≤10)	16	23.2
Grade 4 (SUVmax>10)	29	42.0
NA	10	14.5

TABLE 2. Treatment cycles and cumulative administered radioactivity for Lu-177-, Y-90- and DUO -PRRT (N=69)

			Cumulative radioactivity (N=69)	
	N	%	Mean	SD
Number of PRRT cycles (N=69)				
1	13	18.8	4.3	2.0
2	16	23.2	11.6	3.9
3	12	17.4	16.0	5.4
4	9	13.0	21.0	6.3
5	10	14.5	30.3	5.6
6	6	8.7	32.1	9.5
7	2	2.9	38.2	2.4
8	1	1.4	46.9	/
Number of ^{177}Lu-PRRT cycles (N=29)				
1	6	8.7	6.2	2.1
2	9	13.0	13.6	4.7
3	5	7.2	21.0	7.8
4	3	4.3	23.7	9.9
5	5	7.2	33.5	11.8
6	1	1.4	41.7	/
7	0	0.0	0.0	0.0
8	0	0.0	0.0	0.0
Number of ^{90}Y-PRRT cycles (N=16)				
1	7	10.1	3.2	1.2
2	4	5.8	7.4	2.7
3	3	4.3	9.5	3.7
4	1	1.4	7.3	/
5	0	0.0	0.0	0.0
6	1	1.4	19.0	/
7	0	0.0	0.0	0.0
8	0	0.0	0.0	0.0
DUO PRRT with ^{177}Lu and ^{90}Y (N=24)				
2	3	4.3	10.2	4.8
3	4	5.8	14.6	5.8
4	5	7.2	22.2	8.6
5	5	7.2	27.0	10.6
6	4	5.8	33.0	13.9

7	2	2.9	38.2	/
8	1	1.4	46.9	/

TABLE 3. Treatment response at 3 months post-PRRT (N=55)

Response at 3 months post-PRRT (N=55)	Ki67 ≤ 55%		Ki-67 > 55%		Total	
	N	%	N	%	N	%
SSTR imaging response	N=50		N=5		N=55	
CR	0	0	0	0	0	0
PR	26	52	1	20	27	49.1
SD	11	22	1	20	12	21.8
PD	12	24	3	60	15	27.3
Mixed response	3	6	0		3	5.5
DCR	37	74	2	40	39	70.9
CT and/or MRI response	N=50		N=5		N=55	
CR	0	0	0	0	0	
PR	17	34	0	0	17	30.9
SD	24	48	2	40	26	47.3
PD	9	18	3	60	12	21.8
DCR	41	82	2	40	43	78.2