Patient Selection for Personalized Peptide Receptor Radionuclide Therapy Using Ga-68 Somatostatin Receptor PET/CT

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KEYWORDS

• Ga-68 • PRRT • Somatostatin receptors

KEY POINTS

- Neuroendocrine tumors (NETs) are malignant solid tumors originating from neuroendocrine cells dispersed throughout the body.
- Differentiated NETs overexpress somatostatin receptors (SSTRs), which enable the diagnosis using radiolabeled somatostatin analogues.
- Internalization and retention within the tumor cell are important for peptide receptor radionuclide therapy (PRRT). Use of the same DOTA peptide for SSTR PET/CT using ^{68}Ga and for PRRT using therapeutic radionuclides like ^{177}Lu and ^{90}Y offers a unique theranostic advantage.
- This forms the basis for the role of ^{68}Ga-SSTR PET/CT not only in patient selection for PRRT but also for prognostication, assessment of therapeutic response, and long-term follow-up after PRRT.

HOW DOES SUV RELATE WITH SSTR DENSITY?

PET imaging enables a semi-quantitative analysis of the tracer uptake with standardized uptake values (SUVs).[1,2] It is independent of the amount of injected activity rather a function of time. Our group (Kaemmerer and colleagues[3]) aimed to clarify if there was a correlation between somatostatin receptor (SSTR) PET/CT, using the SUV as a parameter of the SSTR density in gastroenteropancreatic (GEP-NETs) and/or its metastases, and the expression intensity of the 5 SSTR subtypes in surgically removed GEP-NET tissue, evaluated by immunohistochemistry (IHC). Therefore, this study aimed to accurately quantify the SSTR distribution of all 5 SSTR subtypes in different GEP-NETs using IHC. The preoperative ^{68}Ga-SSTR PET/CT was analyzed in 34 histologically documented GEP-NET patients. A total of 44 surgical specimens were generated. Only lesions greater than 1.5 cm on PET/CT were selected to avoid partial volume effect on the semi-quantitative parameters. The IHC scores for SSTR2A and SSTR5 correlated significantly with the SUV_{max} on the PET/CT, whereas only SSTR2A IHC score correlated significantly with SUV_{mean} and CgA staining as well as inversely with the tumor grade.

Miederer and colleagues[4] compared a score of SSTR2 IHC with the in vivo SUV of preoperative or prebiopsy ^{68}Ga-DOTATOC PET/CT in 18 patients. They noted that negative IHC scores were

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consistent with SUV values less than 10 and all specimens with a score of 2 and 3 corresponded with high SUVs (>15). They concluded that because there was a good correlation between SSTR2-IHC scores and SUVs, SSTR2-IHC analysis in patients missing a preoperative PET scan could indicate ^{68}Ga-DOTATOC-PET/CT as method for restaging and follow-up in individual patients. Müssig and colleagues[5] also showed the association of SSTR 2 immunohistochemical expression with ^{111}In-DTPA octreotide scintigraphy and ^{68}Ga-DOTATOC PET/CT in NETs. Boy and colleagues[6] measured the ^{68}Ga-DOTATOC SUV_{max} of normal tissues in 120 patients. Expression of SSTR subtypes 1 to 5 was measured independently in pooled adult normal human tissue by real-time reverse transcriptase polymerase chain reaction. SUV_{max} values exclusively correlated with SSTR 2 expression at the level of mRNA.

IMPACT OF ^{68}GA-SSTR PET/CT ON MANAGEMENT OF NETS

Peptide receptor radionuclide therapy (PRRT) is an effective treatment option for metastasized progressive well-differentiated NETs[1]. ^{68}Ga-SSTR PET/CT provides in vivo histopathology by quantification of the SSTR expression (receptor density) in NETs by the SUV measurement.[3] Thus the way to personalized medicine starts with tissue sampling followed by histopathological analysis, which should consist of grading (ie, based on proliferation rate Ki-67/MIB 1 index), staining for chromogranin A, and synaptophysin, and quantification of the SSTR density on tumor cells. Based on these data, the most appropriate peptide (DOTA-TOC/TATE, broad spectrum agonist, or an antagonist) can be selected for SSTR PET/CT. The theranostic advantage of using the same peptide allows for patient selection and also to predict the effectiveness of PRRT (depending on the strength of uptake) (**Figs. 1** and **2**). The determination of size on CT and MRI alone is not reliable enough because of the possibility of cystic degeneration of metastases. In addition, assessment of the tumor burden (localized disease vs distant metastases) by SSTR PET/CT guides the therapeutic options. For example, localized, bulky liver metastases can be effectively managed by intra-arterial PRRT, although partial hepatectomy and hepatic transplantation are also options. The amount of radioactivity to be administered as well as the

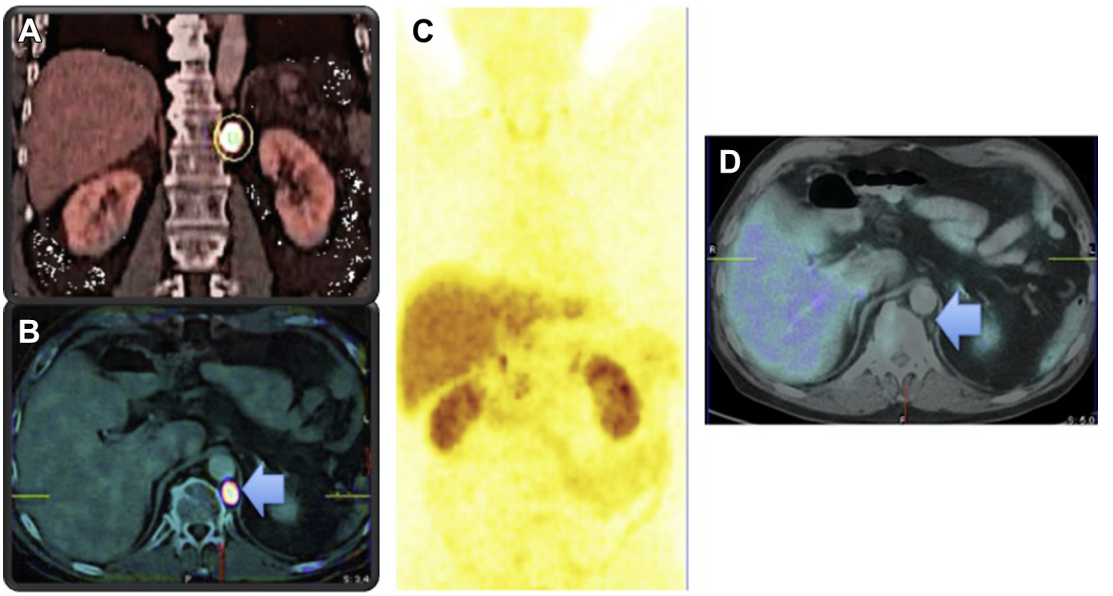

Fig. 1. A 66-year-old patient with well-differentiated, nonfunctioning NET of the pancreas, status post left pancreatectomy, splenectomy, and also metastasectomy in segment 2 of the liver was referred for follow-up ^{68}Ga-SSTR PET/CT after surgery, which revealed a single, very intensely SSTR-positive retrocrural lymph node metastasis with an SUV of 152. Based on this, he underwent 2 cycles of PRRT with 14 GBq ^{177}Lu-DOTATATE. The very high receptor expression and uptake of ^{177}Lu and the resulting high dose delivered to the metastasis resulted in a complete remission according to molecular response criteria, after the 2 PRRT cycles. (*A*) Fused coronal ^{68}Ga-DOTATATE PET/CT before therapy and (*B*) fused transverse image before therapy showing the lymph node metastasis with a *circle* and *arrow*, respectively. (*C*) MIP image of ^{68}Ga-DOTATATE PET/CT after 2 therapy cycles and (*D*) corresponding fused transverse posttherapy image confirmed molecular complete remission, although a small lymph node (*arrow*) is still noted on the CT, which remained stable in size over the next years of follow-up.

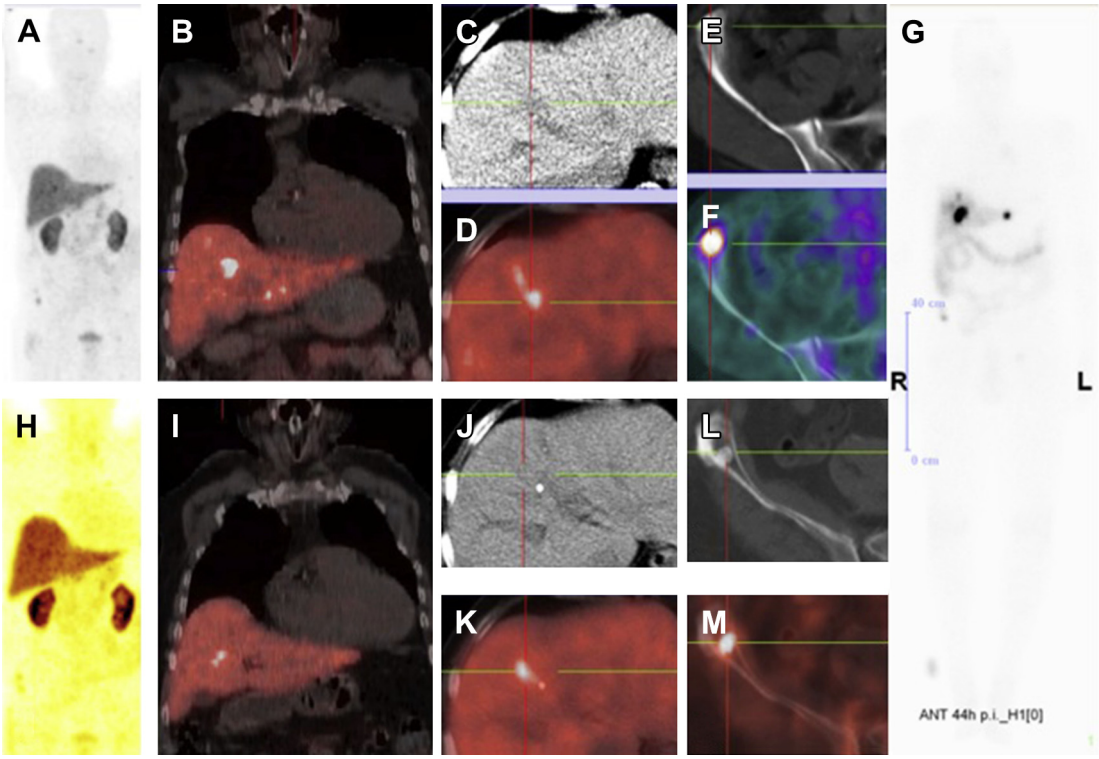

Fig. 2. A 56-year-old man with well-differentiated, nonfunctioning ileal NET status post surgery and 2 cycles of PRRT with ^{90}Y-DOTATOC (performed elsewhere) with complete remission of the hepatic metastases thereafter was referred to the authors' center 5 years after the second PRRT cycle with progressive disease and development of hepatic and osseous metastases. He underwent 2 further cycles of PRRT with a total administered activity of 8 GBq ^{177}Lu-DOTATATE, resulting in a good response of the hepatic metastases (near-complete remission) and of the lesion in right iliac bone (partial remission). (*A–F*, ^{68}Ga-DOTATATE PET/CT images before therapy; *G*, ^{177}Lu-DOTATATE whole-body planar scan 44 hours post-PRRT1; *H-M*, ^{68}Ga-DOTATATE PET/CT images after 2 PRRT cycles; *A* and *H*, MIP; *B* and *I*, fused coronal images; *C* and *J*, transverse CT, and *D* and *K*, fused transverse PET/CT images of liver; *E* and *L*, transverse CT, and *F* and *M*, fused transverse PET/CT images showing metastasis in the right ilium).

timing of PRRT using ^{177}Lu- or ^{90}Y-DOTATATE or DOTATOC depends on - among other factors - the semi-quantitative interpretation of ^{68}Ga-SSTR PET/CT.

Curative treatment of localized NETs is possible by complete surgical resection of the primary tumor with accompanying regional lymph node metastases. However, in advanced disease with metastases, palliative therapies can be administered, taking into account the tumor stage, size, localization, and degree of differentiation. The options available apart from PRRT are surgery, somatostatin (SMS) analogues, immunologic therapy (interferon), targeted therapy with kinase inhibitors, radiofrequency ablation, and transarterial chemoembolization as well as chemotherapy (in pancreatic NETs and fast-growing grade 3 neuroendocrine carcinomas). Receptor PET/CT also helps in therapy stratification and, for example, excluding PRRT as a therapy option when chemotherapy or molecular therapy in the case of inadequate receptor expression is indicated for the selection of patients for local therapy (radiofrequency ablation/trans-arterial chemoembolization) of localized liver disease, and so on.

^{111}In-octreotide has been considered to be the gold standard for the diagnosis of NETs.[7] However, there are several reasons to think that this method will gradually become the "old" standard because the development of novel SMS analogues for labeling with ^{68}Ga has revolutionized the diagnostics of NETs by high specific targeting and paved the way to theranostics. A recent meta-analysis showed its patient-wise pooled sensitivity to be 93% and specificity 91%.[8] As early as in 2001, Hofmann and colleagues[9] had demonstrated that ^{68}Ga-DOTATOC was superior to ^{111}In-octreotide SPECT in detecting upper abdominal metastases. Similarly for the detection of metastases in lungs, bone, liver, and brain ^{68}Ga-DOTATOC PET/CT had a clear edge over ^{111}In-DTPAOC, shown by Buchmann and

colleagues.[10] On a per patient basis, ^{68}Ga-DOTATOC PET (96%) was also found to be more accurate than CT (75%) and ^{111}In-DOTATOC SPECT (58%).[11] Also regarding the sensitivity,[12] ^{68}Ga-DOTATOC PET fared better than ^{111}In-octreotide especially in detecting small tumors or tumors bearing only a low density of SSTRs. In patients with equivocal or negative Octreoscan, ^{68}Ga-DOTATATE PET/CT detected additional lesions and changed management of the disease, notably in 36 patients (70.6%), who were subsequently deemed suitable for PRRT.[13] ^{68}Ga-DOTANOC PET/CT had a significant impact on the therapeutic management, with incremental value over conventional imaging (CT and EUS), affecting either stage or therapy in 50 of 90 (55.5%) patients.[14] The noteworthy and also the most frequent impact on management was either initiation or continuation of PRRT. SSTR PET could also exclude 2 patients from treatment with SMS analogues because the lesions did not express SSTR and could also avoid unnecessary surgery and the accompanying morbidity in 6 patients.

In pulmonary NETs as well, ^{68}Ga-DOTATATE was shown to have a definite incremental value over ^{18}F-FDG for typical bronchial carcinoids and not in atypical carcinoids or higher grades of tumors,[15] Demonstrating the value of SSTR PET/CT for appropriate patient selection for PRRT, namely those with metastatic typical carcinoids. The probability of the presence and/or development of concomitant GEP-NETs should also be borne in mind, which then could be handled in time with PRRT if necessary. SSTR PET/CT with ^{68}Ga should also therefore be used for the long-term follow-up of pulmonary NETs.[16]

In a bicentric study, the role of ^{68}Ga DOTANOC PET/CT was found to be highly superior to ^{111}In-Octreoscan and CT for the detection of an unknown primary (Cancer of unknown Primary [CUP]-NETs).[17] The maximum SUVs of CUP-NETs were also compared with those of known pancreatic NETs and ileal/jejunal/duodenal NETs (small intestinal NETs). Interestingly, the SUV_{max} of the previously unknown pancreatic NETs and small intestinal NETs were significantly lower ($P<.05$) than SUV_{max} of known primary tumors. Ten percent of the patients were operated based on ^{68}Ga-SSTR PET/CT, although in most patients, the primary tumors were not operated because of the presence of distant metastases. These patients could be the candidates for PRRT.

An important difference between ^{68}Ga-SSTR PET/CT and SRS using ^{111}In-pentetreotide is the quantitative assessment of SSTR density before PRRT, rather than just looking at the images. PET/CT enables accurate determination of the disease burden and quantifies the receptor density on tumor cells. Therefore, the next step after patient selection is the planning of PRRT. Prasad and Baum[18] demonstrated the biodistribution of ^{68}Ga-DOTANOC in normal tissues and tumors, which revealed a very wide variation (**Table 1**), emphasizing the importance of determining SUVs for an accurate assessment of disease.

ADDITIONAL ROLE OF FDG PET/CT

Well-differentiated tumors generally do not have significant glucose hypermetabolism. ^{18}F-FDG PET/CT has a role in metabolically highly active tumors and is recommended as a routine investigation for the diagnosis and staging of G3 NETs (**Fig. 3**). However, ^{18}F-FDG PET may also have a role in the assessment of prognosis before PRRT. A correlation between the proliferation rate and detection with ^{18}F-FDG has been demonstrated. Severi and coworkers[19] showed that FDG-PET evaluation is useful for predicting response to PRRT (using ^{177}Lu-DOTATATE) in patients with grade 1/2 advanced NETs. In this study, none of the PET-negative patients had progressed at the first follow-up examination after PRRT. On the other hand, grade 2 and PET-positive NET (arbitrary SUV cutoff >2.5) were frequently associated with more aggressive disease. Indeed 32% of the PET-positive patients with grade 2 NET did not respond to PRRT monotherapy, which led to the

Table 1
Variation of uptake on ^{68}Ga-SSTR PET/CT

Organ	Range
Pituitary	0.8–7.6
Thyroid	0.6–11.4
Lung	0.2–1.8
Liver	4.2–13.4
Spleen	7.2–48.5
Adrenal	2.4–13.9
Kidney	4.1–21.5
Intestine	0.9–4.3
Gluteal	0.4–2.2
Femur	0.4–1.9
Blood pool	0.8–3.9
Uncinate process of pancreas	4–9.7
Tumor	1.6–152

Data from Prasad V, Baum RP. Biodistribution of the Ga-68 labeled somatostatin analogue DOTA-NOC in patients with neuroendocrine tumors: characterization of uptake in normal organs and tumor lesions. Q J Nucl Med Mol Imaging 2010;54:61–7.

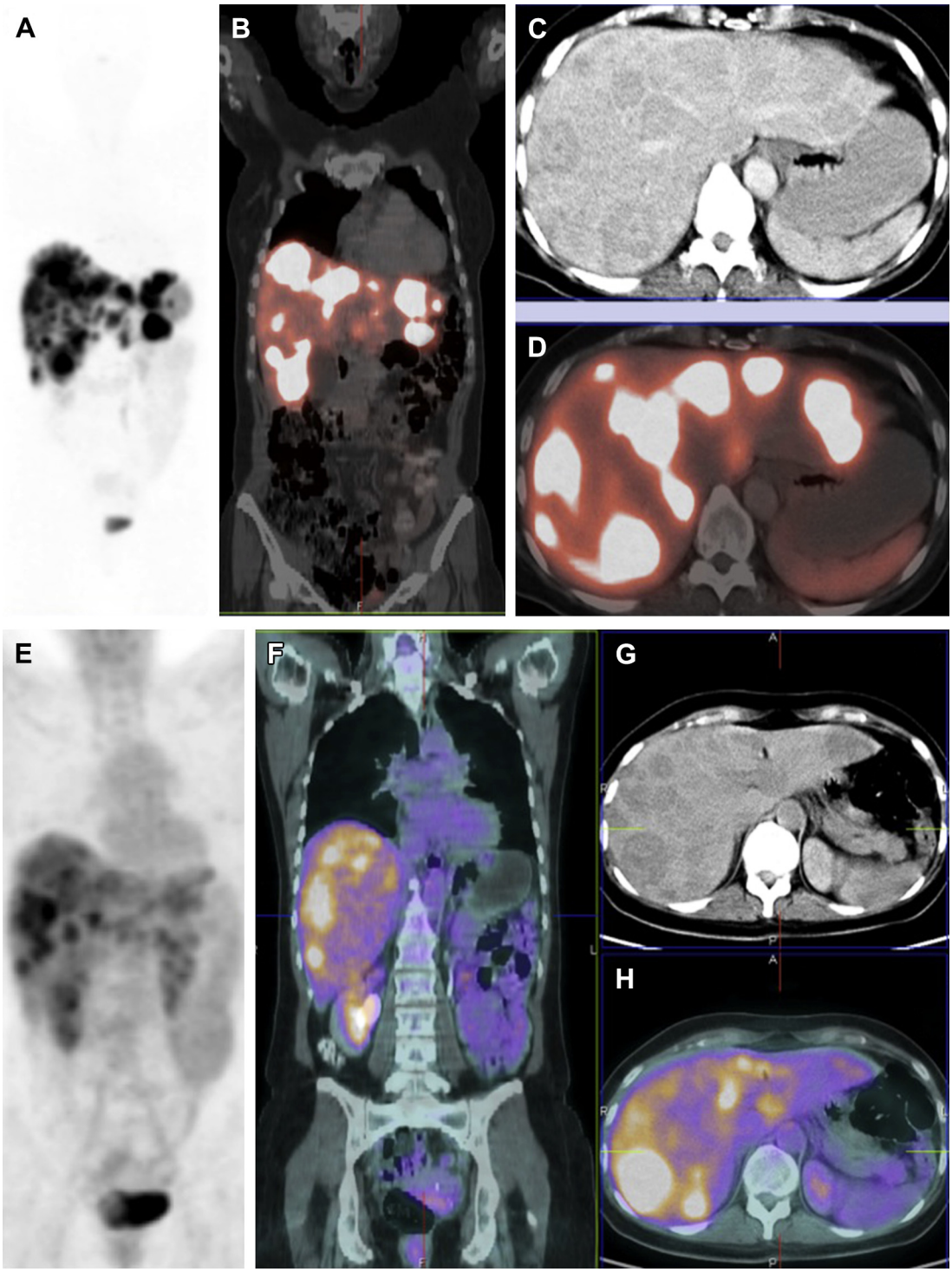

Fig. 3. A 45-year-old female patient with a poorly differentiated (G3), nonfunctional neuroendocrine carcinoma of the pancreas with extensive liver metastases. The proliferation rate (Ki-67) of the tumor was 40% with expression of chromogranin A, synaptophysin, and CD 56. She had undergone chemotherapy with Carboplatin and Etoposide, however, with poor results and progressive leucocytopenia. Both ^{68}Ga-DOTATOC SSTR PET/CT as well as ^{18}F-FDG PET/CT were performed to assess the option of PRRT and to evaluate the prognosis, respectively. Despite a high grade of the tumor, there was a very high SSTR expression by the disseminated hepatic metastases, with an SUV_{max} of 71.7. No extrahepatic metastases were seen. Notably, ^{18}F-FDG PET/CT showed a complete matched finding with glucose hypermetabolism of the liver metastases (SUV_{max} of 9.9). With high SSTR expression by the liver metastases, the indication for PRRT was confirmed, which was further demonstrated by the high uptake of ^{177}Lu-DOTATOC (after the first PRRT cycle) in the metastases. ^{68}Ga-DOTATOC PET/CT: (*A*) MIP; (*B*) fused coronal PET/CT; (*C*) transverse CT; (*D*) fused transverse PET/CT. ^{18}F-FDG PET/CT: (*E*) MIP; (*F*) fused coronal PET/CT; (*G*) transverse CT; (*H*) fused transverse PET/CT. ^{177}Lu-DOTATOC whole-body planar image post-therapy: (*I*) anterior view; (*J*) posterior view.

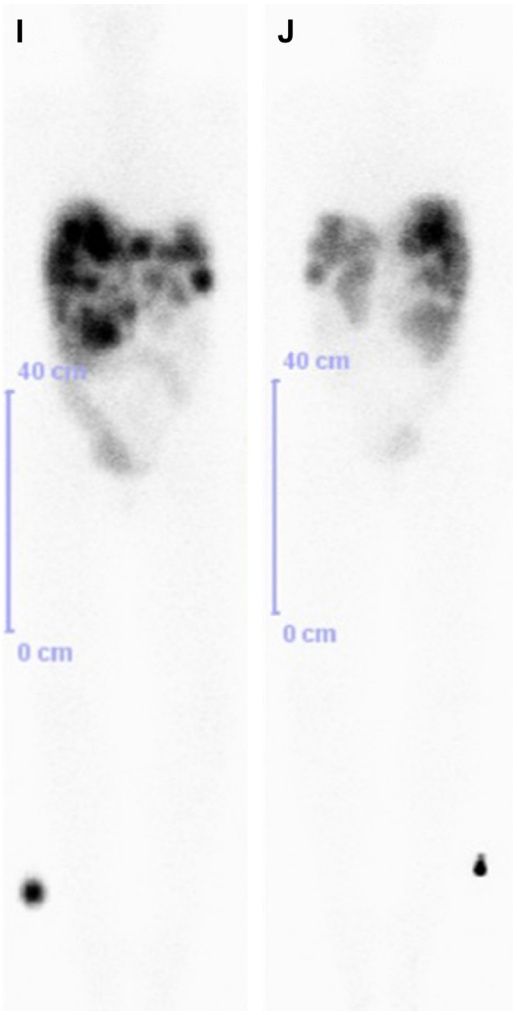

Fig. 3. (*continued*)

conclusion that these patients might benefit from more intensive therapy protocols, such as the combination of chemotherapy and PRRT.

PRETHERAPEUTIC SUVS AND POSTTHERAPEUTIC RESPONSE

Pauwels and coauthors[20] assessed tumor dose-response relationship in 13 patients treated with ^{90}Y-DOTATOC. Tumor volumes were assessed by CT before and after treatment. Tumor dose estimates were derived from CT scan volume measurements and quantitative ^{86}Y-DOTATOC imaging performed before treatment. A good correlation was found between ^{86}Y-DOTATOC dosimetry and treatment outcome. Importantly, a tumor size reduction was always seen with a tumor dose of more than 100 Gy, confirming a tumor dose-response relationship in PRRT.

We presented preliminary results also indicating a relationship between the radiation dose delivered to liver metastases and the molecular response post-PRRT as measured by SSTR PET/CT.[21] Ninety-six liver metastases were analyzed in 67 patients with well-differentiated NETs, undergoing PRRT with 4.8 to 7.5 GBq of ^{177}Lu-DOTA-TOC/-TATE followed by 5 whole-body planar scintigraphies after therapy for dosimetry. Pre- and posttherapy SSTR PET/CT with ^{68}Ga-DOTA-TOC/-TATE were performed to evaluate molecular response to therapy. Liver metastases were divided into 2 groups based on the response according to molecular imaging criteria: partial response (ie, 15% or more fall in SUV_{max} [group 1]) and progressive disease (ie, 25% or more increase in the SUV_{max} [group 2]). Logarithmic increase in molecular response was observed with increasing mean absorbed dose to tumor. Doses delivered (mean/median) to lesions showing a therapy response (143 Gy/79 Gy) were significantly higher than doses to lesions showing minor progression or progressive disease (23 Gy/20 Gy).

Ezziddin and colleagues[22] investigated the correlation between the pretherapeutic tumor SUV in ^{68}Ga-SSTR PET/CT using DOTATOC, and the mean absorbed tumor dose during subsequent PRRT using ^{177}Lu- DOTATATE; this was a retrospective analysis of 21 NET patients with 61 evaluable tumor lesions undergoing both pretherapeutic ^{68}Ga-DOTATOC-PET/CT and PRRT with ^{177}Lu-DOTATATE. The SUVs were compared with tumor-absorbed doses per injected activity (D/A0) of the subsequent first treatment cycle. There was a significant correlation between both, SUV_{mean} and SUV_{max} on the one hand, and the D/A0. Pancreatic origin and hepatic localization were associated with higher D/A0. Chromogranin A level and Ki-67 index had no influence on SUV or D/A0, whereas high-SUV lesions resulted in high D/A0. The authors concluded that SSTR PET imaging may predict the mean absorbed tumor doses, and therefore, could aid in selection of appropriate candidates for PRRT. Keeping the dose-response relationship in mind, this study indicates that the pretherapeutic SUVs could predict the response to PRRT. However, a recently published study indicated a poor correlation between SUV and the tumor dose, and the linear regression analysis provided R2 values, which explained only a small fraction of the total variance. It was concluded that the SUVs derived from ^{68}Ga-SSTR PET/CT images should be used with caution for the prediction of tumor dose on ^{177}Lu-PRRT, as there was a large intra- and interpatient variability.[23]

The role of ^{68}Ga-SSTR PET/CT for the evaluation of prognosis of NETs has been investigated.

Table 2
Factors determining the Bad Berka Score for patient selection

Factor	Means of Determination
Tumor grade	Ki-67 index
Functional activity of the tumor/metastases	Biomarkers, symptoms
Time since first diagnosis and previous therapies	History
General status of the patient	Karnofsky performance score or Eastern Cooperative Oncology Group performance status scale, loss of weight
SSTR density	SUV on ^{68}Ga-receptor PET/CT
Glucose metabolism	^{18}F-FDG PET/CT
Renal functional assessment	Creatinine and blood urea nitrogen
Tubular extraction rate and elimination kinetics	^{99m}Tc-MAG3 scintigraphy
Glomerular filtration rate	^{99m}Tc-DTPA
Hematological status	Blood counts
Hepatic involvement and extrahepatic tumor burden	^{68}Ga-receptor PET/CT
Dynamics of the disease: doubling time, appearance of new lesions	Serial ^{68}Ga-receptor PET/CT

In a study of 47 patients, SUV_{max} was demonstrated to be significantly higher in patients with pancreatic NETs and in those with well-differentiated tumors.[24] On follow-up, stable disease or partial response was observed in 25 patients, and progressive disease in 19 patients. Stable disease or partial response was associated with a significantly higher SUV_{max} than was progressive disease, the best cutoff ranging from 17.9 to 19.3. At univariate and multivariate analysis, the significant positive prognostic factors were well-differentiated NET, a SUV_{max} of 19.3 or more, and a combined treatment with long-acting SMS analogues and radiolabeled SMS analogues. This study thus demonstrated that SUV_{max} correlates with the clinical and pathologic features of NETs and is also an accurate prognostic index.

Taking these factors into consideration, a scoring was devised at the ENETS Center of Excellence, Bad Berka to appropriately select patients for personalized PRRT (influencing decisions on the activity to be administered, number of fractions, time between fractions etc.) This score takes into account various clinical aspects and molecular features, depending on the above-mentioned prerequisites (**Table 2**).[25]

A multidisciplinary team of experienced specialists is required for the appropriate management of patients with NETs. The success of personalized PRRT is determined by appropriate choice of peptide and radionuclide, kidney protection (lysine, arginine, and gelofusine), tumor and organ dosimetry (posttreatment scans), and monitoring of toxicity (follow-up). Above all, appropriate patient selection is the cornerstone of PRRT and presently ^{68}Ga-SSTR PET/CT using SMS analogues has an unparalleled role.

Indications/Prerequisites for PRRT

- Well-differentiated NETs (G1 and G2)
- SSTR expression
- Documented progression of disease with metastasis (in certain cases with high tumor burden without progression might also be considered)
- Inoperability (however, also in neoadjuvant setting, to render an inoperable primary tumor operable)
- For symptomatic improvement in functional NET refractory to octreotide or lanreotide therapy
- Karnofsky index $\geq$60%
- Normal renal function and hematological status

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