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Inflammation-based index and ^{68}Ga-DOTATOC PET-derived uptake and volumetric parameters predict outcome in neuroendocrine tumor patients treated with ^{90}Y-DOTATOC

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Running title: Uptake, volume & IBI impact PRRT outcome

ABSTRACT

We performed post-hoc analyses on the utility of pre-therapeutic and early interim ^{68}Ga-DOTA-Tyr^{3}-octreotide (^{68}Ga-DOTATOC) positron emission tomography (PET) tumor uptake and volumetric parameters and a recently proposed biomarker, the inflammation-based index (IBI), for peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumor (NET) patients treated with ^{90}Y-DOTATOC in the setting of a prospective phase II trial.

Methods: Forty-three NET patients received up to four cycles of 1.85 GBq/m²/cycle ^{90}Y-DOTATOC with a maximal kidney biologic effective dose of 37 Gy. All patients underwent a ^{68}Ga-DOTATOC PET/computed tomography (CT) at baseline and seven weeks after the first PRRT cycle. ^{68}Ga-DOTATOC-avid tumor lesions were semi-automatically delineated using a customized standardized uptake value (SUV) threshold-based approach. PRRT response was assessed on CT using RECIST 1.1.

Results: Median progression-free survival (PFS) and overall survival (OS) were 13.9 and 22.3 months, respectively. An SUV_{mean} higher than 13.7 (75th percentile (P75)) was associated with better survival (hazard ratio (HR) 0.45; p=0.024), whereas a ^{68}Ga-DOTATOC-avid tumor volume higher than 578 ml (P75) was associated with worse OS (HR 2.18; p=0.037). Elevated baseline IBI was associated with worse OS (HR 3.90; p=0.001). Multivariate analysis corroborated independent associations between OS and SUV_{mean} (p=0.016) and IBI (p=0.015). No significant correlations with PFS were found. A composite score based on SUV_{mean} and IBI allowed to further stratify patients in three categories with significantly different survival. On early interim PET, a decrease in SUV_{mean} of more than 17% (P75) was associated with worse survival (HR 2.29; p=0.024).

Conclusion: Normal baseline IBI and high ^{68}Ga-DOTATOC tumor uptake predict better outcome in NET patients treated with ^{90}Y-DOTATOC. This can be used for treatment personalization. Interim ^{68}Ga-DOTATOC PET does not provide information for treatment personalization.

Keywords: PRRT, ^{68}Ga-DOTATOC, ^{90}Y-DOTATOC, neuroendocrine tumors, PET

INTRODUCTION

Peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogs (SSAs), such as ^{90}Y-DOTA-Tyr^3-octreotide (^{90}Y-DOTATOC) and ^{177}Lu-DOTA-Tyr^3-octreotate (^{177}Lu-DOTATATE), is an evidence-based, standard treatment in the management of patients with inoperable or metastasized well-differentiated neuroendocrine tumors (NETs) (*1,2*). This was recently confirmed by the randomized, controlled NETTER-1 trial (*3*). It is likely that in the future PRRT will be more widely used in the treatment of – probably clinically more heterogeneous populations of – NET patients (*4*) and predictive tools to adequately predict response will become increasingly important. However, sufficiently reliable predictors are still lacking. Recently, Bodei *et al.* (*4*) developed and validated a PRRT predictive quotient integrating blood-derived NET gene transcripts with tumor grade, and found it to be a highly specific predictor of PRRT efficacy. However, the need for polymerase chain reaction gene amplification and associated cost might restrict its general application in routine clinical practice. Another recently proposed biomarker for PRRT outcome prediction, is the inflammation-based index (IBI), which is easily derived from serum C-reactive protein (CRP) and albumin, and was reported to be associated with progression-free survival (PFS) and overall survival (OS) (*5*). Further validation in independent patient cohorts is needed.

Apart from blood biomarkers, also molecular imaging parameters may play a role in PRRT response prediction. Sufficient uptake on diagnostic SSTR imaging is an important prerequisite for PRRT (*2*) and was found to be correlated with higher tumor response rates (*6,7*) and OS (*8*). Several studies reported a high maximal standardized uptake value (SUV_{max}) on ^{68}Ga-DOTA-SSA (^{68}Ga-DOTATATE/DOTATOC/DOTA-1-Nal^3-octreotide (DOTANOC)) positron emission tomography (PET) to be predictive for PRRT treatment response (*9-11*), while others observed no significant association (*12,13*). Haug *et al.* (*14*) found that a decrease in ^{68}Ga-DOTATATE tumor

uptake after the first PRRT cycle, expressed in terms of change in tumor-to-spleen SUV ratio ($SUV_{T/S}$), predicted longer PFS. To our knowledge, this has not been further confirmed.

Another imaging parameter that could prove useful for PRRT outcome prediction, is tumor volume (TV). Recently, Tirosh *et al.* (*15*) observed that a high ^{68}Ga-DOTATATE-avid TV is independently associated with shorter PFS and higher disease-specific mortality in NET patients.

The aim of this study was to assess the utility of quantitative tumor uptake and volumetric measurements on pre-therapeutic and early interim ^{68}Ga-DOTATOC PET/computed tomography (CT), along with IBI in NET patients treated with ^{90}Y-DOTATOC.

MATERIALS AND METHODS

Patient Population

We performed retrospective, post-hoc analyses on data from our previous prospective phase II trial with ^{90}Y-DOTATOC (EUDRACT 2008-007965-22) (*16*). Fifty-seven consecutive patients (age 31-80 y), with histologically proven, metastatic NET were recruited between March 2009 and May 2012 in case of progressive disease or recurrent disease after conventional treatment. The main inclusion criteria were: sufficient SSTR expression on tumor cells (higher than on normal liver parenchyma) documented by ^{68}Ga-DOTATOC PET as well as a predicted biological effective dose (BED) to the kidneys less than 37 Gy after three cycles of ^{90}Y-DOTATOC determined by ^{111}In-DTPA-octreotide dosimetry (*17,18*). For details on the dosimetric assessment, we refer to (*17*). Patients not eligible for PRRT, because of insufficient SSTR expression (n = 3) or unacceptable pre-therapeutic kidney BED (n = 3), were excluded. Four patients died and one was progressive before the early interim ^{68}Ga-DOTATOC PET/CT. Two patients in whom PRRT was ended after one cycle because of aberrant biodistribution on early interim PET (*19*), and one patient with atypical disease presentation (multiple brain metastases without other tumor lesions,

possible metastatic spinal paraganglioma on pathology report) and low uptake values in whom PRRT was ended after two cycles, were not included either.

The 43 remaining patients (21 men, 22 women; 33 gastroenteropancreatic NETs (GEP-NETs), 4 NETs of unknown primary (CUP) and 6 NETs of other origin) were treated with up to four cycles of PRRT (1.85 GBq/m² of ^{90}Y-DOTATOC per cycle) every eight weeks with a maximal predicted kidney BED of 37 Gy (*17*). Table 1 presents the patient clinical data and tumor characteristics. Details regarding radiolabeling and administration of ^{90}Y-DOTATOC, can be found in (*17*).

The study was performed at University Hospitals Leuven after approval by the Institute's Ethics Committee and all subjects signed a written informed consent.

IBI Measurement

IBI was derived as previously described (*5,20*). Patients with normal CRP (< 10 mg/l) and albumin (> 35 g/l) levels were assigned score 0. If one of both parameters was abnormal, a score of 1 was allocated. Patients with elevated CRP and hypoalbuminemia received score 2.

Blood samples were collected at baseline within one week prior to PRRT. Serum chemistry tests included CRP and albumin.

^{68}Ga-DOTATOC PET/CT Scans

All patients underwent a ^{68}Ga-DOTATOC PET/CT before PRRT (baseline), seven weeks (early interim) and 40 weeks (post-therapeutic; n = 30) after the first PRRT cycle. The median interval between baseline PET/CT and the first treatment cycle was five weeks (range: 1-22 weeks). For details on the ^{68}Ga-DOTATOC synthesis, we refer to (*16*).

All PET/CT scans were acquired with a Siemens Biograph 16 slice HiRez LSO PET/CT system (Siemens Medical, Erlangen, Germany). Patients on SSA therapy interrupted treatment 12 to 24 hours before scanning, for short-acting SSAs, or four to six weeks before scanning, for

long-acting SSAs. Approximately 30 minutes after injection of 185 MBq ^{68}Ga-DOTATOC, whole-body PET/CT images from head to mid-femur were acquired, as specified in (*16*). Iterative reconstruction of the PET data was done by means of ordered subsets expectation maximization (OSEM, 5 iterations, 8 subsets) using an in-plane post-reconstruction Gaussian smoothing kernel of 6 mm full-width half-maximum.

Quantitative Measurements on ^{68}Ga-DOTATOC PET/CT Scans

Based on the methodology of Tirosh *et al.* (*15*), ^{68}Ga-DOTATOC-avid tumor lesions were semi-automatically delineated using the MIM software v6.7.6 (MIM Software Inc, Cleveland, Ohio, US) (Fig. 1). First, a volume of interest (VOI) containing the whole-body PET image was drawn. Then, an SUV threshold was applied to segment the whole-body VOI. The SUV threshold was customized per patient through visual inspection and comparison of multiple automatically generated segmentations of the whole-body VOI using different threshold values. Resulting VOIs smaller than 0.1 ml were automatically removed. To avoid over- or underestimation of tumor volumes, images were individually scaled from 0 to 2/3 of the tumor SUV_{max}. Subsequently, all regions of physiologic ^{68}Ga-DOTATOC uptake or non-disease related uptake were manually removed. Furthermore, small, but definite tumor lesions with low ^{68}Ga-DOTATOC uptake, missed by the initial segmentation were manually delineated using the PET Edge® tool (*21*). Finally, the union of the resulting VOIs, containing all ^{68}Ga-DOTATOC-avid tumor lesions, was determined from which SUV_{max}, SUV_{mean}, TV and total lesion activity (TLA) were automatically calculated. The latter is derived by multiplying the mean SUV of a VOI by its volume.

Additionally, the spleen was delineated on all PET/CT images with the Region Grow tool and manually retouched. Dividing the tumor SUV_{max} by the spleen SUV_{max} allowed to calculate $SUV_{T/S}$, according to Haug *et al.* (*14*).

Response Evaluation after PRRT

Imaging follow-up was standardized and consisted of ^{68}Ga-DOTATOC PET/CT at 40 weeks after the first PRRT cycle, followed by six-monthly CT scans the first two years post-treatment and at the discretion of the treating physician as of two years. If disease progression was suspected during treatment, an additional CT scan was performed. Response was assessed on the CT images of the post-therapeutic scan using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) by an experienced radiologist. As such, patients were categorized as having controlled disease (stable disease, partial or complete response) or uncontrolled disease (progression).

PFS and OS were the endpoints and were calculated as the time between treatment start and disease progression at follow-up and as the time between treatment start and patient death. PFS was assessed on follow-up CT scans by an experienced radiologist. RECIST 1.1 criteria were used to determine whether patients had stable or progressive disease.

Statistical Analyses

Statistical analyses were performed using the Python packages SciPy (SciPy, RRID:SCR_008058) and lifelines (CamDavidsonPilon/lifelines:v0.14.6.). Kaplan-Meier survival curves with log-rank tests were used to compare PFS and OS between different groups. For continuous PET-derived values, subgroups were defined using the 25th, 50th and 75th percentile (P25, P50 and P75) as cut-off for dichotomization, yielding three comparisons between two subgroups. Uni- and multivariate Cox proportional hazards models were applied to estimate hazard ratios (HR) with 95% confidence intervals (95%CI). Baseline parameters were compared between patients with controlled and uncontrolled disease using the independent-samples t-test or Mann-Whitney U test in case of non-normality, as assessed by a Shapiro-Wilk test, or inequality of variances according to the Levene's test. For categorical baseline parameters, the Fisher's exact test was used. Uptake and volumetric measurements on baseline and interim PET were

compared using a paired sample t-test or Wilcoxon matched-pairs test in case of non-normality. Two-sided p-values less than 0.05 were considered statistically significant.

RESULTS

Response Assessment and Survival

Median PFS and OS were 13.9 months (range: 1.6-68.6) and 22.3 months (range: 3.0-97.4), respectively. Twelve patients (28%) were not able to perform the post-therapeutic PET/CT because of deterioration of the general condition due to progressive disease (3/13) or because of death due to progression (9/13). For one patient the post-therapeutic scan was not available and this patient was consequently left out of the response assessment. In the remaining 30 patients, CT showed progressive disease in seven patients and stable disease in 23. No partial or complete responses were observed on CT. In summary, 23 patients out of 42 showed stable disease (55%) and 19 patients were progressive (45%), with a disease control rate of 55%. OS was significantly better in controlled than uncontrolled disease (HR 6.7, 95%CI 3.1-14.3; $p<0.001$) with a median OS of 37.4 versus 9.9 months, respectively. Baseline clinical and tumor characteristics are compared between the two groups in Supplemental Table 1.

Baseline Parameters and Survival

Baseline SUV_{max}, SUV_{mean}, TV, TLA and $SUV_{T/S}$ are provided in Table 2. No significant differences in PFS were found between the subgroups of these parameters. An SUV_{mean} higher than 13.7 (P75) was associated with better OS (HR 0.45; $p=0.024$), whereas a TV higher than 578 ml (P75) was associated with worse survival (HR 2.18; $p=0.037$) (Table 3; Fig. 2). The subgroups for SUV_{max}, TLA and $SUV_{T/S}$ showed no significant differences in OS.

Baseline IBI could be determined in 42 patients. Elevated baseline IBI was associated with worse OS (HR 3.90; $p=0.001$), but not with PFS ($p=0.132$) (Fig. 2). Multivariate analysis

corroborated independent associations between OS and SUV_{mean} (HR 0.40; p=0.016) and OS and IBI (HR 3.12; p=0.015), but not between OS and TV (p=0.13) (Table 3). However, if only PET parameters were taken into account, disregarding IBI, independent associations with OS were found for both SUV_{mean} (HR 0.45, 95%CI 0.22-0.91; p=0.027) and TV (HR 2.21, 95%CI 1.05-4.67; p=0.037).

Further, we developed a composite score based on baseline SUV_{mean} and IBI. Patients with high SUV_{mean} (> 13.7) and normal IBI received score 0. If SUV_{mean} was ≤ 13.7 and IBI elevated, they received score 2. If only one condition was met, they received score 1. Patients in category 2 showed significantly worse OS than patients in category 1 (p=0.007) and 0 (p<0.001) (HR 4.45; p=0.001), but also category 1 patients showed significantly worse OS than category 0 (p=0.025) (Fig. 3).

Patients with controlled disease showed a significantly higher baseline SUV_{max} (p=0.022) and SUV_{mean} (p=0.012) than those with uncontrolled disease (Supplemental Table 1). No differences were observed for TV, TLA and $SUV_{T/S}$. Also baseline IBI was not significantly different.

Interim Parameters and Survival

On interim PET, SUV_{max}, SUV_{mean} and TLA showed a small but significant decrease, whereas TV and $SUV_{T/S}$ remained unchanged (Table 2). Survival analysis of changes in these parameters between interim and baseline PET revealed no significant differences in PFS. A decrease in SUV_{mean} of more than 17% (P75) was associated with worse survival (HR 2.29; p=0.024) (Table 3; Fig. 2). No other significant associations with OS were found.

DISCUSSION

Median PFS and OS in our study population were 13.9 and 22.3 months, respectively, which are somewhat shorter than reported in other ^{90}Y-DOTATOC PRRT studies, but remain still in line with the literature (*1*). Head-to-head comparisons with other studies, especially on survival, should be interpreted carefully because of differences in study population (e.g. tumor burden, biological aggressiveness…) and PRRT protocol. On the other hand, we observed no partial or complete responses, while other studies observe at least a few partial responses (*1*). This might be explained by differences in population and PRRT protocol, but also by differences in the criteria used for response assessment, where often less stringent definitions than RECIST 1.1 have been used. Moreover, the Rotterdam group has shown that OS is not different in patients with objective response than in patients with stable disease (*6*).

A baseline SUV_{mean} higher than 13.7 was independently associated with better OS, in line with the findings by Imhof *et al.* (*8*) in 1109 NET patients treated with ^{90}Y-DOTATOC. On the other hand, no significant association was found for SUV_{max}. A possible explanation is that SUV_{mean} is a parameter taking into account the whole tumor volume, while SUV_{max} is not necessarily representative for all tumor lesions. In the literature, conflicting results have been published regarding the role of SUV on baseline ^{68}Ga-DOTA-SSA PET in PRRT response prediction. Koch *et al.* (*9*) identified a cut-off for SUV_{max} and SUV_{mean} of 29.4 and 20.3, respectively, to separate patients between long and short PFS (69 versus 26 weeks). Öksüz *et al.* (*10*) found that an SUV_{max} higher than 17.9 as cut-off for favorable outcome was able to predict response in all 20 responders and 15 out of 16 non-responders. Kratochwil *et al.* (*11*) proposed a mean SUV_{max} (from up to four liver metastases per patient) threshold of more than 16.4 to select patients for PRRT, with a sensitivity and specificity in predicting responding lesions of 95% and 60%, respectively. On the other hand, Gabriel *et al.* (*12*) and Soydal *et al.* (*13*) reported that SUVs on baseline ^{68}Ga-DOTA-SSA PET showed no additional value for PRRT response prediction. In all these studies, slightly

different methods were used to define SUV_{max}, which could explain the different results, and in none of them a full segmentation of all tumor lesions was performed. An uptake parameter, taking the whole tumor burden into account, such as SUV_{mean}, could be more suitable for PRRT response prediction. However, since in our study several patients with SUV_{mean} well below 13.7 showed a good PFS and OS, we would not suggest to use this value as threshold to deselect patients from PRRT, but rather consider this as a prognostic factor. Ezzidin *et al.* (*22*) concluded that ^{68}Ga-DOTATOC PET can predict tumor-absorbed doses, and in case of low SUV, and hereby insufficient target irradiation, can deselect inappropriate candidates for PRRT. More studies are needed to provide guidance on ^{68}Ga-DOTA-SSA uptake thresholds for patient selection for PRRT. A priority should be to define a threshold under which PRRT is deemed futile because of insufficient target dose.

In our study population, a baseline ^{68}Ga-DOTATOC TV higher than 578 ml was associated with worse survival. A recent publication reported on the utility of ^{68}Ga-DOTA-SSA-avid TV in a general population of 184 NET patients (*15*). The authors found that a ^{68}Ga-DOTATATE TV of 7.0 ml or more is independently associated with shorter PFS, while a ^{68}Ga-DOTATATE TV of 35.8 ml or more is independently associated with higher disease-specific mortality (*15*). However, these results cannot be extrapolated to our study population, which solely consists of PRRT patients with a much higher tumor burden. Further studies are warranted to evaluate the value of ^{68}Ga-DOTA-SSA-avid TV for PRRT patient stratification.

TLA was not found to be a useful parameter. This is not surprising, since TLA is derived by multiplying the mean SUV of a volume by the volume, while we observed opposite associations between survival and SUV on the one hand, and survival and TV on the other.

In line with the results of Black *et al.* (*5*), elevated baseline IBI was associated with worse survival. Due to the simplicity of this biomarker, it could readily be included in the pre-therapeutic assessment and help guide treatment decisions. Moreover, Black *et al.* (*5*) observed that

persistently elevated IBI throughout PRRT was associated with worse PFS and OS, and therefore could help identify patients who might have little benefit of treatment continuation.

We also found that a composite score, based on tumor uptake and IBI, allows further patient stratification in three groups with significantly different survival. Further validation of this score on external datasets and in a prospective setting is needed.

To our knowledge, there is only one study available on early interim PET-based response prediction for PRRT in NETs. Haug *et al.* (*14*) evaluated changes in SUV_{max} and $SUV_{T/S}$ on ^{68}Ga-DOTATATE PET three months after the first PRRT cycle and found that decreased uptake predicted longer PFS, with independent associations only for $SUV_{T/S}$. However, in our study a major decrease in terms of SUV_{mean} (> 17%) was associated with worse survival, while we found no significant associations for $SUV_{T/S}$. There are of course differences between our data and those of Haug *et al.*, most importantly regarding timing of the interim PET (7 weeks versus 3 months) (*14*). An important uptake decrease may be attributed to several different causes, such as decreased tumor perfusion, tumor dedifferentiation and cell death. All of these causes may lead to worse therapeutic efficacy for future PRRT cycles, the latter as a result of reduced bystander effect. However, with the conflicting results in mind, we do not believe that early interim PET during PRRT has a prognostic value or could justify changes in treatment strategy.

Limitations of our study include the relatively small sample size restricting statistical power, and the post-hoc nature of our analyses. Our patient cohort was very mature for survival analysis, since OS was known for all patients. On the other hand, accurate follow-up data was not always available after the first two years of follow-up. Therefore, the uncertainty on longer PFS values is larger. Furthermore, no partial-volume correction was used, resulting in underestimation of uptake in the smallest lesions. However, the influence on our results is deemed negligible, because of the high tumor burden in our study population. Finally, it should be noted that the generalizability of our findings to ^{177}Lu-DOTATATE needs to be confirmed, especially since ^{90}Y-DOTATOC is less routinely used in clinical practice.

CONCLUSION

Normal baseline IBI and high ^{68}Ga-DOTATOC tumor uptake (SUV_{mean} > 13.7) were independently associated with better survival, whereas high ^{68}Ga-DOTATOC-avid TV (> 578 ml) was associated with worse survival in NET patients treated with ^{90}Y-DOTATOC. Adding these parameters to the pre-therapeutic work-up may be helpful to guide treatment decisions, however none of these parameters should be used as the sole basis to deselect patients from PRRT. Early interim ^{68}Ga-DOTATOC PET did not allow to identify patients with poorer prognosis that would justify a change in treatment strategy.

CONFLICT OF INTEREST DISCLOSURE STATEMENT

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KEY POINTS

QUESTION: Are quantitative tumor uptake and volumetric measurements on pre-therapeutic and early interim ^{68}Ga-DOTATOC PET/CT, and inflammation-based index (IBI), useful for outcome prediction in NET patients treated with ^{90}Y-DOTATOC?

PERTINENT FINDINGS: Post-hoc analyses were performed on baseline and early interim ^{68}Ga-DOTATOC PET/CT data from 43 NET patients treated with ^{90}Y-DOTATOC in the setting of a phase II trial. Normal baseline IBI and high ^{68}Ga-DOTATOC tumor uptake, in terms of SUV_{mean}, are independently associated with better overall survival

IMPLICATIONS FOR PATIENT CARE: A more accurate quantification of baseline tumor uptake on ^{68}Ga-DOTA-SSA PET, taking into account the whole tumor burden, and IBI can help guide PRRT treatment decisions, whereas the value of early interim PET is limited.

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Table 1: Clinical and tumor characteristics of the patient cohort (n=43)

Characteristic	Number (%) of patients or Median (range)
Age (years)	59 (31-80)
Sex	
Male	21 (49%)
Female	22 (51%)
Primary tumor	
Intestine	27 (63%)
Pancreas	6 (14%)
CUP	6 (14%)
Other	4 (9%)
Ki67 (%)	3.5 (1-44)
Time between diagnosis and PRRT (months)	37 (4-223)
Number of PRRT cycles	
1	1 (2%)
2	3 (7%)
3	15 (35%)
4	24 (56%)
IBI	
0	34 (81%)
1	6 (14%)
2	2 (5%)
PFS (months)	13.9 (1.6-68.6)
OS (months)	22.3 (3.0-97.4)

Ki67: Ki-67 proliferation index; PRRT: peptide receptor radionuclide therapy; IBI: inflammation-based-index; PFS: progression-free survival; OS: overall survival

Table 2: Comparison between baseline and early interim ^{68}Ga-DOTATOC PET tumor uptake and volumetric parameters

	Baseline		Interim		
Parameter	**Mean ± SD**	**Median (range)**	**Mean ± SD**	**Median (range)**	**p-value**
SUV_{max}	25.8 ± 10.1	26.3 (7.4-58.7)	22.7 ± 9.8	22.5 (7.4-47.4)	< 0.001
SUV_{mean}	11.3 ± 3.6	10.4 (3.9-20.1)	10.1 ± 3.6	9.4 (3.5-18.5)	< 0.001
TV (ml)	504 ± 627	266 (24-3334)	492 ± 608	290 (24-3217)	0.966
TLA (SUV*ml)	5867 ± 7062	3760 (104-33559)	5151 ± 6224	2831 (143-28234)	< 0.001
$SUV_{T/S}$	1.76 ± 1.08	1.69 (0.5-4.8)	1.77 ± 1.01	1.66 (0.31-4.31)	0.815

SUV: standardized uptake value; TV: tumor volume; TLA: total lesion activity; T/S: tumor-to-spleen ratio

Table 3: Uni- and multivariate analysis for overall survival according to baseline mean standardized uptake value (SUV_{mean}), tumor volume (TV) and inflammation-based index (IBI), and decrease in SUV_{mean} ($-\Delta SUV_{mean}$) between interim and baseline PET

	Univariate analysis		Multivariate analysis	
Variable	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
SUV_{mean} > 13.7	0.45 (0.22-0.92)	0.024	0.40 (0.19-0.85)	0.016
TV > 578 ml	2.18 (1.04-4.60)	0.037	1.85 (0.83-4.12)	0.130
IBI	3.90 (1.62-9.38)	0.001	3.12 (1.24-7.83)	0.015
$-\Delta SUV_{mean}$ > 17%	2.29 (1.09-4.80)	0.024		

HR: hazard; CI: confidence interval

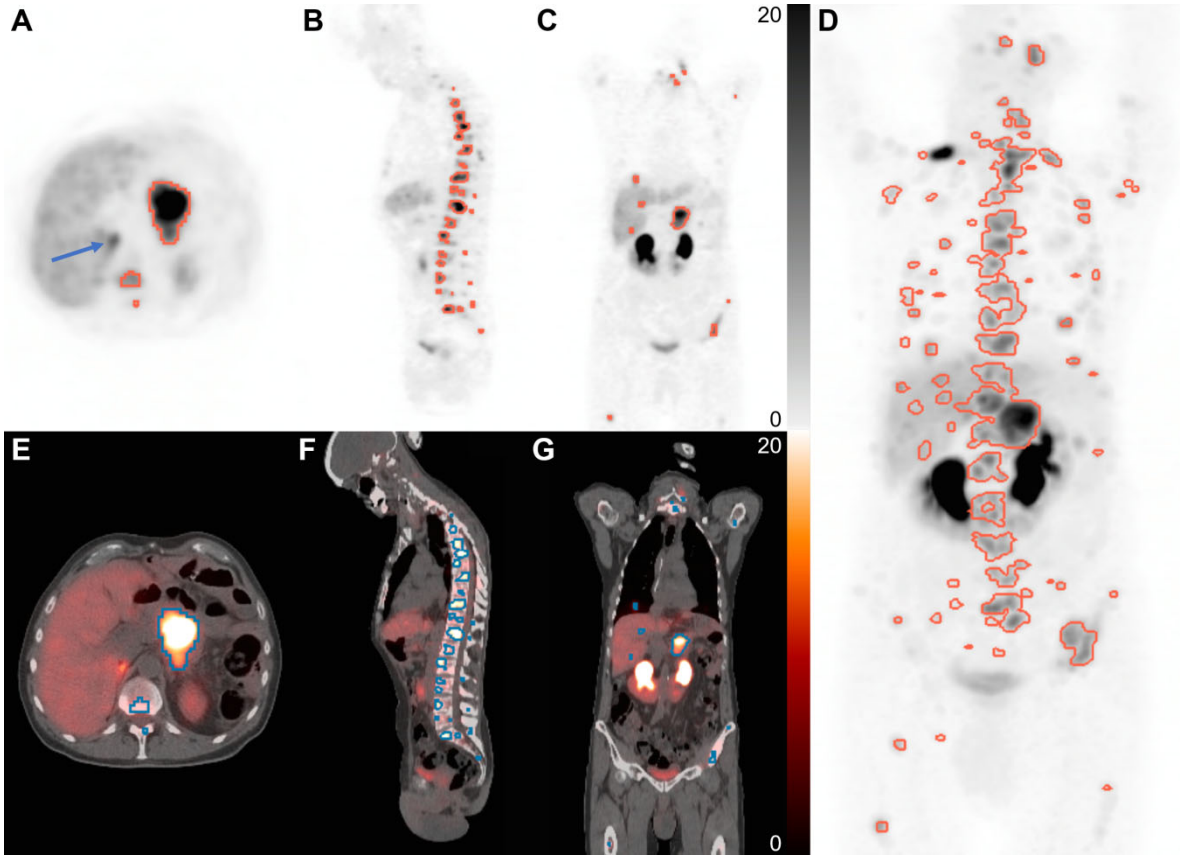

Figure 1: Example of tumor delineation in a 65-year old male patient with pancreatic NET and multiple liver, lymph node and bone metastases on transversal (A;E), sagittal (B;F) and coronal (C;G) PET/CT and MIP (D) images. The arrow indicates physiologic uptake in the right adrenal gland. Both scale bars apply to PET images in unit SUV

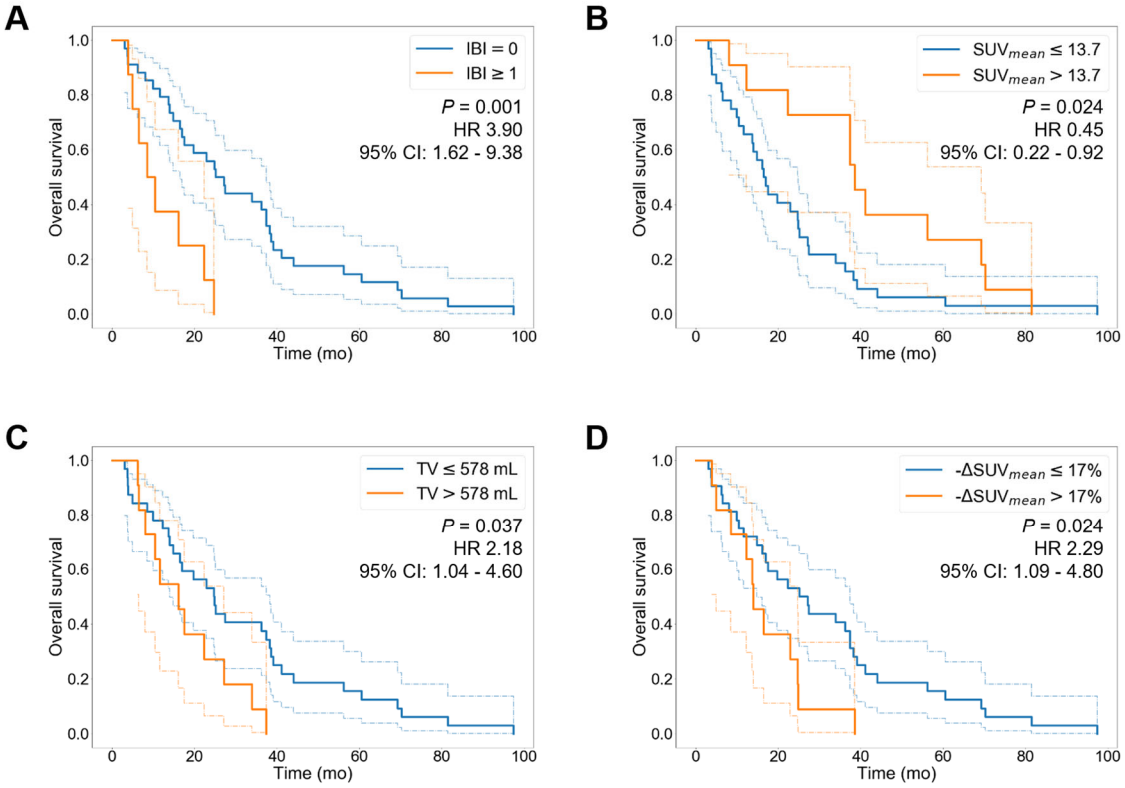

Figure 2: Survival analysis according to baseline (A) inflammation-based index (IBI), (B) mean standardized uptake value (SUV_{mean}) and (C) ^{68}Ga-DOTATOC avid tumor volume (TV), and decrease in SUV_{mean} ($-\Delta SUV_{mean}$) between interim and baseline PET. HR: hazard ratio, CI: confidence interval

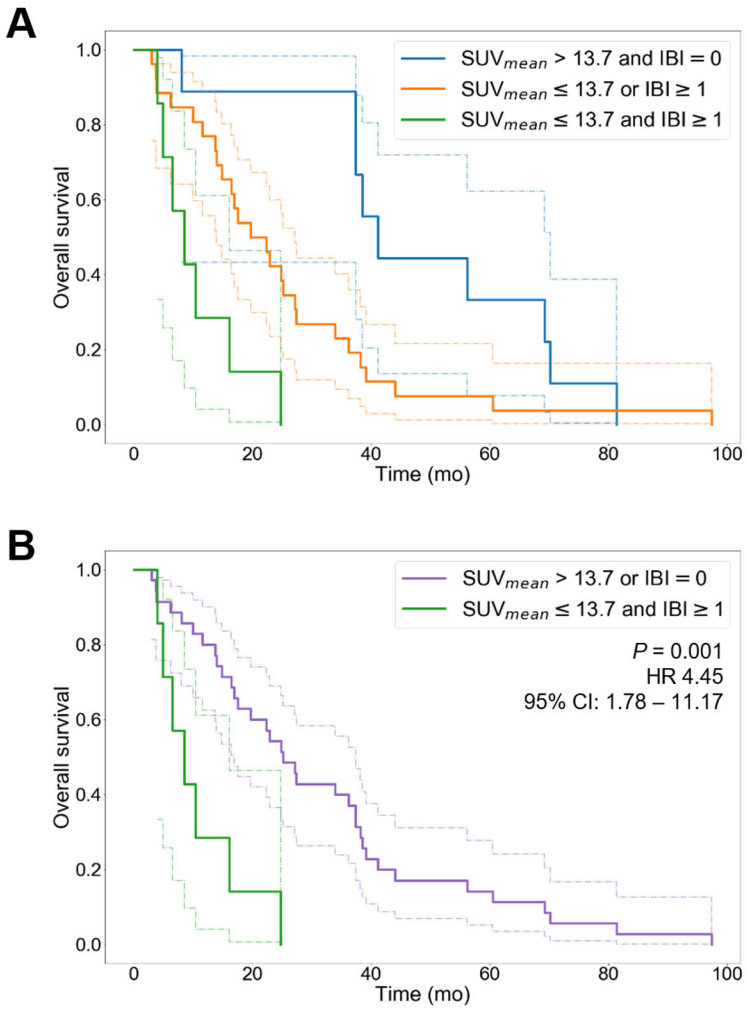

Figure 3: Survival analysis according to a composite score based on mean standardized uptake value (SUV_{mean}) and inflammation-based index (IBI). HR: hazard ratio, CI: confidence interval

Supplemental Table 1: Comparison of baseline clinical and tumor characteristics, including PET-derived values, between patients with controlled and uncontrolled disease. Values are presented as mean ± SD or number of patients.

	Controlled (n = 23)	**Uncontrolled (n = 19)**	**p-value**
Age (years)	63 ± 10	58 ± 12	0.128
Sex			0.536
Male	13	8	
Female	10	11	
Ki67 (%)	4.5 ± 5.1	9.9 ± 12.3	0.025
Time between diagnosis and PRRT (months)	63 ± 51	48 ± 40	0.300
IBI			0.267
0	20	13	
> 0	3	5	
Baseline SUV_{max}	29.3 ± 9.5	22.4 ± 8.9	0.022
Baseline SUV_{mean}	12.7 ± 3.6	10.1 ± 2.8	0.012
Baseline TV (ml)	453 ± 477	591 ± 785	0.860
Baseline TLA (SUV*ml)	5935 ± 6080	6088 ± 8323	0.668
Baseline $SUV_{T/S}$	2.03 ± 1.07	1.52 ± 1.05	0.075

Ki67: Ki-67 proliferation index; PRRT: peptide receptor radionuclide therapy; IBI: inflammation-based-index; SUV: standardized uptake value; TV: tumor volume; TLA: total lesion activity; T/S: tumor-to-spleen ratio