

# Inflammation-Based Index and $^{68}\text{Ga}$ -DOTATOC PET-Derived Uptake and Volumetric Parameters Predict Outcome in Neuroendocrine Tumor Patients Treated with $^{90}\text{Y}$ -DOTATOC

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We performed post hoc analyses on the utility of pretherapeutic and early interim  $^{68}\text{Ga}$ -DOTATOC 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  $^{90}\text{Y}$ -DOTATOC in the setting of a prospective phase II trial. **Methods:** Forty-three NET patients received up to 4 cycles of  $^{90}\text{Y}$ -DOTATOC at 1.85 GBq/m<sup>2</sup>/cycle with a maximal kidney biologic effective dose of 37 Gy. All patients underwent  $^{68}\text{Ga}$ -DOTATOC PET/CT at baseline and 7 wk after the first PRRT cycle.  $^{68}\text{Ga}$ -DOTATOC-avid tumor lesions were semiautomatically delineated using a customized SUV threshold-based approach. PRRT response was assessed on CT using RECIST 1.1. **Results:** Median progression-free survival and overall survival (OS) were 13.9 and 22.3 mo, respectively. An SUV<sub>mean</sub> higher than 13.7 (75th percentile) was associated with better survival (hazard ratio [HR], 0.45;  $P = 0.024$ ), whereas a  $^{68}\text{Ga}$ -DOTATOC-avid tumor volume higher than 578 cm<sup>3</sup> (75th percentile) 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<sub>mean</sub> ( $P = 0.016$ ) and IBI ( $P = 0.015$ ). No significant correlations with progression-free survival were found. A composite score based on SUV<sub>mean</sub> and IBI allowed us to further stratify patients into 3 categories with significantly different survival. On early interim PET, a decrease in SUV<sub>mean</sub> of more than 17% (75th percentile) was associated with worse survival (HR, 2.29;  $P = 0.024$ ). **Conclusion:** Normal baseline IBI and high  $^{68}\text{Ga}$ -DOTATOC tumor uptake predict better outcome in NET patients treated with  $^{90}\text{Y}$ -DOTATOC. This method can be used for treatment personalization. Interim  $^{68}\text{Ga}$ -DOTATOC PET does not provide information for treatment personalization.

**Key Words:** PRRT;  $^{68}\text{Ga}$ -DOTATOC;  $^{90}\text{Y}$ -DOTATOC; neuroendocrine tumors; PET

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**P**eptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogs (SSAs) such as  $^{90}\text{Y}$ -DOTATOC and  $^{177}\text{Lu}$ -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 the 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 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, molecular imaging parameters also 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 SUV<sub>max</sub> on  $^{68}\text{Ga}$ -DOTA-SSA ( $^{68}\text{Ga}$ -DOTATATE/DOTATOC/DOTANOC) PET to be predictive for PRRT treatment response (9–11), whereas others observed no significant association (12,13). Haug et al. (14) found that a decrease in  $^{68}\text{Ga}$ -DOTATATE tumor uptake after the first PRRT

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cycle, expressed in terms of change in tumor-to-spleen SUV ratio ( $SUV_{T/S}$ ), predicted a longer PFS. To our knowledge, this finding 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  $^{68}\text{Ga}$ -DOTATATE-avid TV is independently associated with a shorter PFS and a 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 pretherapeutic and early interim  $^{68}\text{Ga}$ -DOTATOC PET/CT, along with IBI, in NET patients treated with  $^{90}\text{Y}$ -DOTATOC.

## MATERIALS AND METHODS

### Patient Population

We performed retrospective, post hoc analyses on data from our previous prospective phase II trial with  $^{90}\text{Y}$ -DOTATOC (EUDRACT 2008-007965-22) (16). Fifty-seven consecutive patients (aged 31–80 y) with histologically proven, metastatic NETs and progressive or recurrent disease after conventional treatment were recruited between March 2009 and May 2012. The main inclusion criteria were sufficient SSTR expression on tumor cells (higher than on normal liver parenchyma) documented by  $^{68}\text{Ga}$ -DOTATOC PET, as well as a predicted biologic effective dose to the kidneys of less than 37 Gy after 3 cycles of  $^{90}\text{Y}$ -DOTATOC determined by  $^{111}\text{In}$ -DTPA-octreotide dosimetry (17,18). Details on the dosimetric assessment have been previously published (17). Patients not eligible for PRRT because of insufficient SSTR expression ( $n = 3$ ) or an unacceptable pretherapeutic kidney biologic effective dose ( $n = 3$ ) were excluded. Four patients died, and 1 had progressive disease before the early interim  $^{68}\text{Ga}$ -DOTATOC PET/CT exam. Two patients for whom PRRT was ended after 1 cycle because of an aberrant biodistribution on early interim PET (19), and 1 patient with an atypical disease presentation (multiple brain metastases without other tumor lesions; possible metastatic spinal paraganglioma on pathology report) and low uptake values, and for whom PRRT was ended after 2 cycles, were not included either.

The 43 remaining patients (21 men, 22 women; 33 gastroenteropancreatic NETs, 4 NETs of unknown primary, and 6 NETs of other origin) were treated with up to 4 cycles of PRRT (1.85 GBq/m<sup>2</sup> dose of  $^{90}\text{Y}$ -DOTATOC per cycle) every 8 wk, with a maximal predicted kidney biologic effective dose of 37 Gy (17). Table 1 presents the patient clinical data and tumor characteristics. Details on radiolabeling and administration of  $^{90}\text{Y}$ -DOTATOC were previously published (17).

The study was performed at University Hospitals Leuven after approval by the institute's Ethics Committee, and all subjects gave written informed consent.

### IBI Measurement

IBI was derived as previously described (5,20). Patients with normal C-reactive protein (<10 mg/L) and albumin (>35 g/L) levels were assigned a score of 0. If one or both parameters were abnormal, a score of 1 was allocated. Patients with an elevated level of C-reactive protein and hypoalbuminemia received a score of 2.

Blood samples were collected at baseline within 1 wk before PRRT. Serum chemistry tests included C-reactive protein and albumin.

### $^{68}\text{Ga}$ -DOTATOC PET/CT Scans

All patients underwent  $^{68}\text{Ga}$ -DOTATOC PET/CT before (baseline), 7 wk after (early interim), and 40 wk after (posttherapeutic;  $n = 30$ ) the first PRRT cycle. The median interval between baseline PET/CT and the first treatment cycle was 5 wk (range, 1–22 wk). Details on the  $^{68}\text{Ga}$ -DOTATOC synthesis have been previously published (16).

**TABLE 1**

Clinical and Tumor Characteristics of Patient Cohort ( $n = 43$ )

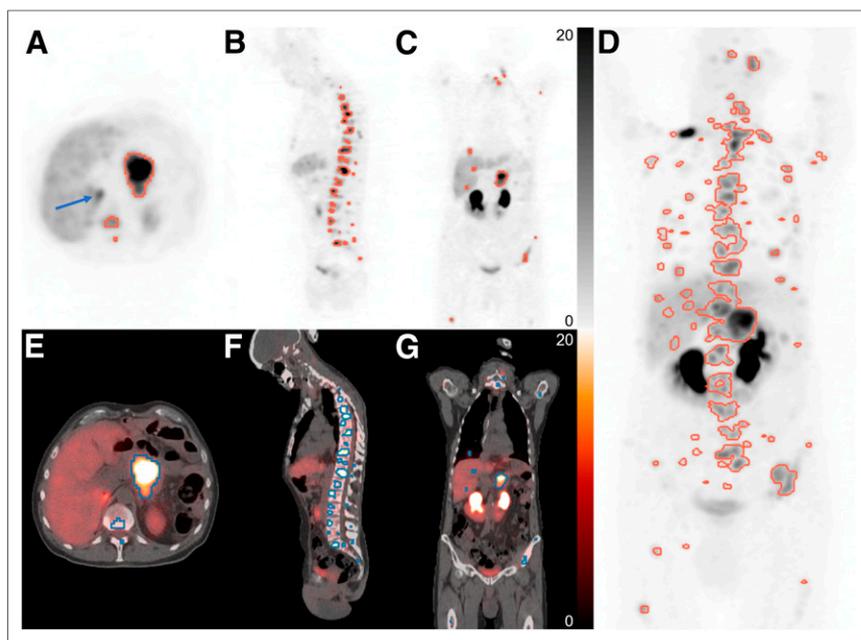
Characteristic	Data
Age (y)	59 (31–80)
Sex	
Male	21 (49%)
Female	22 (51%)
Primary tumor	
Intestine	27 (63%)
Pancreas	6 (14%)
NETs of unknown primary	6 (14%)
Other	4 (9%)
Ki-67 (%)	3.5 (1–44)
Time between diagnosis and PRRT (mo)	37 (4–223)
Number of PRRT cycles	
1	1 (2%)
2	3 (7%)
3	15 (35%)
4	24 (56%)
IBI	
0	34 (81%)
1	6 (14%)
2	2 (5%)
PFS (mo)	13.9 (1.6–68.6)
OS (mo)	22.3 (3.0–97.4)

Qualitative data are expressed as numbers followed by percentages in parentheses; continuous data are expressed as median followed by range in parentheses.

All PET/CT scans were acquired on a Biograph 16-slice HiRez LSO PET/CT system (Siemens). Patients on SSA therapy interrupted treatment 12–24 h before scanning for short-acting SSAs or 4–6 wk before scanning for long-acting SSAs. Approximately 30 min after injection of 185 MBq of  $^{68}\text{Ga}$ -DOTATOC, whole-body PET/CT images from head to mid femur were acquired, as specified in a previous publication (16). Iterative reconstruction of the PET data was done by means of ordered-subsets expectation maximization (5 iterations, 8 subsets) using an in-plane postreconstruction gaussian smoothing kernel of 6 mm in full width at half maximum.

### Quantitative Measurements on $^{68}\text{Ga}$ -DOTATOC PET/CT Scans

On the basis of the methodology of Tirosh et al. (15),  $^{68}\text{Ga}$ -DOTATOC-avid tumor lesions were semiautomatically delineated using MIM software, version 6.7.6 (MIM Software Inc.) (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 thresholds. Resulting VOIs smaller than 0.1 cm<sup>3</sup> were automatically removed. To avoid over- or underestimation of TVs, images were individually scaled from 0 to two thirds of the tumor  $SUV_{\text{max}}$ . Subsequently, all regions of physiologic  $^{68}\text{Ga}$ -DOTATOC uptake or non-disease-related uptake were manually



**FIGURE 1.** Example of tumor delineation in 65-y-old male patient with pancreatic NET and multiple liver, lymph node, and bone metastases on transversal (A and E), sagittal (B and F), and coronal (C and G) PET/CT and maximum-intensity-projection (D) images. Arrow indicates physiologic uptake in right adrenal gland. Both scale bars apply to PET images in unit SUV.

removed. Furthermore, small but definite tumor lesions with low  $^{68}\text{Ga}$ -DOTATOC uptake missed by the initial segmentation were manually delineated using the PET Edge tool (MIM software v6.7.6, MIM software Inc.) (21). Finally, the union of the resulting VOIs, containing all  $^{68}\text{Ga}$ -DOTATOC-avid tumor lesions, was determined, from which  $\text{SUV}_{\text{max}}$ ,  $\text{SUV}_{\text{mean}}$ , TV, and total lesion activity (TLA) were automatically calculated. The last of these is derived by multiplying the  $\text{SUV}_{\text{mean}}$  of a VOI by its volume.

Additionally, the spleen was delineated on all PET/CT images with the Region Grow tool (MIM software v6.7.6, MIM software Inc.) and manually retouched. Dividing the tumor  $\text{SUV}_{\text{max}}$  by the spleen  $\text{SUV}_{\text{max}}$  allowed us to calculate  $\text{SUV}_{\text{T/S}}$ , according to the method of Haug et al. (14).

### Response Evaluation After PRRT

Imaging follow-up was standardized and consisted of  $^{68}\text{Ga}$ -DOTATOC PET/CT at 40 wk after the first PRRT cycle, followed by 6-monthly CT scans during the first 2 y after treatment and at the discretion of the treating physician as of 2 y. If disease progression was suspected during treatment, an additional CT scan was performed. Response was assessed on the CT images of the posttherapeutic scan using RECIST 1.1 by an experienced radiologist. As such, patients were categorized as having controlled disease (stable disease, partial response, or complete response) or uncontrolled disease (progression).

PFS and OS were the endpoints and were calculated as, respectively, 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 was used to determine whether patients had stable or progressive disease.

### Statistical Analyses

Statistical analyses were performed using the Python package SciPy (SciPy, RRID:SCR\_008058) and CamDavidsonPilon/lifelines (version 0.14.6.). 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 percentiles as cutoffs for dichotomization, yielding 3 comparisons between 2 subgroups. Uni- and multivariate Cox proportional-hazards models were applied to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). Baseline parameters were compared between patients with controlled and uncontrolled disease using the independent-samples  $t$  test or Mann–Whitney  $U$  test in cases of nonnormality, as assessed by a Shapiro–Wilk test, or inequality of variances according to the Levene test. For categorical baseline parameters, the Fisher 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 cases of nonnormality. Two-sided  $P$  values of less than 0.05 were considered statistically significant.

## RESULTS

### Response Assessment and Survival

Median PFS and OS were 13.9 mo (range, 1.6–68.6 mo) and 22.3 mo (range, 3.0–97.4 mo), respectively. Twelve patients (28%) were not able to undergo the posttherapeutic PET/CT scan because of deterioration of their general condition due to progressive disease (3/13) or because of death due to progression (9/13). For 1 patient, the posttherapeutic scan was not available, and this patient was consequently left out of the response assessment. Of the remaining 30 patients, CT showed progressive disease in 7 and stable disease in 23. No partial or complete responses were observed on CT. In summary, 23 patients 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 mo, respectively. Baseline clinical and tumor characteristics are compared between the 2 groups in Supplemental Table 1 (supplemental materials are available at <http://jnm.snmjournals.org>).

### Baseline Parameters and Survival

Baseline  $\text{SUV}_{\text{max}}$ ,  $\text{SUV}_{\text{mean}}$ , TV, TLA, and  $\text{SUV}_{\text{T/S}}$  are provided in Table 2. No significant differences in PFS were found between the subgroups of these parameters. An  $\text{SUV}_{\text{mean}}$  higher than 13.7 (75th percentile) was associated with better OS (HR, 0.45;  $P = 0.024$ ), whereas a TV higher than 578  $\text{cm}^3$  (75th percentile) was associated with worse survival (HR, 2.18;  $P = 0.037$ ) (Table 3; Fig. 2). The subgroups for  $\text{SUV}_{\text{max}}$ , TLA, and  $\text{SUV}_{\text{T/S}}$  showed no significant differences in OS.

Baseline IBI could be determined for 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  $\text{SUV}_{\text{mean}}$  (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 considered, disregarding IBI, independent associations with OS were found for

**TABLE 2**  
Comparison Between Baseline and Early Interim <sup>68</sup>Ga-DOTATOC PET Tumor Uptake and Volumetric Parameters

Parameter	Baseline		Interim		P
	Mean ± SD	Median	Mean ± SD	Median	
SUV <sub>max</sub>	25.8 ± 10.1	26.3 (range, 7.4–58.7)	22.7 ± 9.8	22.5 (range, 7.4–47.4)	<0.001
SUV <sub>mean</sub>	11.3 ± 3.6	10.4 (range, 3.9–20.1)	10.1 ± 3.6	9.4 (range, 3.5–18.5)	<0.001
TV (cm <sup>3</sup> )	504 ± 627	266 (range, 24–3,334)	492 ± 608	290 (range, 24–3,217)	0.966
TLA (SUV × cm <sup>3</sup> )	5,867 ± 7,062	3760 (range, 104–33,559)	5,151 ± 6,224	2,831 (range, 143–28,234)	<0.001
SUV <sub>T/S</sub>	1.76 ± 1.08	1.69 (range, 0.5–4.8)	1.77 ± 1.01	1.66 (range, 0.31–4.31)	0.815

T/S = tumor-to-spleen ratio.

both SUV<sub>mean</sub> (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<sub>mean</sub> and IBI. Patients with a high SUV<sub>mean</sub> (>13.7) and normal IBI received a score of 0. If SUV<sub>mean</sub> was 13.7 or less and IBI elevated, they received a score of 2. If only 1 condition was met, they received a score of 1. Patients in category 2 showed significantly worse OS than did patients in category 1 (*P* = 0.007) or 0 (*P* < 0.001) (HR 4.45; *P* = 0.001), but also category 1 patients showed significantly worse OS than did category 0 (*P* = 0.025) (Fig. 3).

Patients with controlled disease showed a significantly higher baseline SUV<sub>max</sub> (*P* = 0.022) and SUV<sub>mean</sub> (*P* = 0.012) than did those with uncontrolled disease (Supplemental Table 1). No differences were observed for TV, TLA, or SUV<sub>T/S</sub>. Also, baseline IBI was not significantly different.

#### Interim Parameters and Survival

On interim PET, SUV<sub>max</sub>, SUV<sub>mean</sub>, and TLA showed a small but significant decrease, whereas TV and SUV<sub>T/S</sub> 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<sub>mean</sub> of more than 17% (75th percentile) 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 mo, respectively, which are somewhat shorter than reported in

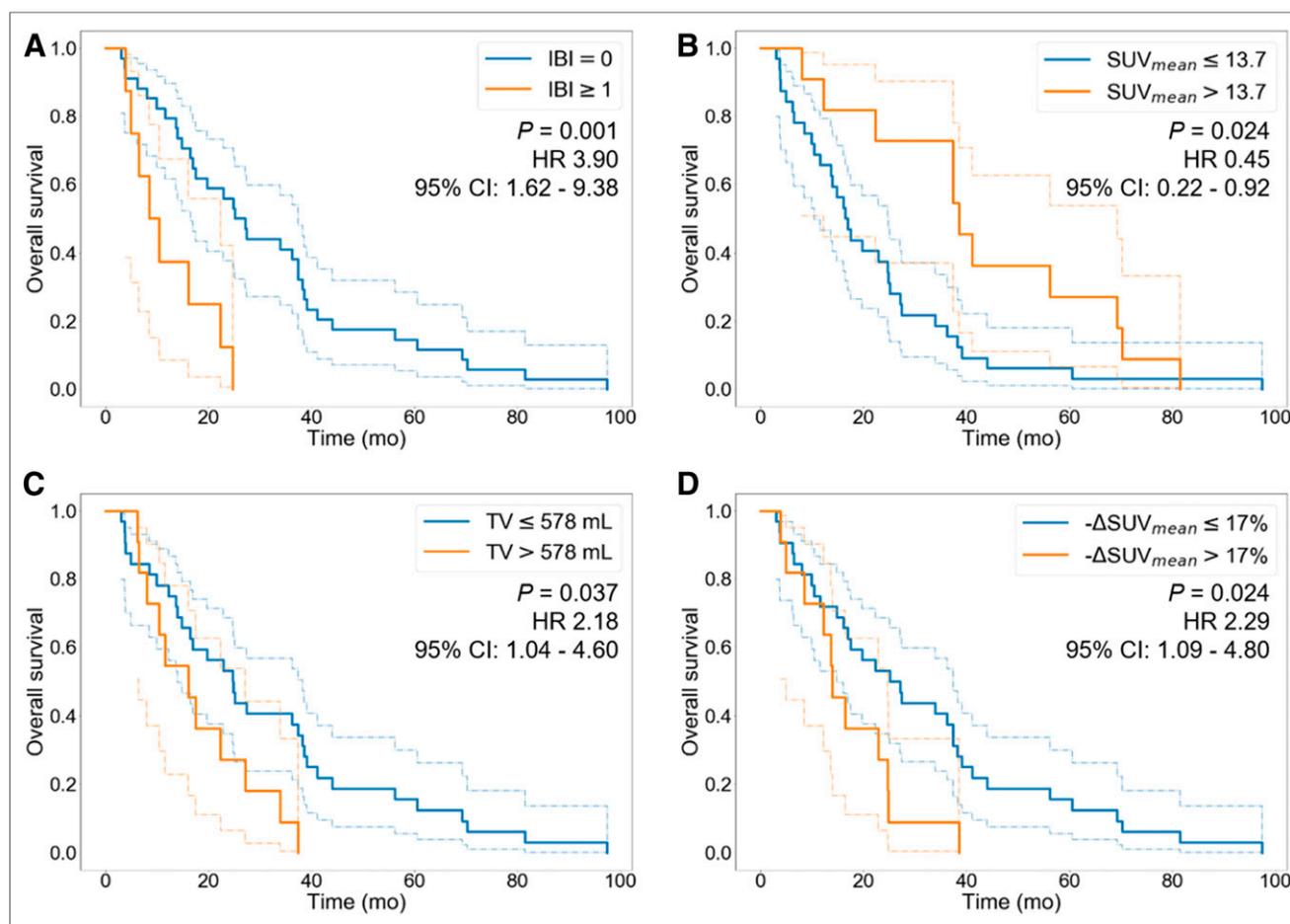
other <sup>90</sup>Y-DOTATOC PRRT studies but still remain in line with the literature (1). Head-to-head comparisons with other studies, especially on survival, should be interpreted carefully because of differences in study populations (e.g., tumor burden and biologic aggressiveness) and PRRT protocols. On the other hand, we observed no partial or complete responses, whereas other studies observed at least a few partial responses (1). This difference might be explained by differences in populations and PRRT protocols but also by differences in the criteria used for response assessment, with criteria that are often less stringent definitions than RECIST 1.1 having been used. Moreover, the Rotterdam group has shown that OS in patients with an objective response is not different from OS in patients with stable disease (6).

A baseline SUV<sub>mean</sub> higher than 13.7 was independently associated with better OS, in line with the findings of Imhof et al. (8) in 1,109 NET patients treated with <sup>90</sup>Y-DOTATOC. On the other hand, no significant association was found for SUV<sub>max</sub>. A possible explanation is that SUV<sub>mean</sub> is a parameter taking into account the whole TV, whereas SUV<sub>max</sub> is not necessarily representative of all tumor lesions. In the literature, conflicting results have been published on the role of SUV on baseline <sup>68</sup>Ga-DOTA-SSA PET in PRRT response prediction. Koch et al. (9) identified a cutoff for SUV<sub>max</sub> and SUV<sub>mean</sub> of 29.4 and 20.3, respectively, to separate patients between long and short PFS (69 vs. 26 wk). Öksüz et al. (10) found that an SUV<sub>max</sub> higher than 17.9 as a cutoff for favorable outcome was able to predict response in all 20 responders and 15 of 16 nonresponders. Kratochwil et al. (11) proposed a mean SUV<sub>max</sub> (from up to 4 liver metastases per patient) threshold of more than 16.4 to select patients for PRRT, with a sensitivity and

**TABLE 3**  
Uni- and Multivariate Analysis for OS According to Baseline SUV<sub>mean</sub>, TV, and IBI and Decrease in SUV<sub>mean</sub> (−ΔSUV<sub>mean</sub>) Between Interim and Baseline PET

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
SUV <sub>mean</sub> > 13.7	0.45	0.22–0.92	0.024	0.40	0.19–0.85	0.016
TV > 578 cm <sup>3</sup>	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
−ΔSUV <sub>mean</sub> > 17%	2.29	1.09–4.80	0.024			

−ΔSUV<sub>mean</sub> = decrease in SUV<sub>mean</sub>.



**FIGURE 2.** Survival analysis according to baseline (A) IBI, (B)  $SUV_{mean}$  (C), and  $^{68}\text{Ga}$ -DOTATOC-avid TV (D) and decrease in  $SUV_{mean}$  ( $-\Delta SUV_{mean}$ ) between interim and baseline PET.

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  $^{68}\text{Ga}$ -DOTA-SSA PET showed no additional value for PRRT response prediction. In all these studies, the fact that slightly different methods were used to define  $SUV_{max}$  could explain the different results, and in none of them was a full segmentation of all tumor lesions 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 an  $SUV_{mean}$  well below 13.7 showed a good PFS and OS, we would not suggest use of this value as a threshold to deselect patients from PRRT; rather, we would consider this a prognostic factor. Ezziddin et al. (22) concluded that  $^{68}\text{Ga}$ -DOTATOC PET can predict tumor-absorbed doses, and in cases of low SUV—and hereby insufficient target irradiation—can deselect inappropriate candidates for PRRT. More studies are needed to provide guidance on  $^{68}\text{Ga}$ -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 an insufficient target dose.

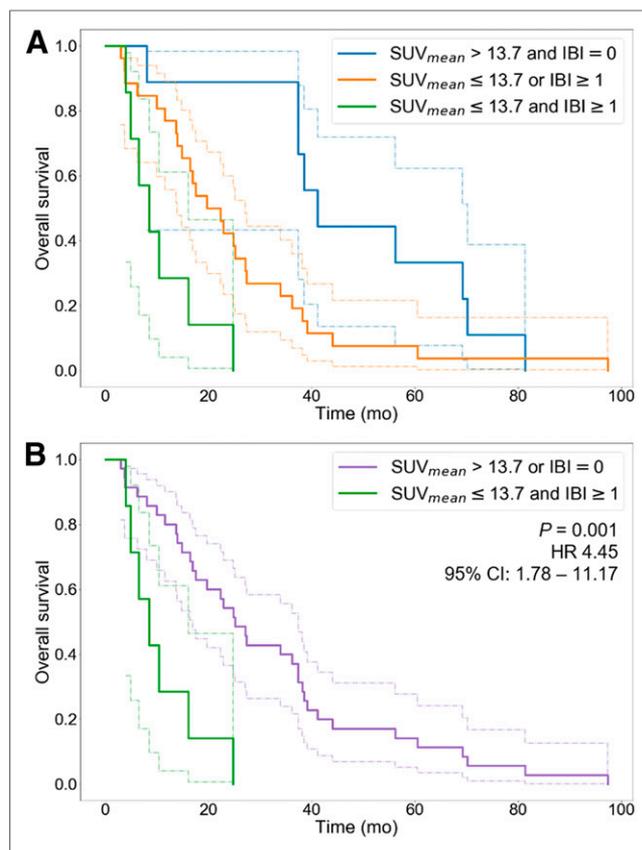
In our study population, a baseline  $^{68}\text{Ga}$ -DOTATOC TV higher than 578  $\text{cm}^3$  was associated with worse survival. A recent publication reported on the utility of  $^{68}\text{Ga}$ -DOTA-SSA-avid TV in a general population of 184 NET patients (15). The authors found

that a  $^{68}\text{Ga}$ -DOTATATE TV of 7.0  $\text{cm}^3$  or more is independently associated with shorter PFS, whereas a  $^{68}\text{Ga}$ -DOTATATE TV of 35.8  $\text{cm}^3$  or more is independently associated with higher disease-specific mortality (15). However, these results cannot be extrapolated to our study population, which consisted solely of PRRT patients with a much higher tumor burden. Further studies are warranted to evaluate the value of  $^{68}\text{Ga}$ -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  $SUV_{mean}$  of a volume by the volume, whereas we observed opposite associations between survival and SUV on the one hand and between survival and TV on the other.

In line with the results of Black et al. (5), an elevated baseline IBI was associated with worse survival. Because of the simplicity of this biomarker, it could readily be included in the pretherapeutic assessment and help guide treatment decisions. Moreover, Black et al. observed that a persistently elevated IBI throughout PRRT was associated with worse PFS and OS and therefore could help identify patients who might have little benefit from treatment continuation.

We also found that a composite score, based on tumor uptake and IBI, allows further patient stratification into 3 groups with significantly different survival. Further validation of this score on external datasets and in a prospective setting is needed.



**FIGURE 3.** Survival analysis according to composite score based on  $SUV_{mean}$  and IBI.

To our knowledge, there is only 1 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  $^{68}\text{Ga}$ -DOTATATE PET 3 mo after the first PRRT cycle and found that decreased uptake predicted a longer PFS, with independent associations only for  $SUV_{T/S}$ . However, in our study a major decrease in  $SUV_{mean}$  ( $>17\%$ ) was associated with worse survival, whereas 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 wk vs. 3 mo) (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 were not always available after the first 2 y 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, the generalizability of our findings to  $^{177}\text{Lu}$ -DOTATATE needs to be confirmed, especially since  $^{90}\text{Y}$ -DOTATOC is less routinely used in clinical practice.

## CONCLUSION

Normal baseline IBI and high  $^{68}\text{Ga}$ -DOTATOC tumor uptake ( $SUV_{mean} > 13.7$ ) were independently associated with better survival in NET patients treated with  $^{90}\text{Y}$ -DOTATOC, whereas a high  $^{68}\text{Ga}$ -DOTATOC-avid TV ( $>578\text{ cm}^3$ ) was associated with worse survival. Adding these parameters to the pretherapeutic 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  $^{68}\text{Ga}$ -DOTATOC PET did not allow us to identify patients with a poorer prognosis that would justify a change in treatment strategy.

## DISCLOSURE

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## KEY POINTS

**QUESTION:** Are quantitative tumor uptake and volumetric measurements on pretherapeutic and early interim  $^{68}\text{Ga}$ -DOTATOC PET/CT, along with IBI, useful for outcome prediction in NET patients treated with  $^{90}\text{Y}$ -DOTATOC?

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

**IMPLICATIONS FOR PATIENT CARE:** A more accurate quantification of baseline tumor uptake on  $^{68}\text{Ga}$ -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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