Prognostic Value of Whole-Body PET Volumetric Parameters Extracted from ^{68}Ga-DOTATOC PET/CT in Well-Differentiated Neuroendocrine Tumors

Philippe Thuillier[1,2], Virginia Liberini[1], Serena Grimaldi[1], Osvaldo Rampado[3], Elena Gallio[3], Bruno De Santi[4], Emanuela Arvat[5], Alessandro Piovesan[5], Roberto Filippi[6], Ronan Abgral[7], Filippo Molinari[4], and Désirée Deandreis[1]

[1]Nuclear Medicine Unit, Department of Medical Sciences, University of Turin, Turin, Italy; [2]Department of Endocrinology, University Hospital of Brest, Brest, France; [3]Medical Physics Unit, AOU Città della Salute e della Scienza, Turin, Italy; [4]Biolab, Department of Electronics and Telecomunications, Politecnico di Torino, Turin, Italy; [5]Oncological Endocrinology Unit, Department of Medical Sciences, University of Turin, Turin, Italy; [6]Departments of Oncology and Medical Sciences, University of Turin, Turin, Italy; and [7]Department of Nuclear Medicine, University Hospital of Brest, Brest, France

Our objective was to evaluate the prognostic value of somatostatin receptor tumor burden on ^{68}Ga-DOTATOC PET/CT in patients with well-differentiated (WD) neuroendocrine tumors (NETs). **Methods:** We retrospectively analyzed the ^{68}Ga-DOTATOC PET/CT scans of 84 patients with histologically confirmed WD NETs (51 grade 1, 30 grade 2, and 3 grade 3). For each PET/CT scan, all ^{68}Ga-DOTATOC–avid lesions were independently segmented by 2 operators using a customized threshold based on the healthy liver SUV_{max} (LIFEx, version 5.1). Somatostatin receptor–expressing tumor volume (SRETV) and total lesion somatostatin receptor expression (TLSRE = SRETV × SUV_{mean}) were extracted for each lesion, and then whole-body SRETV and TLSRE (SRETVwb and TLSREwb, respectively) were defined as the sum of SRETV and TLSRE, respectively, for all segmented lesions in each patient. Time to progression (TTP) was defined as the combination of disease-free survival in patients undergoing curative surgery ($n = 10$) and progression-free survival for patients with unresectable or metastatic disease ($n = 74$). TTP and overall survival were calculated by Kaplan–Meier analysis, log-rank testing, and the Cox proportional-hazards regression model. **Results:** After a median follow-up of 15.5 mo, disease progression was confirmed in 35 patients (41.7%) and 14 patients died. A higher SRETVwb (>39.1 cm^3) and TLSREwb (>306.8 g) correlated significantly with a shorter median TTP (12 mo vs. not reached; $P < 0.001$). In multivariate analysis, SRETVwb ($P = 0.005$) was the only independent predictor of TTP regardless of histopathologic grade and TNM staging. **Conclusion:** According to our results, SRETVwb and TLSREwb extracted from ^{68}Ga-DOTATOC PET/CT could predict TTP or overall survival and might have important clinical utility in the management of patients with WD NETs.

Key Words: neuroendocrine tumors; ^{68}Ga-DOTATOC PET/CT; tumor burden; prognosis; somatostatin receptor expressing tumor volume; total lesion somatostatin receptor expression

Neuroendocrine neoplasms (NENs) are a group of tumors of common embryologic origin but leading to a variety of clinical presentations and prognosis. The most frequent sites are the gastroenteropancreatic tract and the bronchopulmonary system. Although relatively rare, NENs have had a greatly increasing incidence in the last 30 years, and the incidence is currently estimated at approximately 5 cases per 100,000 population per year (1). According to the World Health Organization classification (based on Ki-67 percentage or number of mitoses per high-power field), NENs range from well-differentiated (WD) neuroendocrine tumors (NETs) to poorly differentiated carcinomas (2).

PET/CT imaging with a ^{68}Ga-DOTA–labeled somatostatin analog (SSTa) is the mainstay for in vivo evaluation of somatostatin receptor expression in NETs (3,4), and almost 90% of primary grade 1 or 2 gastroenteropancreatic NETs are PET-positive because of the high somatostatin receptor expression (5). In clinical practice, ^{68}Ga-DOTA-SSTa PET/CT has become the gold standard in the diagnosis and management of WD NETs, as it plays a major role in tumor characterization, in the assessment of disease extension, and in proper selection of patient candidates for peptide receptor radionuclide therapy (6,7). The prognostic value of ^{68}Ga-DOTA-SSTa PET/CT imaging has been widely assessed in the literature but has been focused mainly on semiquantitative parameters such as SUV (8,9).

In several tumor models over the last few years, metabolic tumor burden on ^{18}F-FDG PET has shown major prognostic value compared with semiquantitative parameters. Calculation of metabolic tumor burden integrates the volume of metabolically active tumor, expressed by metabolic tumor volume, and total lesion glycolysis, which is the product of SUV_{mean} and metabolic tumor volume. Two studies (10,11) have interestingly demonstrated the prognostic utility of somatostatin receptor tumor burden (SRTB) in patients with WD NETs, obtained by measuring whole-body total lesion somatostatin receptor expression (TLSREwb) and whole-body somatostatin receptor–expressing tumor volume (SRETVwb) from ^{68}Ga-DOTATATE PET/CT images.

Hence, the objective of this study was to evaluate the prognostic value of SRTB extracted from ^{68}Ga-DOTATOC PET/CT in a large cohort of patients with WD NETs.

MATERIALS AND METHODS

Population

All patients ($n = 322$) consecutively referred for ^{68}Ga-DOTATOC PET/CT to the Nuclear Medicine Division of "AOU Città della Salute

e della Scienza," from January 1, 2017, to January 4, 2020, were retrospectively evaluated and included if they had histologically proven grades 1–3 WD NETs, gastroenteropancreatic or bronchopulmonary NETs or an unknown primary site, ^{68}Ga-DOTATOC PET with at least 1 positive lesion, and follow-up at least 6 mo after PET. Exclusion criteria were an age of less than 18 y, incomplete histologic data, a neuroendocrine carcinoma, concomitant metastatic neoplasia other than NET, or negative findings on ^{68}Ga-DOTATOC PET/CT. The CONSORT diagram of the study (Consolidated Standards of Reporting Trials) is presented in Figure 1.

The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki and was approved by the local ethical committee (approval 0004004; protocol: "NET PET Tumor Burden Study"). All enrolled patients signed an informed consent form.

FIGURE 1. CONSORT diagram of study.

Data on age, sex, TNM stage at the time of PET imaging, tumor grade according to the World Health Organization classification (12) (Ki-67 for grade 1, <3%; grade 2, 3%–20%; grade 3, >20%), functional status, and previous locoregional and systemic treatments were collected. Patients were considered treatment-naïve if they had received no previous treatment except for surgery of the primary tumor.

All patients underwent PET/CT on an analog 3-dimensional (3D) PET scanner (Philips Gemini Dual-slice EXP scanner—PET AllegroTM system with Brilliance CT scanner—Philips Medical Systems, Cleveland, OH) according to guidelines (7). The median injected tracer activity was 148 MBq (range, 92–250 MBq). After a minimal time of 45–60 min, and after a free-breathing CT acquisition for attenuation correction from the vertex to the mid thigh (5-mm slices, 40 mAs, and 120 kVp), PET data were acquired in 3-dimensional mode at 2.5 min per bed position and 6–8 bed positions per patient. The PET scans were reconstructed by ordered-subset expectation maximization (3-dimensional row-action maximum-likelihood algorithm), and the matrix size was 144 × 144 voxels, resulting in voxels of 4.0 × 4.0 × 4.0 mm. All acquisitions were corrected for attenuation, scatter, and random coincidences.

Image Analysis and SRTB Extraction

For each PET/CT scan, all ^{68}Ga-DOTATOC–avid lesions were segmented independently by 2 nuclear medicine physicians using a semiautomatic method through freely available software (LIFEx, version 5.1; IMIV [Imagerie Moléculaire In Vivo] Lab/CEA [Le Commissariat à l'Énergie Atomique et aux Énergies Alternatives]) (13) and based on the SUV threshold method to avoid intra- and interoperator variability in manual segmentation (14,15).

The SUV_{max} threshold based on healthy-liver uptake was chosen. SUV_{max} was assessed by placing a spheric volume of interest 3 cm in diameter in the right upper lobe of the liver, as previously reported (16). For each lesion, the SRETV and TLSRE were semiautomatically extracted. TLSRE was obtained by multiplying the SRETV of each lesion by its corresponding SUV_{mean}. A visual inspection of the resulting automated volume segmentation was performed
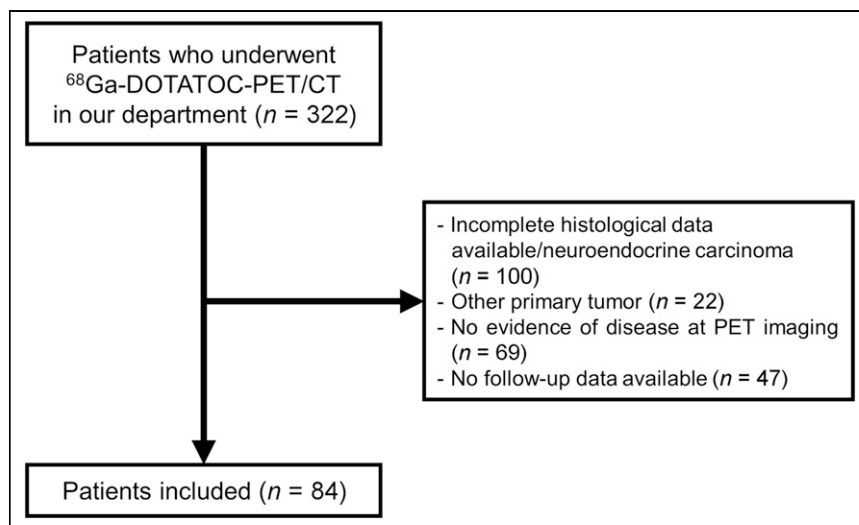
to remove background physiologic uptake (e.g., spleen, kidney, and bladder). The same analysis was performed for each patient by both operators to evaluate reproducibility.

We classified each lesion according to its site: primary tumor, lymph node, liver, bone, or other (e.g., peritoneum and lung). Then, SRETVwb and TLSREwb, defined as the sum of SRETV and TLSRE, respectively, for all lesions in each patient, were calculated (Fig. 2). When all lesions were equal to or lower than the liver SUV_{max} cutoff, SRETVwb and TLSREwb were defined as equal to 0 as previously mentioned (17). We also separated the corresponding SRETVwb (primary, lymph node, liver, bone, and other) and TLSREwb (primary, lymph node, liver, bone, and other) according to each tumor site. The details of the entire process are described in Supplemental Figure 1 (supplemental materials are available at http://jnm.snmjournals.org).

Statistical Analysis

Quantitative variables were expressed as median with range. The primary clinical endpoint was the time to progression (TTP), defined as the time from PET/CT imaging to the first event (progression or relapse).
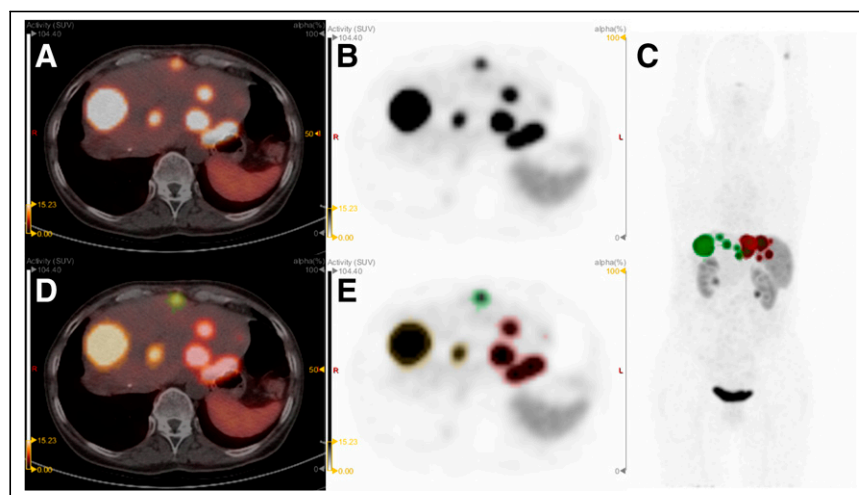

FIGURE 2. ^{68}Ga-DOTATOC PET/CT in WD pancreatic NET (PET/CT [A] and PET imaging [B]) showing high uptake in all lesions (highest SUV_{max}, 104.4). SRTB analysis (maximum-intensity projection [C], PET/CT [D], and PET imaging [E]) highlighted SRETVwb and TLSREwb values of 249 cm^3 and 4,191 g, respectively.

Because anatomopathologic confirmation of all lesions is not achievable, the TTP of the disease was based on morphologic imaging criteria or functional criteria (18). Disease progression was defined as the appearance of a new lesion or a significant increase in the size of known lesions. The secondary clinical endpoint was overall survival (OS), defined as the time from PET/CT to NET-related death. Patients were followed up until the occurrence of the primary endpoints or until October 2020.

Kaplan–Meier curves and the log-rank test were applied for survival analysis. Receiver-operating-characteristic analysis was applied to determine the best cutoff for SRETVwb and TLSREwb parameters to predict the patient's outcome using the Youden index (19). The area under the curve, sensitivity, specificity, and accuracy were reported.

For TTP, multivariate analysis was performed by the Cox proportional-hazards regression model to estimate hazard ratios with 95% CIs, including variables that had clinical relevance or a P value of less than 0.05 in univariate analysis. Because of the low number of events, we did not perform multivariate analysis for OS.

We performed a subgroup analysis on patients with metastatic NETs at the time of PET/CT, using the same SRETVwb and TLSREwb thresholds as found for the whole cohort. Moreover, an exploratory analysis to assess the repartition of SRTB according to tumor site and progressive versus nonprogressive disease during follow-up was performed through the nonparametric Mann–Whitney U test with Bonferroni adjustment.

Interobserver agreement was evaluated for SRETVwb and TLSREwb using intraclass correlation coefficient values of between 0 and 1, with a value of more than 0.9 defining the parameter as robust (20).

All statistical tests were 2-sided, and a P value of less than 0.05 indicated a statistically significant difference. All analyses were performed on XLSTAT (version 2019.2.2; Addinsoft).

RESULTS

Among the 322 patients screened, 84 (38 male and 46 female; median age at PET, 60.5 y [range, 25–86 y]) were included in the study. The main characteristics of the patients are represented in Table 1. The pancreas was the most frequent site (39/84, 46.4%), and 40.5%, 55.9%, and 3.6% of the tumors were classified as grades 1, 2, and 3, respectively. Fifty-four (64.3%) patients had metastatic disease at the time of PET/CT, and 47 patients (55.9%) were defined as treatment-naïve.

SRTB

In the whole cohort, 442 lesions and subsequent volumes of interest were segmented, including primary ($n = 36$, 8.1%), lymph node ($n = 72$, 16.3%), liver ($n = 185$, 41.9%), bone ($n = 114$, 25.8%), and other sites ($n = 35$, 7.9%). The median SUV_{max}, SRETV, and TLSRE per lesion were 9.7 (range, 3.3–116.5), 4.0 cm^3 (range, 0.5–1,980.3 cm^3), and 24.8 g (range, 1.8–21,819.5 g), respectively. The median SRETVwb and TLSREwb were 32.4 cm^3 (range, 0–3,078.7 cm^3) and 338.3 g (range, 0–22,658.6 g), respectively. In 5 patients, the SRETVwb was equal to zero because the lesions were ^{68}Ga-DOTATOC–avid but with an SUV_{max} lower than the liver background.

Survival Analysis

Progression was detected in 35 patients (41.7%), and 14 patients died after a median follow-up of 23 mo (range, 0–41 mo). In the entire cohort, the median TTP was 22 mo (interquartile range, from 10 mo to not reached). Ten patients underwent curative surgery of the primary tumor after PET and did not show disease relapse during the follow-up.

TABLE 1
Characteristics of Patients

Characteristic	Value (total $n = 84$)
Sex	
Male	48 (57.1)
Female	36 (42.9)
Median age (y)	60.5 (range, 25–86)
Primary site	
Gastroenteropancreatic ($n = 72$)	72 (85.7)
Pancreas	39
Small intestine	21
Duodenum	3
Cecum or colon	4
Rectum	1
Stomach	4
Lung	9 (10.7)
Unknown	3 (3.6)
TNM stage	
Only primary tumor	20 (23.8)
Locoregional extension	10 (11.9)
Metastatic	54 (64.3)
Ki-67 (%)	
<3	34 (40.5)
3 to ≤20	47 (55.9)
>20	3 (3.6)
Functional	12 (14.3)
Treatment before PET	
Surgery	42 (50)
SSTa	46 (54.8)
Systemic treatment	16 (19.0)
Chemotherapy	13
Everolimus	8
Others	2
Locoregional treatment	12 (14.3)
Peptide receptor radionuclide therapy	5 (6)
Treatment after PET	
Surgery	13 (15.5)
SSTa	63 (75.0)
Systemic treatment	16 (19.0)
Chemotherapy	12
Everolimus	8
Other	0
Locoregional treatment	7 (8.3)
Peptide receptor radionuclide therapy	7 (8.3)

Data are number followed by percentage in parentheses, except for age.

Univariate Analysis for TTP/OS. For SRETVwb, the area under the receiver-operating-characteristic curve was 0.83 (best cutoff, 39.1 cm^3), with a sensitivity, specificity, and accuracy of 0.86, 0.76, and 0.8, respectively. For TLSREwb, the area under the curve was 0.79 (best cutoff, 306.8 g), with a sensitivity, specificity, and accuracy of 0.86, 0.74, and 0.79, respectively. A higher SRETVwb (≥39.1 cm^3) and TLSREwb (>306.8 g) correlated with a significantly shorter median TTP (12 mo [95% CI, 10–23 mo] vs. not reached for both; $P < 0.001$) and a shorter median OS (not reached for both; $P < 0.001$). SUV$_{max}$ was not associated with TTP or OS ($P = 0.08$ and $P = 0.09$, respectively; Fig. 3).

The TNM stage at the time of PET, the Ki-67 percentage, and treatment history (naïve vs. previous line of treatment) were also significantly associated with a shorter TTP and OS ($P < 0.05$; Supplemental Fig. 2), whereas age, sex, and secretory syndrome were not (P = not statistically significant).

Multivariate Analysis. SRETVwb and TLSREwb were strongly correlated in our study ($R = 0.916$ in Pearson correlation analysis). Thus, we performed a multivariate analysis using the Cox proportional-hazards regression model including only SRETVwb (>39.1 cm^3). SRETVwb was the only independent predictor of TTP

(hazard ratio, 4.8 [95% CI, 1.6–14.5]; $P = 0.006$) regardless of TNM stage, Ki-67 percentage, and treatment history ($P = 0.58$, 0.85, and 0.39, respectively) (Table 2).

Subgroup Analysis in Metastasis-Positive Patients. The diagnostic performance of SRTB to predict TTP and OS was assessed according to lesion site in a subgroup of patients with metastatic disease ($n = 54$). Using the same threshold, Kaplan–Meier analysis revealed a significant difference, with a shorter median TTP and OS for a higher value of both SRETVwb and TLSREwb ($P = 0.002$ and $P = 0.016$, respectively; Supplemental Fig. 3). SRTB analysis according to each lesion site did not reveal any difference between patients with progressive disease and patients with nonprogressive disease (Supplemental Table 1).

Interobserver Agreement

The mean liver threshold was 5.4 ± 2.2 (range, 2.1–12.9) for operator 1 and 5.3 ± 2.0 (range, 2.1–12.2) for operator 2. The median SRETVwb and TLSREwb were 32.4 cm^3 (range, 0–3,078.7 cm^3) and 338.3 g (range, 0–22,658.6), respectively, for operator 1, and 32.0 cm^3 (range, 0–3,100.0 cm^3) and 282.0 g (range, 0–22,789.0), respectively, for operator 2. The intraclass correlation coefficients were, respectively, 0.963, 0.988, and 0.997 for liver threshold, SRETVwb, and TLSREwb.

DISCUSSION

We investigated the prognostic value of SRTB extracted from ^{68}Ga-DOTATOC PET/CT in patients with WD NET. SRETVwb (≥39.1 cm^3) and TLSREwb (≥306.8 g) were significantly associated with TTP, but at multivariate analysis, SRETVwb was an independent prognostic parameter regardless of Ki-67 percentage, TNM stage, or treatment.

Several previous studies assessed the prognostic significance of ^{68}Ga-DOTA-TOC (17,21) and ^{68}Ga-DOTATATE PET/CT (10,11,22,23) volumetric parameters in patients with NETs. In a prospective study including a large population of 184 patients with grades 1–3 NETs, Tirosh et al. reported that SRETVwb of at least 7.0 cm^3 and at least 35.8 cm^3 obtained by ^{68}Ga-DOTATATE PET/CT were significantly associated with progression-free survival (PFS) and OS ($P < 0.001$ both), respectively (10). In another prospective study, including only grade 1 or 2 gastroenteropancreatic NETs, Toriihara et al. found that an SRETVwb of at least 11.1 cm^3 and a TLSREwb of at least 146.48 g obtained by ^{68}Ga-DOTATATE PET/CT were associated with PFS but that only SRETVwb was independently associated with PFS in a survival analysis, in accordance with our study (11). Kim et al. (17), in a retrospective study including 31 patients with unresectable or metastatic WD gastroenteropancreatic NETs undergoing ^{68}Ga-DOTATOC PET/CT before receiving lanreotide, showed that a lower tumor-to-liver ratio, lower SUV$_{max}$,
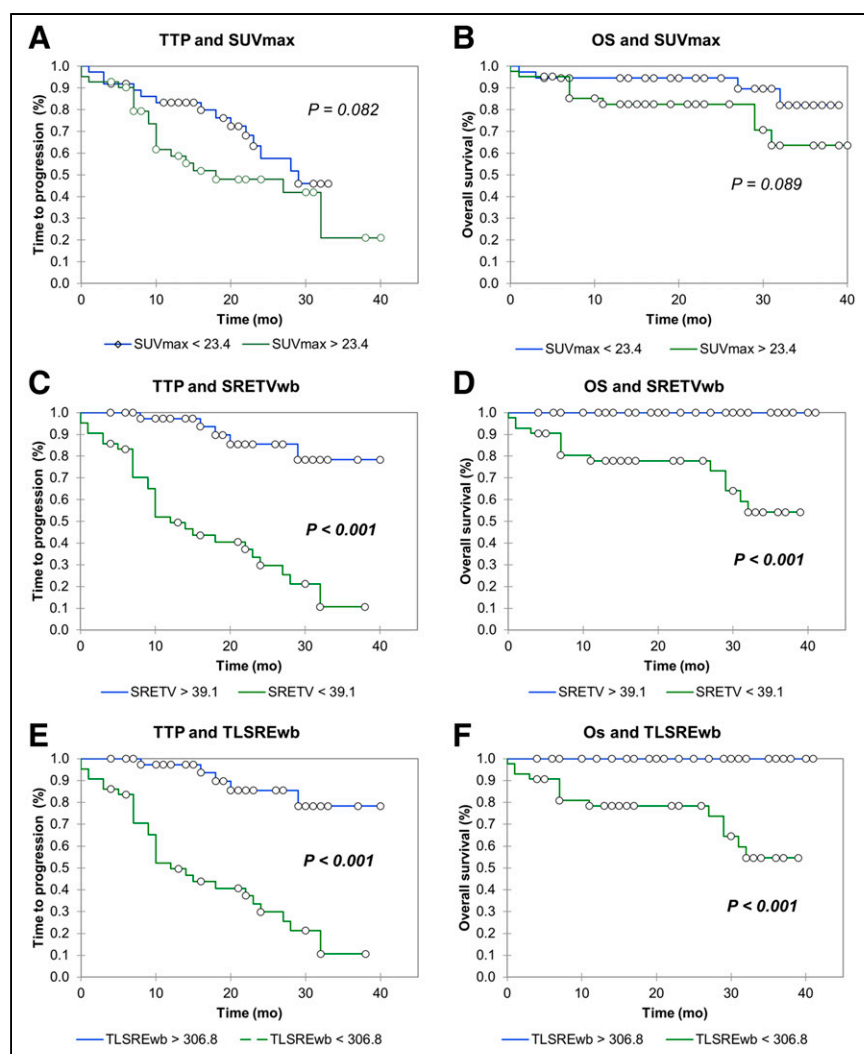

FIGURE 3. TTP (left) and OS (right) in patients according to SUV$_{max}$ (A and B), SRETVwb (C and D), and TLSREwb (E and F).

TABLE 2
Univariate and Multivariate Analyses Using Cox Regression for TTP According to SRETVwb, TLSREwb, and Other Characteristics of Cohort

Characteristic	Univariate analysis		Multivariate analysis	
	Hazard ratio	P	Hazard ratio	P
Sex		0.31		
Male (reference)	1			
Female	0.70 (0.35–1.39)			
Age		0.58		
≥64 y (reference)	1			
<64 y	0.83 (0.43–1.61)			
Ki-67%		0.013		0.85
<3 (reference)	1		1	
3–20	2.60 (1.16–5.81)		1.02 (0.41–2.53)	
>20	6.28 (1.64–24.00)		1.45 (0.35–6.07)	
Stage at time of PET		0.009		0.58
Local (reference)	1		1	
Locoregional	1.79 (0.11–28.75)		1.88 (0.10–34.10)	
Metastatic	12.39 (1.69–90.62)		3.22 (0.33–31.21)	
Treatment-naïve		0.001		0.39
No (reference)	1		1	
Yes	0.20 (0.00–0.515)		0.60 (0.19–1.88)	
SUV$_{max}$		0.09		
≥23.4 (reference)	1			
<23.4	0.56 (0.28–1.1)			
SRETV (cm^3)		<0.001		0.006
<39.1 (reference)	1		1	
≥39.1	8.48 (3.28–21.91)		4.76 (1.56–14.53)	
TLSRE (g)		<0.001		
<306.8 (reference)	1			
≥306.8	8.41 (3.25–21.74)			

Data in parentheses are 95% CIs.

and higher SRETVwb (>58.9 cm^3) were significantly associated with a shorter PFS in univariate analysis, but only tumor-to-liver ratio (hazard ratio, 3.182; $P = 0.021$) remained an independent factor for PFS in multivariate analysis. In our study, SUV$_{max}$ was not associated with TTP, as is consistent with findings by Tirosh et al. and Toriihara et al. (10,11). One potential explanation is the differences in selection criteria. In fact, Kim et al. included a more homogeneous population of patients at an early stage of disease, most of whom had not undergone other types of treatment (87.1%, excluding surgery) (17). Although a high SUV on ^{18}F-FDG PET/CT is positively associated with prognosis in almost all cancers, including NETs (24)—explaining the interest in using total lesion glycolysis—a lower SUV$_{max}$ on ^{68}Ga-DOTA-SSTa PET/CT is associated with poorer prognosis in patients with WD NETs (8,9,25,26). Thus, for the same SRETVwb value, patients in whom lesions with a low SUV$_{mean}$—and thus a low TLSREwb value—are disclosed might tend to present a less favorable prognosis, leading to conflicting results among different studies that include different patient populations. For this reason, SRETVwb seems to be

the most prognostic parameter, but its use should be validated in further prospective future studies including populations that are more homogeneous in terms of primary site, disease course, and treatment setting.

Furthermore, the proper methodology to evaluate SRTB should be considered. In our study, a customized threshold based on liver SUV$_{max}$ was chosen, and to our knowledge, this was the second study in which such a segmentation method was applied to ^{68}Ga-DOTATOC PET/CT (17). This methodology presents the advantage of being fast; hence, it could represent a useful tool in clinical practice. Interestingly, we found higher cutoffs for SRETVwb and TLSREwb than did studies assessing SRTB using ^{68}Ga-DOTA-TATE, whereas the SRETVwb and TLSREwb cutoffs were consistent with the study of Kim et al., performed with the same radiopharmaceutical, ^{68}Ga-DOTATOC (10,11,17). The literature showed that tumor uptake is higher and liver uptake lower with ^{68}Ga-DOTATOC than with ^{68}Ga-DOTATATE, leading to a higher tumor-to-liver ratio (27,28). Hence, we can assume that SRETVwb

and TLSREwb might be lower using ^{68}Ga-DOTATATE. These differences could also be explained by the difference in segmentation methodology. Toriihara et al. used a 50% threshold of SUV$_{max}$ to segment each lesion, leading to a lower SRETVwb value, especially in patients with intense radiotracer uptake ([11]). An example of the impact of different segmentation methods on SRTB is reported in Supplemental Figure 4.

In addition, assessing the reproducibility and robustness of SRTB calculation is important. In our study, reproducibility between the 2 operators was excellent, with an intraclass correlation coefficient of more than 0.9 for both SRETVwb and TLSREwb. To our knowledge, no study has assessed the reproducibility of SRTB parameters on ^{68}Ga-DOTA-SSTa PET/CT. Many studies showed that the segmentation method can impact the interoperator reproducibility of whole-body metabolic tumor volume on ^{18}F-FDG PET/CT imaging, especially threshold methods based on 41% of SUV$_{max}$ ([29,30]). SRTB parameters in ^{68}Ga-DOTA-SSTa PET/CT might be more reproducible than whole-body metabolic tumor volume because of the higher signal-to-noise ratio. This point is a crucial one; studies are needed of the reproducibility and robustness of whole-body volumetric parameters in ^{68}Ga-DOTA-SSTa PET/CT, especially between different PET systems.

Beyond the prognostic role, evaluation of changes in SRETVwb and TLSREwb (namely change in SRETVwb and change in TLSREwb) after the initiation of systemic therapy may offer promising perspectives, especially for patients treated with peptide receptor radionuclide therapy ([31]), and need to be assessed. However, SSA treatment or peptide receptor radionuclide therapy can modify liver uptake, as previously reported ([32]), impacting the calculation of SRTB. Therefore, the systematic use of the pretherapeutic liver SUV$_{max}$ cutoff could be a solution to following the evolution of SRTB parameters ([31,33]).

Our study presents some limitations. First, it was retrospective, included a heterogenous cohort, and was conducted at a single center and on a single PET/CT scanner. Second, we included only patients with ^{68}Ga-DOTATOC–avid lesions, and using the liver SUV$_{max}$ as the cutoff, the SRETVwb was equal to zero in 5 patients. This finding is explained by the low lesion volume in these patients, which did not impact their classification as good-prognosis patients. This point is crucial, because the same assertion should not be followed in patients with a high tumor burden without ^{68}Ga-DOTATOC uptake. In such a situation, the prognosis would be worse and ^{18}F-FDG PET/CT should be performed ([5,23,24]).

CONCLUSION

In our cohort, whole-body volumetric ^{68}Ga-DOTATOC PET/CT parameters (SRETVwb and TLSREwb) were associated with TTP and OS. SRTB could add value to conventional clinical prognostic parameters and other standard PET parameters (e.g., SUV$_{max}$) in predicting a patient's prognosis and guiding treatment decisions, thus supporting the implementation of SRTB in clinical practice. As previously mentioned, our results remain preliminary and applicable to ^{68}Ga-DOTATOC PET/CT but need to be validated in prospective studies and explored with other ^{68}Ga-peptides.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Can whole-body volumetric parameters extracted from ^{68}Ga-DOTATOC PET/CT be useful in assessing the prognosis of WD NETs?

PERTINENT FINDINGS: In our cohort, whole-body volumetric ^{68}Ga-DOTATOC PET/CT parameters (SRETV and TLSRE) were associated with TTP and OS. SRETVwb was the only independent prognostic parameter, regardless of Ki-67 percentage, TNM stage at the time of PET, and treatment history (naïve vs. previous treatments) before PET scanning.

IMPLICATIONS FOR PATIENT CARE: In the future, whole-body volumetric ^{68}Ga-DOTATOC PET/CT parameters may add value to conventional prognostic parameters in predicting the prognosis of patients with WD NETs.

REFERENCES

1. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol.* 2008;26:3063–3072.

2. Hentic O, Couvelard A, Rebours V, et al. Ki-67 index, tumor differentiation, and extent of liver involvement are independent prognostic factors in patients with liver metastases of digestive endocrine carcinomas. *Endocr Relat Cancer.* 2010;18:51–59.

3. Antunes P, Ginj M, Zhang H, et al. Are radiogallium-labelled DOTA-conjugated somatostatin analogues superior to those labelled with other radiometals? *Eur J Nucl Med Mol Imaging.* 2007;34:982–993.

4. Rufini V, Calcagni ML, Baum RP. Imaging of neuroendocrine tumors. *Semin Nucl Med.* 2006;36:228–247.

5. Carideo L, Prosperi D, Panzuto F, et al. Role of combined [^{68}Ga]Ga-DOTA-SST analogues and [^{18}F]FDG PET/CT in the management of GEP-NENs: a systematic review. *J Clin Med.* 2019;8:1032.

6. Shah MH, Goldner WS, Halfdanarson TR, et al. NCCN guidelines insights: neuroendocrine and adrenal tumors, version 2.2018. *J Natl Compr Canc Netw.* 2018;16:693–702.

7. Bozkurt MF, Virgolini I, Balogova S, et al. Guideline for PET/CT imaging of neuroendocrine neoplasms with ^{68}Ga-DOTA-conjugated somatostatin receptor targeting peptides and ^{18}F-DOPA. *Eur J Nucl Med Mol Imaging.* 2017;44:1588–1601.

8. Ambrosini V, Campana D, Bodei L, et al. ^{68}Ga-DOTANOC PET/CT clinical impact in patients with neuroendocrine tumors. *J Nucl Med.* 2010;51:669–673.

9. Sharma P, Naswa N, Kc SS, et al. Comparison of the prognostic values of ^{68}Ga-DOTANOC PET/CT and ^{18}F-FDG PET/CT in patients with well-differentiated neuroendocrine tumor. *Eur J Nucl Med Mol Imaging.* 2014;41:2194–2202.

10. Tirosh A, Papadakis GZ, Millo C, et al. Prognostic utility of total ^{68}Ga-DOTA-TATE-avid tumor volume in patients with neuroendocrine tumors. *Gastroenterology.* 2018;154:998–1008.e1.

11. Toriihara A, Baratto L, Nobashi T, et al. Prognostic value of somatostatin receptor expressing tumor volume calculated from ^{68}Ga-DOTATATE PET/CT in patients with well-differentiated neuroendocrine tumors. *Eur J Nucl Med Mol Imaging.* 2019;46:2244–2251.

12. Inzani F, Petrone G, Rindi G. The new World Health Organization classification for pancreatic neuroendocrine neoplasia. *Endocrinol Metab Clin North Am.* 2018;47:463–470.

13. Nioche C, Orlhac F, Boughdad S, et al. LIFEx: a freeware for radiomic feature calculation in multimodality imaging to accelerate advances in the characterization of tumor heterogeneity. *Cancer Res.* 2018;78:4786–4789.

14. Foster B, Bagci U, Mansoor A, Xu Z, Mollura DJ. A review on segmentation of positron emission tomography images. *Comput Biol Med.* 2014;50:76–96.

15. Liberini V, De Santi B, Rampado O, et al. Impact of segmentation and discretization on radiomic features in ^{68}Ga-DOTA-TOC PET/CT images of neuroendocrine tumor. *EJNMMI Phys.* 2021;8:21.

16. Thuillier P, Maajem M, Schick U, et al. Clinical assessment of ^{177}Lu-DOTATATE quantification by comparison of SUV-based parameters measured on both post-PRRT SPECT/CT and ^{68}Ga-DOTATOC PET/CT in patients with neuroendocrine tumors: a feasibility study. *Clin Nucl Med.* 2021;46:111–118.

17. Kim Y, Yoo C, Oh SJ, et al. Tumour-to-liver ratio determined by [^{68}Ga]Ga-DOTA-TOC PET/CT as a prognostic factor of lanreotide efficacy for patients with

well-differentiated gastroenteropancreatic-neuroendocrine tumours. *EJNMMI Res.* 2020; 15;10:63.

18. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45: 228–247.

19. Youden WJ. Index for rating diagnostic tests. *Cancer.* 1950;3:32–35.

20. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med.* 2016;15:155–163.

21. Ohnona J, Nataf V, Gauthe M, et al. Prognostic value of functional tumor burden on ^{68}Ga-DOTATOC PET/CT in patients with pancreatic neuro-endocrine tumors. *Neoplasma.* 2019;66:140–148.

22. Ohlendorf F, Henkenberens C, Brunkhorst T, et al. Volumetric ^{68}Ga-DOTA-TATE PET/CT for assessment of whole-body tumor burden as a quantitative imaging biomarker in patients with metastatic gastroenteropancreatic neuroendocrine tumors. *Q J Nucl Med Mol Imaging.* April 14, 2020 [Epub ahead of print].

23. Abdulrezzak U, Kurt YK, Kula M, Tutus A. Combined imaging with ^{68}Ga-DOTA-TATE and ^{18}F-FDG PET/CT on the basis of volumetric parameters in neuroendocrine tumors. *Nucl Med Commun.* 2016;37:874–881.

24. Abgral R, Leboulleux S, Deandreis D, et al. Performance of [18]fluorodeoxyglucose-positron emission tomography and somatostatin receptor scintigraphy for high Ki67 (≥10%) well-differentiated endocrine carcinoma staging. *J Clin Endocrinol Metab.* 2011;96:665–671.

25. Campana D, Ambrosini V, Pezzilli R, et al. Standardized uptake values of ^{68}Ga-DOTANOC PET: a promising prognostic tool in neuroendocrine tumors. *J Nucl Med.* 2010;51:353–359.

26. Koch W, Auernhammer CJ, Geisler J, et al. Treatment with octreotide in patients with well-differentiated neuroendocrine tumors of the ileum: prognostic stratification with Ga-68-DOTA-TATE positron emission tomography. *Mol Imaging.* 2014;13:1–10.

27. Velikyan I, Sundin A, Sorensen J, et al. Quantitative and qualitative intrapatient comparison of ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE: net uptake rate for accurate quantification. *J Nucl Med.* 2014;55:204–210.

28. Poeppel TD, Binse I, Petersenn S, et al. ^{68}Ga-DOTATOC versus ^{68}Ga-DOTA-TATE PET/CT in functional imaging of neuroendocrine tumors. *J Nucl Med.* 2011;52:1864–1870.

29. Eude F, Toledano MN, Vera P, Tilly H, Mihailescu S-D, Becker S. Reproducibility of baseline tumour metabolic volume measurements in diffuse large B-cell lymphoma: is there a superior method? *Metabolites.* 2021;11:72.

30. Tutino F, Puccini G, Linguanti F, et al. Baseline metabolic tumor volume calculation using different SUV thresholding methods in Hodgkin lymphoma patients: interobserver agreement and reproducibility across software platforms. *Nucl Med Commun.* 2021;42:284–291.

31. Liberini V, Rampado O, Gallio E, et al. ^{68}Ga-DOTATOC PET/CT-based radiomic analysis and PRRT outcome: a preliminary evaluation based on an exploratory radiomic analysis on two patients. *Front Med (Lausanne).* 2021;7:601853.

32. Cherk MH, Kong G, Hicks RJ, Hofman MS. Changes in biodistribution on ^{68}Ga-DOTA-octreotate PET/CT after long acting somatostatin analogue therapy in neuroendocrine tumour patients may result in pseudoprogression. *Cancer Imaging.* 2018;18:3.

33. Liberini V, Huellner MW, Grimaldi S, et al. The challenge of evaluating response to peptide receptor radionuclide therapy in gastroenteropancreatic neuroendocrine tumors: the present and the future. *Diagnostics (Basel).* 2020;10:1083.