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ORIGINAL ARTICLE

Prognostic value of somatostatin receptor expressing tumor volume calculated from ^{68}Ga-DOTATATE PET/CT in patients with well-differentiated neuroendocrine tumors

Akira Toriihara[1] · Lucia Baratto[1] · Tomomi Nobashi[1] · Sonya Park[1] · Negin Hatami[1] · Guido Davidzon[1] · Pamela L. Kunz[2] · Andrei Iagaru[1]

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Abstract

Purpose To evaluate the prognostic value of volumetric parameters calculated from ^{68}Ga-1,4,7,10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid (DOTA)-Thr^3-octreotate (^{68}Ga-DOTATATE) positron emission tomography/computed tomography (PET/CT) in patients with well-differentiated neuroendocrine tumor (WD-NET).

Methods Ninety-two patients (44 men and 48 women, mean age of 59.5-year-old) with pathologically confirmed WD-NET (grades 1 or 2) were enrolled in a prospective expanded access protocol. Selected data was analyzed retrospectively for this project. Maximum standardized uptake value (SUV_{max}) in the lesion with the highest ^{68}Ga-DOTATATE uptake was measured and recorded for each patient. In addition, two volumetric parameters, namely, somatostatin receptor expressing tumor volume (SRETV) and total lesion somatostatin receptor expression (TLSRE), were calculated in each ^{68}Ga-DOTATATE-avid lesion. SRETV was defined as tumor volume with higher ^{68}Ga-DOTATATE uptake than the 50% of SUV_{max} within the volume of interest (VOI) for each lesion. TLSRE was calculated by multiplying SRETV and mean SUV within the same VOI. Thereafter, the sum of SRETV (ΣSRETV) and TLSRE (ΣTLSRE) for all detected lesions per patient were calculated. Progression-free survival (PFS) was set as primary endpoint. Kaplan-Meier survival analysis, log-rank test, and Cox's proportional hazard model were used for statistical analysis.

Results Univariate analyses revealed significant difference of PFS for WHO tumor grade and ΣSRETV ($P < 0.05$), while there were no significant differences in age, sex, SUV_{max}, and ΣTLSRE ($P > 0.05$). Multivariate analysis identified WHO tumor grade and ΣSRETV as independent predictors of PFS.

Conclusion ΣSRETV calculated from ^{68}Ga-DOTATATE PET/CT may have prognostic value of PFS in WD-NET patients.

Keywords Well-differentiated · Neuroendocrine tumor · ^{68}Ga-DOTATATE · PET/CT · Prognosis · Somatostatin receptor expressing tumor volume

Introduction

Neuroendocrine tumors (NETs) are rare neoplasms originating from neuroendocrine cells in various organs. NETs have an incidence of approximately 7.0 in 100,000 in the USA [1]. According to 2010 WHO classification, gastroenteropancreatic NETs were classified to three groups based on pathological findings (mitotic count and Ki-67 labelling index): well-differentiated NET (WD-NET) grades 1 and 2, and poorly differentiated neuroendocrine carcinoma grade 3 (NEC) [2]. In addition, the most recent WHO classification in 2017 includes a category of WD-NET grade 3 for pancreatic NET [2].

Most WD-NET cells express somatostatin receptors (SSTRs), particularly type 2, which can be targets of imaging and therapy [3]. Positron emission tomography/computed tomography (PET/CT) using ^{68}Ga-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-conjugated peptides enables specific

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✉ Andrei Iagaru
aiagaru@stanford.edu

[1] Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Stanford University, 300 Pasteur Drive, Stanford, CA 94305-5281, USA

[2] Division of Oncology, Department of Medicine, Stanford University, 875 Blake Wilbur Dr, Stanford, CA 94305-5826, USA

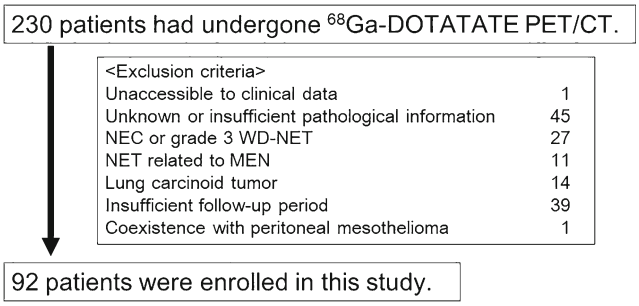

Fig. 1 Flowchart illustrating the patient selection process

evaluation of NETs by targeting SSTRs on the cell surface. A previous meta-analysis revealed high pooled sensitivity (93%) and specificity (96%) of diagnosing NET by PET/CT using ^{68}Ga-DOTA-conjugated peptides [4]. Recent guidelines from both the USA [5] and Europe [6] recommend the use of ^{68}Ga-DOTA-conjugated peptides PET/CT for diagnosis, staging, restaging, and determination of SSTR status of patients with NETs.

Generally, uptake of ^{68}Ga-DOTA-conjugated peptides in NETs decreases as tumor grade becomes higher. High-grade neuroendocrine neoplasms (NENs) often have high uptake of 2-deoxy-2-(^{18}F)fluoro-D-glucose (^{18}F-FDG) rather than ^{68}Ga-DOTA-conjugated peptides [7–11]. Although some previous studies have shown a relationship between patients' prognosis and ^{18}F-FDG PET/CT [12–17], most of them included some patients with high-grade NEN. WD-NETs does not usually show high ^{18}F-FDG uptake; therefore, PET/CT using ^{68}Ga-DOTA-conjugated peptides might be more suitable for predicting prognosis of patients with WD-NET.

Previous studies evaluated the relationship between ^{68}Ga-DOTA-conjugated peptide uptake and patients' prognosis [18–21]. However, ^{68}Ga-DOTA-conjugated peptides uptake was analyzed based on maximum standardized uptake value (SUV_{max}) measurements in the lesion with the highest uptake. SUV_{max} reflects SSTR expression in only the pixel with the highest uptake in a lesion. To take account of the entire tumor, volumetric parameters, similar to metabolic tumor volume (MTV) and total lesion glycolysis (TLG) used in ^{18}F-FDG PET/CT, should be evaluated.

Recently, Abdulrezzak et al. introduced volumetric parameters that can be applied in ^{68}Ga-DOTA-Thr^3-octreotate (^{68}Ga-DOTATATE) PET/CT to reflect both SSTR expression and tumor volume in patients with NETs [22]. To our knowledge, there are few studies that assessed the prognostic value of ^{68}Ga-DOTATATE PET/CT using volumetric parameters [23]. Here we evaluated the prognostic value of volumetric parameters calculated from ^{68}Ga-DOTATATE PET/CT in patients with WD-NET.

Table 1 Patients' characteristics

	N (%)
Gender	
Male	44 (47.8)
Female	48 (52.2)
WHO grade	
1	55 (60.0)
2	37 (40.0)
Primary organ	
Small bowel	40 (43.5)
Pancreas	23 (25.0)
Stomach/duodenum	4 (4.3)
Large bowel	4 (4.3)
Appendix	2 (2.2)
Unknown	19 (20.7)
Treatment	
Before PET/CT	
Surgical	57 (62.0)
Medical[a]	40 (43.5)
Liver-directed treatment[b]	12 (13.0)
Radiation	5 (5.4)
PRRT	5 (5.4)
No treatment	20 (21.7)
After PET/CT	
Surgical	37 (40.2)
Medical[a]	61 (66.3)
Liver-directed treatment[b]	10 (10.9)
Radiation	5 (5.4)
PRRT	4 (4.3)
No treatment	18 (19.6)
^{68}Ga-DOTATATE-avid lesion	
Yes	76 (82.6)
No	16 (17.4)
Tumor progression	
Yes	36 (39.1)
No	56 (60.9)

^{68}Ga-DOTATATE, ^{68}Ga-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-Thy^3-octreotate; *PET/CT*, positron emission tomography/computed tomography; *PRRT*, peptide receptor radionuclide therapy

[a] Medical treatment includes cold somatostatin analog and other anticancer drugs

[b] Liver-directed treatment includes transcatheter arterial chemo- or radioembolization and microwave ablation for liver metastases

Materials and methods

Patients

The local institutional review board (Stanford University Research Compliance Office) approved this prospective

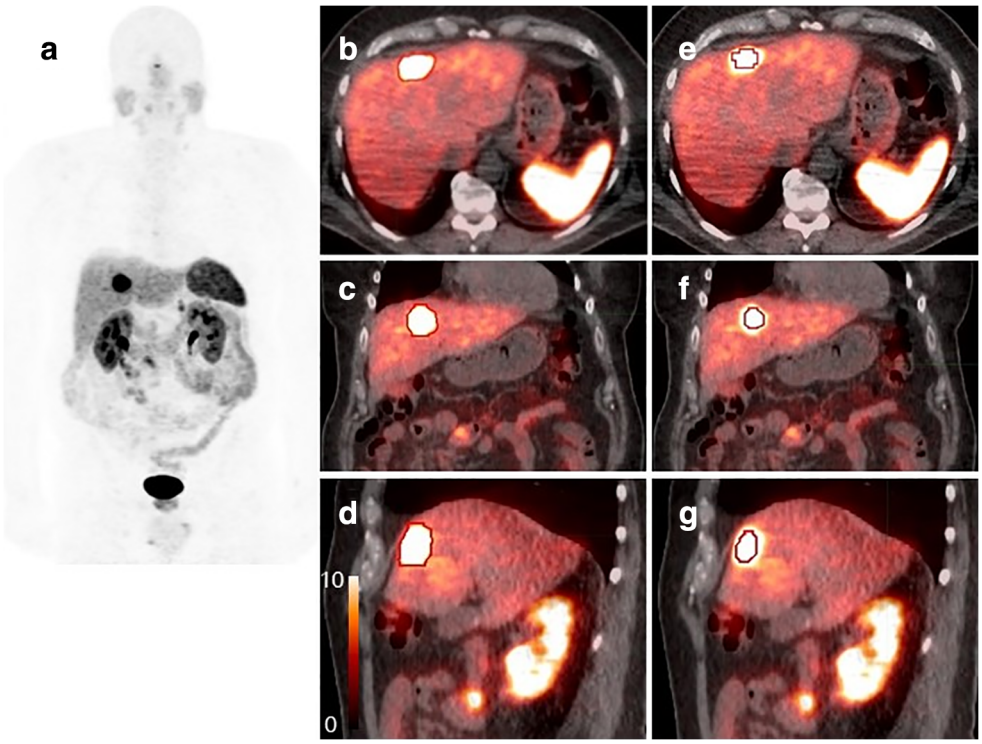

Fig. 2 Illustration of the placement of volume of interest (VOI) on ^{68}Ga-DOTATATE-avid lesion. Maximum intensity projection image (**a**), fused axial (**b**, **e**), coronal (**c**, **f**), and sagittal (**d**, **g**) PET/CT images are shown. A manual VOI on the liver metastasis was placed so as to exclude surrounding physiological uptake as far as possible (**b**–**d**). Thereafter, irregular VOI inside containing voxels with higher SUV than 50% of SUV_{max} was automatically extracted to calculate volumetric parameters (**e**–**g**)

expanded access protocol. Informed consent was obtained from all individual participants included in the study. Selected data was analyzed retrospectively for this project.

Two-hundred thirty patients had undergone ^{68}Ga-DOTATATE PET/CT in our hospital between January 2014 and December 2016. One patient, whose clinical and radiological data were not accessible, was excluded from our study. We excluded 137 patients according to the following criteria: (1) unknown or insufficient pathological information, (2) diagnosed as NEC or grade 3 WD-NET, (3) NET related to multiple endocrine neoplasia (MEN), (4) lung carcinoid tumor, and (5) insufficient follow-up period after ^{68}Ga-DOTATATE PET/CT (< 6 months) except patients with early tumor progression. In addition, we excluded one patient with coexistence of WD-NET and peritoneal mesothelioma because differentiation between the two types of neoplasm in each lesion was impossible. Finally, 92 patients (44 men and 48 women; mean age ± SD 59.5 ± 12.7 years old; range 25–84 years old) were enrolled in this retrospective study (Fig. 1). Of these 92 patients, 55 and 37 patients were pathologically diagnosed as WD-NET grades 1 and 2, respectively. Characteristics of the enrolled patients are shown in Table 1. The mean follow-up period ranged 59–1250 days (mean ± SD 551.4 ± 296.1 days).

PET/CT protocol

Patients were not required to follow specific preparation prior to the scanning. The scans were performed using Discovery 600 or Discovery 690 PET/CT scanners (GE Healthcare, Waukesha, WI, USA). The details about the preparation of ^{68}Ga-DOTATATE had been presented in the previous report [24]. Approximately 45–60 min after intravenous injection of ^{68}Ga-DOTATATE (range 129.5–262.7 MBq, mean ± SD 224.2 ± 28.1 MBq), CT was acquired for attenuation correction and anatomical localization using the following parameters: 120 kV, 10 mAs, matrix size of 512 × 512, field of view of 867 mm, in 22.5 s. PET data acquisition followed from vertex to mid-thighs, with an acquisition time of 3 min per bed position. The PET datasets were reconstructed with an ordered subsets expectation maximization (OSEM) method with 2 iterations and 32 subsets for the Discovery 600 scanner and 2 iterations and 24 subsets for the Discovery 690 scanner. A previous study has shown that these two scanners can be used without clinical compromise to quantitative measurements [25].

Image analysis

^{68}Ga-DOTATATE PET/CT images were evaluated using a commercially available workstation (the MIM Vista workstation, version 6.7.11, MIM Software Inc.). Two nuclear medicine physicians evaluated all PET/CT images by consensus. ^{68}Ga-DOTATATE uptakes above the background which did not correspond to physiological uptakes were considered to be significant. All ^{68}Ga-DOTATATE-avid lesions were identified in each patient. In addition to SUV_{max} measurements, two volumetric parameters, namely, somatostatin receptor expressing tumor volume (SRETV) and total lesion somatostatin

Table 2 Results of univariate analysis for predicting progression-free survival

Variables	*N*	Median PFS (days)			*p*
		Median	95% confidence interval		
			Lower limit	Upper limit	
Age, years					
< 61	45	NA	627	NA	0.384
≥ 61	47	910	488	1158	
Gender					
Male	44	1158	627	NA	0.261
Female	48	757	457	NA	
WHO grade					
1	55	1000	802	NA	0.006*
2	37	579	345	NA	
^{68}Ga-DOTATATE-avid lesion					
Yes	76	802	539	1158	0.046*
No	16	NA	627	NA	
SUV_{max}					
< 25.2	46	NA	627	NA	0.174
≥ 25.2	46	1000	457	NA	
ΣSRETV					
< 11.29 ml	46	1158	757	NA	0.009*
≥ 11.29 ml	46	579	389	1000	
ΣTLSRE					
< 146.48 g	46	1158	757	NA	0.056
≥ 146.48 g	46	579	457	NA	

^{68} Ga-DOTATATE, ^{68} Ga-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-Thy^{3} -octreotate; *NA*, not applicable; *PFS*, progression-free survival; *SRETV*, somatostatin receptor expressing tumor volume; *SUV_{max}*, maximum standardized uptake value; *TLSRE*, total lesion somatostatin receptor expression

* $p < 0.05$

receptor expression (TLSRE), were calculated for each ^{68}Ga-DOTATATE-avid lesion. These volumetric parameters were defined as in the previous study by Abdulrezzak et al. [22]: SRETV is the tumor volume with higher ^{68}Ga-DOTATATE uptake than the 50% of SUV_{max} within the volume of interest (VOI) for each lesion, while TLSRE is calculated by multiplying SRETV and mean SUV within the same VOI. VOI for each lesion was manually placed so as to exclude both surrounding physiological uptake and adjacent lesions' uptake (Fig. 2). To minimize overestimation of volumetric parameters, overlap between adjacent VOIs was strictly avoided.

SUV_{max} in the lesion with the highest ^{68}Ga-DOTATATE uptake in each patient was used in the statistical analysis. The sum of SRETV (ΣSRETV) and TLSRE (ΣTLSRE) for all detected lesions per patient was calculated and used in the analysis.

Table 3 Results of multivariate analysis for predicting progression-free survival

Variables	*p*	Hazard ratio	95% confidence interval
WHO grade	0.013*	2.525	1.281–4.976
SUV_{max}	0.507	1.308	0.593–2.885
ΣSRETV	0.036*	3.917	1.091–14.07
ΣTLSRE	0.257	0.447	0.112–1.796

SRETV, somatostatin receptor expressing tumor volume; *TLSRE*, total lesion somatostatin receptor expression

* $p < 0.05$

Statistical analysis

We used EZR software for the statistical analyses [26]. Progression-free survival (PFS), defined as days from ^{68}Ga-DOTATATE PET/CT to tumor progression or patient's death, was set as a primary endpoint in this study. Tumor progression was defined as significant increase of tumor size or appearance of new metastatic lesions based on RECIST 1.1 criteria [27]. Patients' cohort was divided in separate groups based on the following parameters: age, sex, tumor grade according to 2010 WHO classification, SUV_{max}, ΣSRETV, and ΣTLSRE. Cutoff values of age and PET/CT parameters were set on median values. PFS was estimated by Kaplan-Meier survival analysis. As a univariate analysis, the log-rank test was used to compare PFS between two subgroups. Cox's proportional hazard model was used for multivariate analysis to find independent predictor of PFS. A $P < 0.05$ was considered to be statistically significant.

Results

Seventy-six of the enrolled 92 patients had one or more ^{68}Ga-DOTATATE-avid lesions, while the other 16 patients had no ^{68}Ga-DOTATATE-avid lesions. All were included in the PFS analyses. Mean SUV_{max}, ΣSRETV, and ΣTLSRE calculated from PET/CT data of 76 patients with ^{68}Ga-DOTATATE-avid lesions were 37.2 ± 25.8 (range 3.0–120.6), 48.5 ± 87.9 ml (range 0.6–620.0 ml), and 949.4 ± 1687.7 (range 4.0–10778.7), respectively.

Tumor progression based on RECIST 1.1 criteria was confirmed in 36 patients (39.1%) in the follow-up period. Their median PFS was 373.5 days (95% confidence interval 303–457 days). The results of univariate and multivariate analyses are shown in Tables 2 and 3. According to univariate analyses, patients with grade 2 WD-NET and higher ΣSRETV (≥ 11.29 ml) showed significantly shorter PFS compared to the others ($P < 0.05$). SUV_{max} and ΣTLSRE did not show significant difference of PFS between the two groups ($P = 0.174$

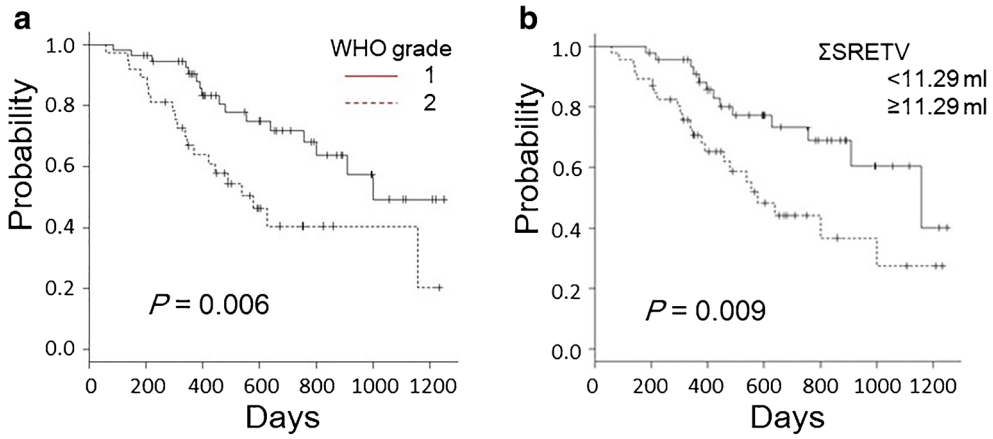

Fig. 3 Kaplan-Meier curves of patients. Patients with WHO grade 2 tumors (**a**) or greater somatostatin receptor expressing tumor volume (**b**) showed significantly shorter progression-free survival compared to the others

and 0.056, respectively). A multivariate analysis found WHO tumor grade and ΣSRETV to be independent predictors of PFS ($P < 0.05$). Kaplan-Meier curves drawn according to tumor grade and ΣSRETV are shown in Fig. 3.

Discussion

Our study revealed that tumor grade and ΣSRETV calculated from ^{68}Ga-DOTATATE PET/CT have an important potential for prediction of PFS in patients with WD-NET. This may

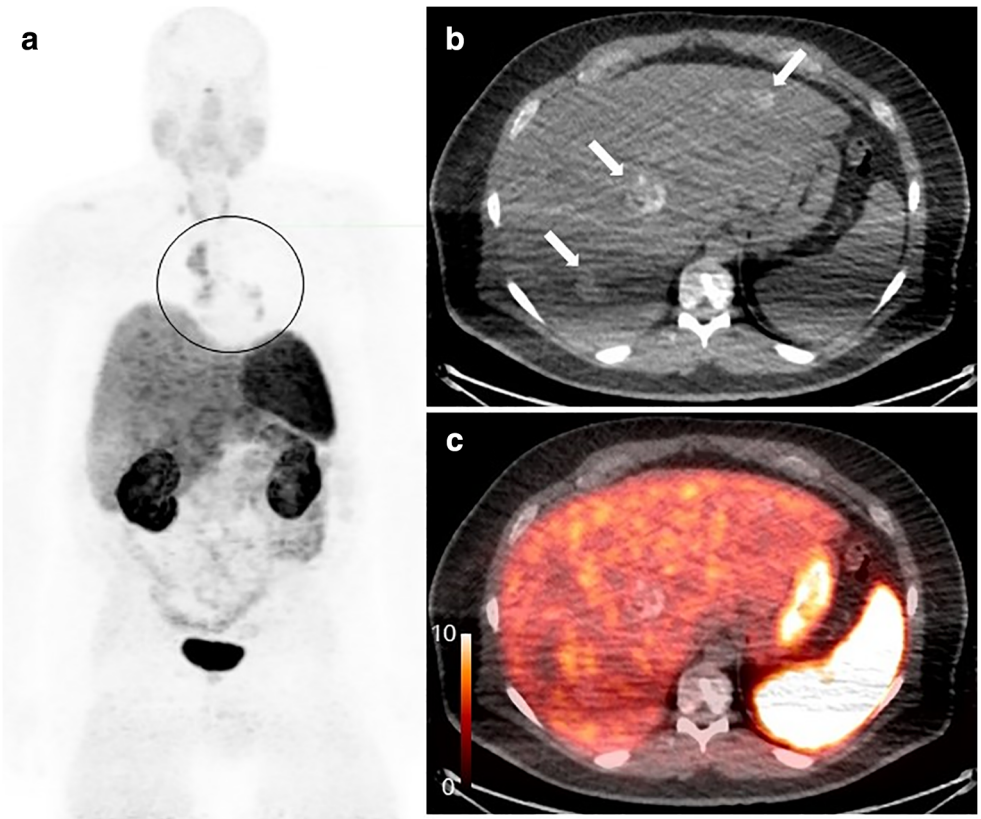

Fig. 4 A 50-year-old man with biopsy-proven liver metastasis of well-differentiated neuroendocrine tumor (WHO grade 2). ^{68}Ga-DOTATATE PET/CT was performed 3 months after liver biopsy. A maximum intensity projection image suggested multiple lymph node metastases with elevated ^{68}Ga-DOTATATE uptake in bilateral hilum and mediastinum (**a**, black circle). Although multiple liver metastases with partial calcification were detected in non-contrast CT images (**b**, white arrows), these lesions did not show significant ^{68}Ga-DOTATATE uptake (**c**, fused PET/CT image). Even though pathological assessments had not been performed for the thoracic lymph nodes, size increase both in hepatic and nodal lesions was confirmed on the follow-up CT study (39.8% increase in the sum of diameters based on RECIST 1.1 criteria). Thus, in this case, tumor progression was confirmed 136 days later. Volumetric parameters calculated from ^{68}Ga-DOTATATE PET/CT can be underestimated in such a case

expand the value of these scans in the management of such patients.

A recent study by Tirosh et al. demonstrated similar results for the prognostic utility of ^{68}Ga-DOTATATE-avid tumor volume in terms of PFS [23]. In our study, ΣSRETV showed a prognostic value as well in both univariate and multivariate analyses. However, ΣTLSRE did not show significant difference in PFS by a univariate analysis, and it was not determined to be an independent predictor of PFS by a multivariate analysis. TLSRE is a parameter reflecting SSTR expression in lesions, in addition to volume. SSTR affinity is essential information for patients with NET to select a treatment option, particularly peptide receptor radionuclide therapy (PRRT) [5, 6, 28, 29]. On the other hand, our study suggests that it might not be mandatory to consider the degree of SSTR expression in each lesion for prognostication.

Previous studies have shown significant correlation between lower SUV_{max} calculated from ^{68}Ga-DOTA-conjugated peptides PET/CT and poorer prognosis in patients with WD-NET [18–21]. Here we did not find any significant differences in PFS based on SUV_{max}. The reason for this discrepancy is unclear, and patients' selection criteria might have affected to some extent. Our results suggest that tumor volume may be better suited PET/CT-based parameter than SUV_{max} for prediction of PFS in patients with WD-NET. For patients with greater tumor volume, modifying treatment such as dose escalation or additional medication might be effective to prolong survival. Further studies are needed to assess an actual impact of PET/CT-based volumetric parameters on treatment strategy.

There are shortcomings to be considered when using ^{68}Ga-DOTATATE PET/CT for patients' prognostication. As previous studies had shown, NET lesions with different tumor grade can often coexist within a single patient [30–32]. It is known that some patients with grade 2 WD-NET do not show elevated ^{68}Ga-DOTA-conjugated peptides uptake compared to ^{18}F-FDG [8, 11]. In such patients, high-grade components of NET, which have higher affinity for ^{18}F-FDG rather than ^{68}Ga-DOTA-conjugated peptides, can result in underestimation of actual tumor volumes by ^{68}Ga-DOTATATE PET/CT (Fig. 4). These characteristics of NETs can lead to pitfalls when considering only the SUV_{max} in a single lesion as it was performed in some studies [18–21]. A combination of ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT may address this issue in such cases [7]. In one of our participants without DOTATATE-avid lesions, small liver metastases (< 10 mm) were detected by MRI performed 4 months after DOTATATE PET/CT. Such small lesions may not have conspicuous radiotracer uptake due to the partial volume effect and respiratory motion artefacts, leading to underestimation of tumor volumes.

We did not evaluate the change in the ^{68}Ga-DOTATATE PET/CT findings before and after treatment in this study. Haug et al. reported that percentage change in tumor-to-spleen SUV ratio after the first cycle of PRRT predicted time to progression and clinical improvement [33]. However, their analyses had been performed based on SUV_{max} measured in up to 3 tumors. ΣSRETV and ΣTLSRE can reflect not only SSTR expression but also tumor volumes in DOTATATE-avid lesions. Their change after PRRT therapy might be more useful parameters for assessment of response to PRRT and predicting outcome in patients with WD-NET.

Our study has some limitations. First, we did not control the treatment options used in these patients given the retrospective analysis of data. Although therapeutic strategy prior to and following the ^{68}Ga-DOTATATE PET/CT should have some impacts on the patients' prognosis, we could not include treatment options in statistical analyses due to quite heterogeneous strategies between enrolled patients. We believe that results of a previous study [23] and ours could indicate prognostic value of volumetric parameters calculated from ^{68}Ga-DOTATATE PET/CT. However, further studies which focus on more specific situations (e.g., patients who will undergo PRRT for multiple metastatic WD-NETs) may be needed before applying prognostication by ^{68}Ga-DOTATATE PET/CT in clinical settings. Second, we could not obtain tumor markers such as chromogranin-A (Cg-A) in about half the patients in this study cohort. A good correlation between volumetric parameters calculated from ^{68}Ga-DOTATATE PET/CT and Cg-A level has been shown in previous studies [19, 34]. Whether calculating ΣSRETV is superior to Cg-A remains unclear.

In conclusion, ΣSRETV calculated from ^{68}Ga-DOTATATE PET/CT may have prognostic value for PFS in WD-NET patients, as larger tumor volumes showed a correlation with shorter PFS.

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Compliance with ethical standards

Conflict of interest Andrei Iagaru receives institutional research support from GE Healthcare and Advanced Accelerator Applications, unrelated to this work. The other authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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