Original article

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Defining the optimal segmentation method for measuring somatostatin receptor expressing tumor volume on ^{68}Ga-DOTATATE positron emission tomography/computed tomography to predict prognosis in patients with gastroenteropancreatic neuroendocrine tumors

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Objective **We aimed to compare different segmentation methods used to calculate prognostically valuable volumetric parameters, somatostatin receptor expressing tumor volume (SRETV), and total lesion somatostatin receptor expression (TLSRE), measured by ^{68}Ga-DOTATATE PET/CT and to find the optimal segmentation method to predict prognosis.**

Patients and methods **Images of 34 patients diagnosed with gastroenteropancreatic neuroendocrine tumor (GEPNET) who underwent ^{68}Ga-DOTATATE PET/CT imaging were reanalyzed. Four different threshold-based methods (fixed relative threshold method, normal liver background threshold method, fixed absolute standardized uptake value (SUV) threshold method, and adaptive threshold method) were used to calculate SRETV and TLSRE values. SRETV of all lesions of a patient was summarized as whole body SRETV (WB-SRETV) and TLSRE of all lesions of a patient was computed as whole body TLSRE (WB-TLSRE).**

Results **WB-SRETVs calculated with all segmentation methods were statistically significantly associated with progression-free survival except WB-SRETV$_{at}$ which was calculated using adaptive threshold method. The fixed relative threshold methods calculated by using 45% (WB-SRETV$_{45\%}$) and 60% (WB-SRETV$_{60\%}$) of the SUV value as threshold respectively, were found to have statistically significant highest prognostic value (C-index = 0.704, CI = 0.622–0.786, P = 0.007). Among WB-TLSRE parameters, WB-TLSRE$_{35\%}$, WB-TLSRE$_{40\%}$, and WB-TLSRE$_{50\%}$ had the highest prognostic value (C-index = 0.689, CI = 0.604–0.774, P = 0.008).**

Conclusion **The fixed relative threshold method was found to be the most effective and easily applicable method to measure SRETV on pretreatment ^{68}Ga-DOTATATE PET/CT to predict prognosis in GEPNET patients. WB-SRETV$_{45\%}$ (cutoff value of 11.8 cm^3) and WB-SRETV$_{60\%}$ (cutoff value of 6.3 cm^3) were found to be the strongest predictors of prognosis in GEPNET patients.**

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Keywords: ^{68}Ga-DOTATATE, neuroendocrine tumor, PET/CT, progression-free survival, segmentation method, somatostatin receptor expression, tumor burden

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Introduction

Gastroenteropancreatic neuroendocrine tumors (GEPNETs) are a heterogeneous group of neoplasms arising from neuroendocrine cells. The development of new diagnostic modalities has increased the incidence and prevalence of GEPNETs by improving the detection rate of early-stage GEPNETs and metastases. Vast differences, however, observed in survival outcomes between patients with the same tumor stage and grade. Therefore, the identification of prognostic factors is crucial for the management of GEPNETs [1]. Conventional imaging methods and commonly used biomarkers such as chromogranin A and synaptophysin are inadequate to predict survival, progression, and response to treatment in GEPNETs [2]. Hence, tumor burden calculated by functional imaging methods can be used to anticipate prognosis.

G-protein-coupled somatostatin receptors (SSTRs), particularly type 2 (SSTR2), regulates the cell proliferation and secretory activity, are overexpressed in NETs and forms the basis of functional imaging with radiopharmaceuticals and somatostatin analog treatment. ^{68}Ga-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-peptides can demonstrate SSTR expression, especially in well-differentiated NETs [3]. ^{68}Ga-DOTA-peptides uptake in NETs generally decreases with increasing tumor grade and a higher

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maximum standardized uptake value (SUVmax) has been associated with better progression-free survival (PFS) [4]. In fact, SUVmax reflects only the SSTR expression in the pixel with the highest uptake in a lesion and does not represent tumor heterogeneity. Recent studies have demonstrated the potential prognostic role of volumetric parameters such as somatostatin receptor expressing tumor volume (SRETV) and total lesion somatostatin receptor expression (TLSRE) measured by ^{68}Ga-DOTA-peptide PET/computed tomography (PET/CT) in NETs [5]. Volumetric parameters of ^{68}Ga-DOTA-peptide PET/CT, however, have not yet been integrated into standard clinical practice. This is because, unlike SUVmax, volumetric measurements of ^{68}Ga-DOTA-peptide PET/CT require accurate segmentation of the tumor [6]. Nevertheless, the optimal segmentation method to measure volumetric parameters of ^{68}Ga-DOTA-peptide PET/CT has not been determined yet.

In this study, we aimed to compare different segmentation methods for quantitative measurement of tumor burden calculated from ^{68}Ga-DOTATATE PET/CT in patients with GEPNET and to find the optimal segmentation method to predict prognosis.

Patients and methods

Study design and patients population

Thirty-four patients with well-differentiated GEPNET who underwent ^{68}Ga-DOTATATE PET/CT between September 2015 to April 2023 were retrospectively evaluated. Only patients with well-differentiated (G1 and G2) metastatic GEPNET who underwent ^{68}Ga-DOTATATE PET/CT imaging prior to medical treatment and received octreotide long-acting release (LAR) as first-line therapy were included in the study. Patients with tumors smaller than 1 cm^3 and patients receiving adjunctive therapy with octreotide LAR were excluded. Patients with lesions which were positive on computed tomography (CT) or MRI but negative on ^{68}Ga-DOTATATE PET/CT were also excluded to ensure reproducibility of the study.

The authors declare that this study was approved by the institutional ethics committee with protocol number 09.2022.1144. The study was conducted in accordance with the principles stated in the Declaration of Helsinki, and written informed consent was obtained from the patients.

Preparation of ^{68}Ga-DOTATATE

^{68}Ga-DOTATATE was prepared in a fully automated system using a standardized procedure. Basically, a ^{68}Ge/^{68}Ga generator (iThemba Labs, Cape Town, South Africa) was eluted with 0.6 M hydrochloric acid. The liquid containing the ^{68}Ga fraction was filtered through a PS-H+ cartridge to collect and remove residual ^{68}Ge from the generator. The purified ^{68}Ga was subsequently eluted into the reaction vial with 1.7 ml of 5 M sodium chloride (NaCl). Twenty-five micrograms DOTATATE (ABX, Radeberg, Germany) was dissolved in the reaction vial by adding 1.5 M 3 mL HEPES buffer solution. The reaction was performed at 100°C for 8 min. The reaction solution was passed through a C-18 light cassette to isolate ^{68}Ga-DOTATATE. The purified ^{68}Ga-DOTATATE was eluted with a solution consisting of 1 ml of ethanol and 1 ml of water and then transferred to a sterile vial. Radiochemical purity, as assessed by HPLC, was greater than 95% in all cases.

PET/CT protocol

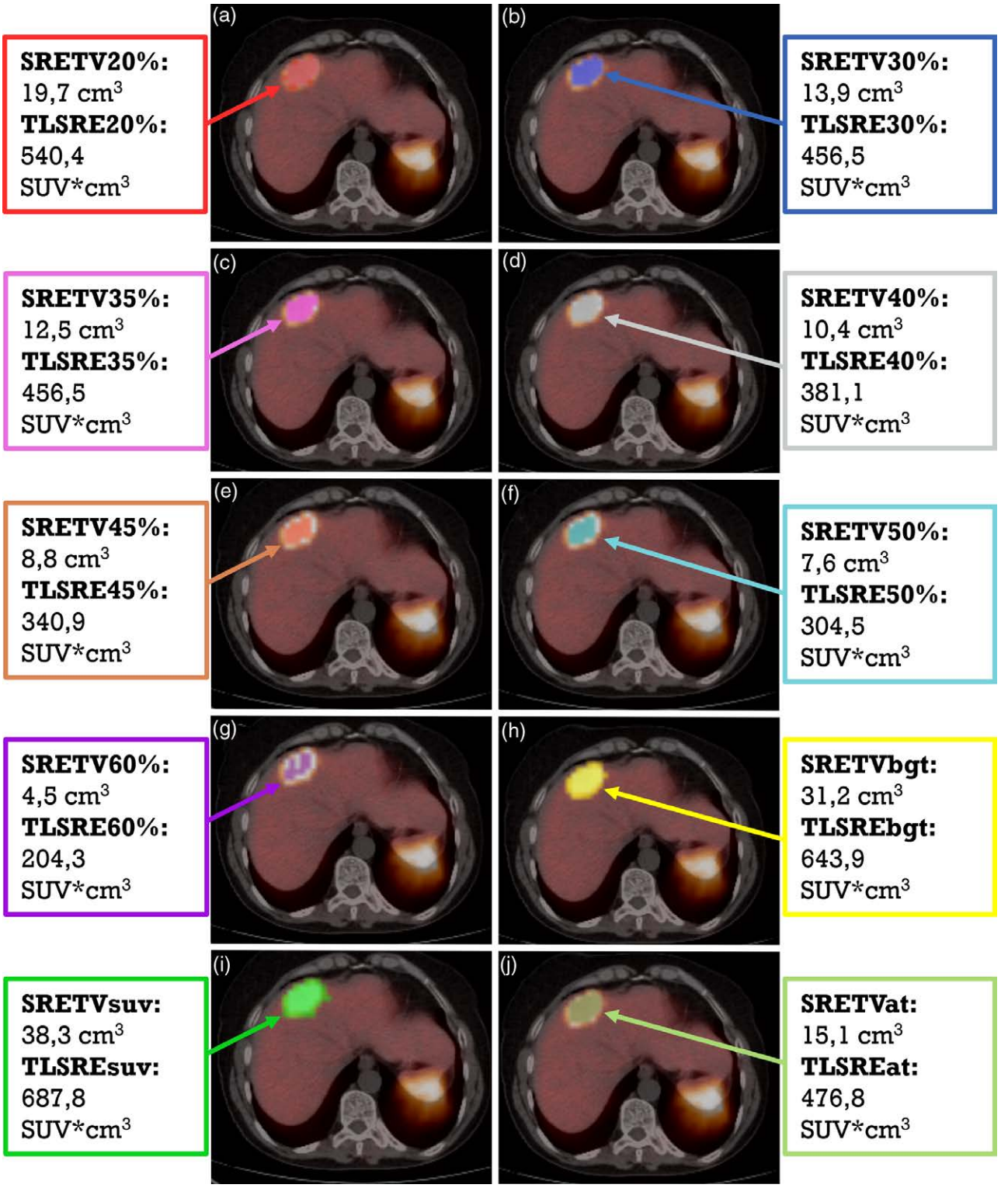
All ^{68}Ga-DOTATATE PET/CT scans were performed using a PET/CT scanner (Discovery 16 LS; GE Healthcare, Waukesha, Wisconsin, USA). ^{68}Ga-DOTATATE (2 MBq/kg) was administered by intravenous injection. Whole-body images from the base of the skull to the mid-thigh were obtained 60 ± 10 min after injection. A low-dose multidetector CT scan was performed using a 16-slice multidetector scanner (parameters: 80 mA, 140 kV, table speed 27 mm/rotation, and slice thickness 5.0 mm) from the mid-thigh to the base of the skull. A standard 3D whole-body PET scan was performed with a 3-min acquisition time per bed position (six to eight bed positions), covering the same area as CT. PET images were reconstructed with and without attenuation correction using the iterative algorithm. The recorded data were then transferred to a workstation (Advantage Windows Workstation 4.6; GE Advantage, GE Healthcare, Chicago, Illinois, USA) for further processing and evaluation.

Image analysis

All ^{68}Ga-DOTATATE PET/CT images were reanalyzed using LIFEx v7.3.0 software (www.lifexsoft.org) [7]. Two experienced nuclear medicine physicians reevaluated the PET/CT images for local recurrence, malignant lymph node involvement, and distant metastasis. Any focal uptake higher than the surrounding background activity was considered malignant based on location, intensity, shape, and size. Physiologic activity in the pituitary gland, liver, spleen, kidneys, adrenal glands, urinary tract, and the uncinate process of the pancreas was manually deleted. Four different threshold-based methods (fixed relative threshold method, normal liver background threshold method, fixed absolute SUV threshold method, and adaptive threshold method) were used to measure SRETV and TLSRE values. SRETV of all lesions was summed as whole-body-SRETV (WB-SRETV) and TLSRE of all lesions was calculated as whole-body-TLSRE (WB-TLSRE) (Fig. 1).

The first segmentation method evaluated was the fixed relative threshold method. Seven different fixed relative thresholds of 20, 30, 35, 40, 45, 50, or 60% of SUVmax value of the evaluated lesions were selected as the fixed relative thresholds to segment the lesions. SRETV represented the total volume of the tumor cells which

Fig. 1



Example of variable SRETV and TLSRE values of a liver lesion measured by different segmentation methods. Fixed relative thresholds of (a) 20%, (b) 30%, (c) 35%, (d) 40%, (e) 45%, (f) 50%, (g) 60%, (h) background threshold method, (i) fixed absolute SUV threshold method, and (j) adaptive threshold method. SRETV, somatostatin receptor expressing tumor volume; SUV, standardized uptake value; TLSRE, total lesion somatostatin receptor expression.

shows ^{68}Ga-DOTATATE uptake greater than a fixed relative threshold of SUVmax in the VOI. SRETVs of all lesions of a patient were summed as the WB-SRETV (WB-SRETV$_{20\%}$, WB-SRETV$_{30\%}$, WB-SRETV$_{35\%}$, WB-SRETV$_{40\%}$, WB-SRETV$_{45\%}$, WB-SRETV$_{50\%}$, and WB-SRETV$_{60\%}$, respectively). The corresponding WB-TLSRE values, including WB-TLSRE$_{20\%}$, WB-TLSRE$_{30\%}$, WB-TLSRE$_{35\%}$, WB-TLSRE$_{40\%}$, WB-TLSRE$_{45\%}$, WB-TLSRE$_{50\%}$, and WB-TLSRE$_{60\%}$, were calculated simultaneously.

The normal liver background threshold value was used as the second segmentation method. In detail, a 3 cm region of interest was placed in the normal liver then SUV$_{mean}$ and SD were calculated. The liver background threshold was calculated as $1.5 \times \text{SUV}_{mean} + 2 \times \text{SD}$. Subsequently, SRETV was calculated as the total volume of tumor cells demonstrating ^{68}Ga-DOTATATE uptake exceeding a liver background threshold of SUVmax in the volume of interest (VOI). SRETV values of all lesions summed as WB-SRETV$_{bgt}$. The corresponding WB-TLSRE$_{bgt}$ values were obtained by simultaneously summing the TLSRE$_{bgt}$ values of all lesions.

The fixed absolute SUV threshold method was used as the third method to segment the lesions. The mean SUVmean value of normal liver in normal subjects was found as 5.58 in the literature [8]. In our study, we also accepted 5.58 as the fixed absolute SUV value and calculated the total volume of areas above this value in all lesions as WB-SRETV$_{suv}$. Simultaneously, we calculated the sum of the corresponding TLSRE$_{suv}$ values in all lesions as WB-TLSRE$_{suv}$.

Lastly, the adaptive threshold method was used for segmentation. We calculated WB-SRETV$_{at}$ and WB-TLSRE$_{at}$ parameters using the adaptive threshold method based on tumor and background uptake found by Nestle *et al.* [9]. The determination of volume contouring thresholds is based on a function of tumor and background intensities (*I*). Specifically, the threshold is calculated as Ithreshold = (0.15 × Imean) + Ibackground.

Statistical analysis

All data were analyzed with Statistical Package for Social Sciences (SPSS) software (version 25.0, SPSS Inc., Chicago, Illinois, USA) and MedCalc Software Ltd. (MedCalc, MedCalc Software Ltd, Ostend, Belgium). PFS of patients receiving octreotide LAR were measured from the start of treatment until the date of disease progression or the last follow-up. Response Evaluation Criteria in Solid Tumors v1.1 (RECIST) were used to assess tumor progression. Descriptive analyses were performed to summarize patients' demographic information, tumor grade, primary localization, and ki-67 index. To determine the optimal cutoff values for WB-SRETV and WB-TLSRE values, receiver operating characteristic (ROC) curve analysis was performed to estimate 1-year PFS rates. By determining the area under the curve (AUC) values for each ROC curve, the most appropriate cutoff values were selected for survival analysis. Before survival analysis, all variables were grouped into two categories according to the cutoff value which were determined by the Youden index. Survival rates were determined using the Kaplan–Meier method and survival differences between groups were compared using log-rank tests. Multivariate cox regression analysis was performed to determine which of the WB-SRETV and WB-TLSRE parameters derived from the different segmentation method was better at predicting PFS. The multivariate analysis was adjusted for other prognostic factors including age, sex, primary site, metastatic site, and ki-67 index. The C-index of each method was determined and $P < 0.05$ was considered statistically significant.

Results

The general characteristics of the patients were summarized in Table 1. WB-SRETV and WB-TLSRE parameters obtained with all segmentation methods were evaluated using ROC curve analysis. The AUC values of WB-SRETV and WB-TLSRE parameters obtained from seven fixed relative thresholds (20, 30, 35, 40, 45, 50, and 60%), fixed absolute SUV threshold, background threshold, and adaptive threshold methods for predicting 1-year PFS are shown in Fig. 2. Since the AUC values of WB-SRETV and WB-TLSRE calculated with all segmentation methods were close to each other in the ROC curve analysis, survival analysis was performed for all methods using the cutoff values determined by the Youden index. The results of the univariate survival analysis are shown in Figs. 3 and 4. In multivariate survival analysis, WB-SRETV$_{45\%}$ with a cutoff value of 11.8 cm^3 (C-index = 0.704), WB-SRETV$_{60\%}$ with a cutoff value

Table 1 The basic characteristics of the patients with neuroendocrine tumor

Characteristics	Number of patients ($n = 34$)
Age, years	53 ± 10 (31–77)
Sex	
Male	18 (52.9)
Female	16 (47.1)
Primary site, *n* (%)	
Pancreas	16 (47.1)
Small intestine	7 (20.6)
Colon	3 (8.8)
Stomach	3 (8.8)
Esophagus	1 (2.9)
Unknown	4 (11.8)
Metastatic site, *n* (%)	27 (79.4)
Liver	16 (47)
Lymph nodes	11(32.3)
Bones	3 (8.8)
Lung	
Grade, *n* (%)	
G1	14 (41.2)
G2	20 (58.8)
Ki-67 index	5 ± 4, 4 (1–15)

of 6.3 cm^3 (C-index = 0.704), and WB-SRETV$_{suv}$ with a cutoff value of 60 cm^3 (C-index = 0.700) stood out as the values with the highest C-index. Among TV-TLSRE parameters, WB-TLSRE$_{35\%}$, WB-TLSRE$_{40\%}$, and WB-TLSRE$_{50\%}$ featured as the highest C-index. Details of the multivariate survival analysis are shown in Table 2.

Discussion

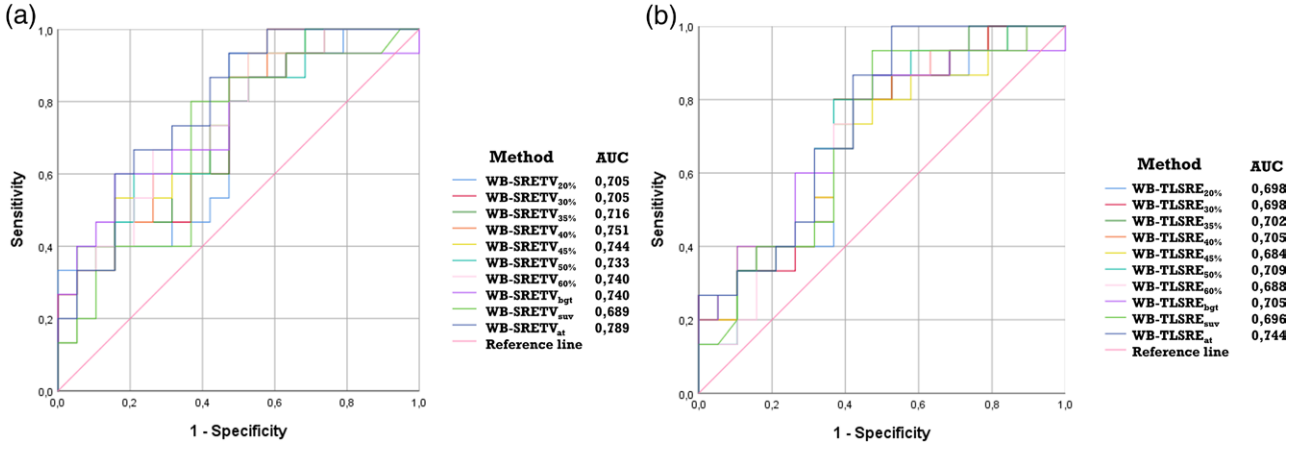
In the literature, several studies have shown the prognostic value of quantitative tumor burden calculated from ^{68}Ga-DOTA-peptide PET/CT in patients with GEPNET [6]. While most of these studies used a fixed relative threshold method, Carlsen *et al.* used a semi-automatic method based on a background threshold to calculate tumor burden and assess its prognostic value [10]. In another study, Pauwels *et al.* preferred the adaptive threshold method [11]. There is no study that shows the prognostic value of the volumetric parameters obtained with the fixed absolute SUV threshold method in ^{68}Ga DOTA-peptide PET/CT. Although it is known that different segmentation methods have been used in the literature to measure quantitative tumor burden on ^{68}Ga-DOTA-peptide PET/CT, there are still insufficient data to determine which method is more applicable in clinical practice and has a higher prognostic value.

The present study is the first to compare the prognostic value of volumetric parameters derived from all threshold-based methods on ^{68}Ga-DOTA-peptide PET/CT in patients with GEPNET. We found that WB-SRETVs generated by all segmentation methods were associated with PFS, except for WB-SRETV$_{at}$, which was calculated with the adaptive threshold method. In contrast to our results, Tirosh *et al.* reported that WB-SRETV values were correlated with PFS in their study using the adaptive threshold method [12]. Differences in softwares may explain the discrepancy between the two studies. Since the adaptive threshold method takes multiple factors into account, there is more than one way to calculate and this may lead to the differences in the results of the adaptive threshold method from one software to another and between centers [13].

In our study, all WB-SRETV parameters obtained from fixed relative thresholds were statistically significantly associated with PFS in univariate analysis, consistent with the literature [6]. In multivariate analysis, among these parameters, WB-SRETV values calculated with 45 and 60% thresholds had a higher predictive accuracy than the other parameters (C-indices = 0.704). In the literature, only fixed relative thresholds of 30, 40, and 50% have been used to date [14–16]. In addition to these thresholds, we calculated WB-SRETV parameters with fixed relative thresholds of 20, 35, 45, 60% and showed that fixed relative thresholds of 45 and 60% had higher C-indices. Therefore, considering the wider threshold range of our study compared to the current literature, it can be concluded that WB-SRETV parameters derived from 45 or 60% of SUVmax as a fixed relative threshold is more suitable for predicting PFS with tumor burden in patients with GEPNET.

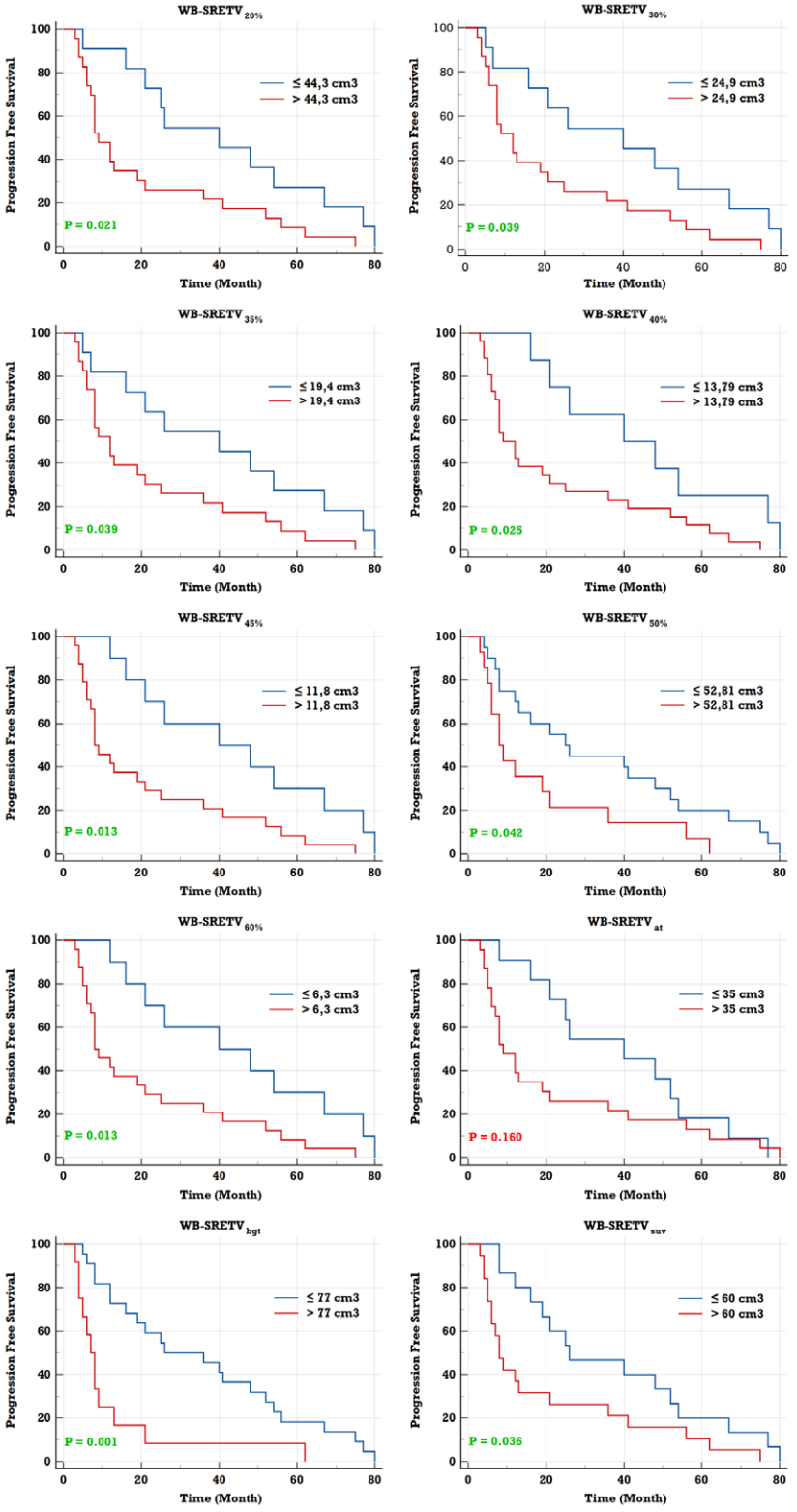
The current study demonstrated that WB-TLSRE values measured by fixed relative thresholds were less correlated with PFS prediction than the corresponding

Fig. 2



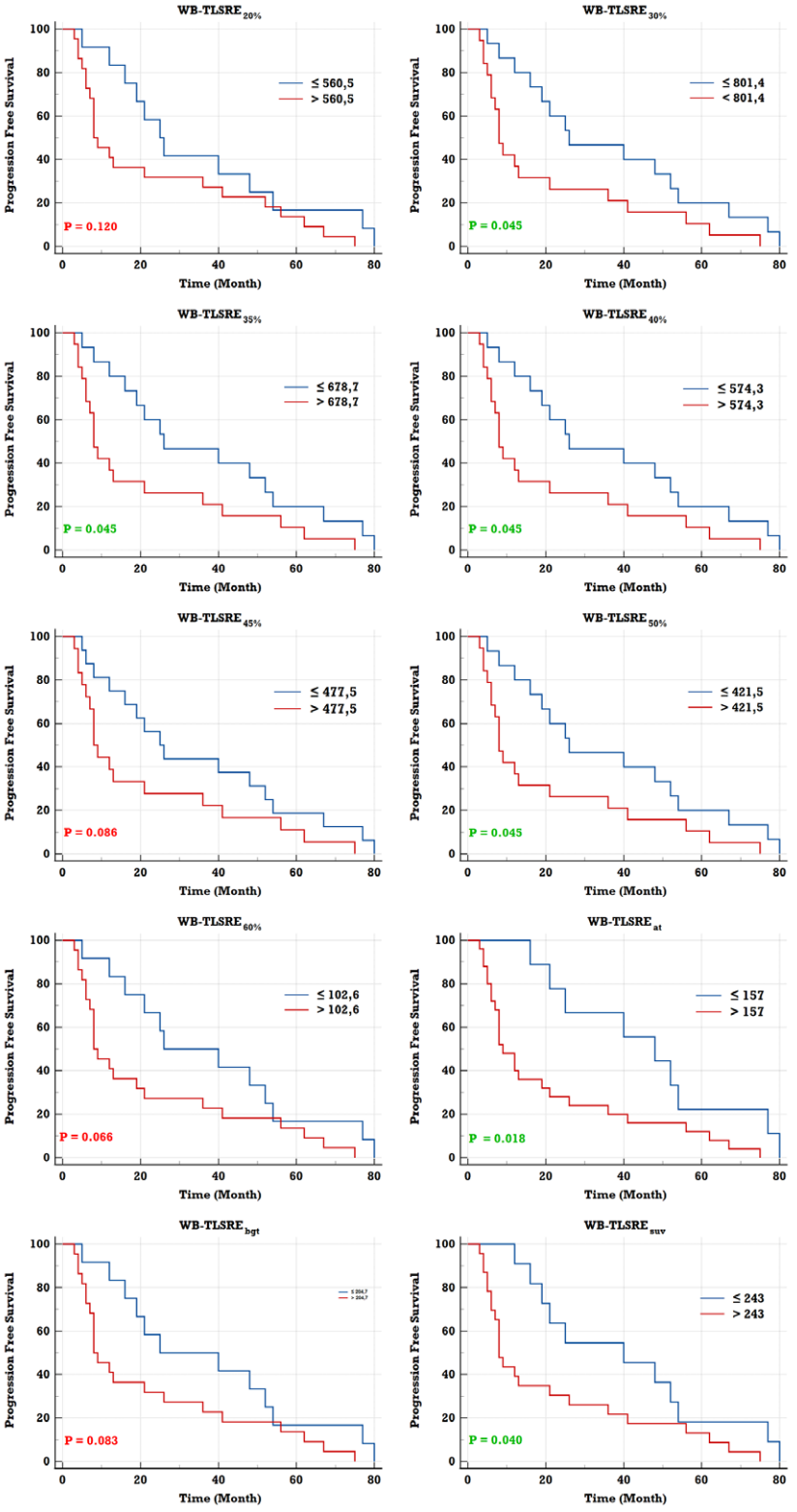
ROC curves for determining the optimal threshold value of WB-SRETV and WB-TLSRE parameters calculated by seven different fixed relative thresholds (20, 30, 35, 40, 45, 50, and 60), fixed absolute SUV threshold, background threshold, and adaptive threshold methods for predicting 1-year PFS. The tables on the right of the graphs show AUC with 95% confidence intervals for each method. AUC, area under the curve; PFS, progression-free survival; ROC, receiver operating characteristic; SUV, standardized uptake value; WB-SRETV, whole body somatostatin receptor expressing tumor volume; WB-TLSRE, whole body total lesion somatostatin receptor expression.

Fig. 3



The results of the univariate survival analysis of all the WB-SRETV values obtained from all the segmentation methods. WB-SRETV$_{20\%}$, WB-SRETV$_{30\%}$, WB-SRETV$_{35\%}$, WB-SRETV$_{40\%}$, WB-SRETV$_{45\%}$, WB-SRETV$_{50\%}$, WB-SRETV$_{60\%}$, WB-SRETV$_{bgt}$, and WB-SRETV$_{suv}$ (cutoff value of 44.3, 24.9, 19.4, 13.79, 11.8, 52.81, 6.3, 77, and 60 cm^3, respectively) were statistically significantly associated with PFS. Among these parameters, only the WB-SRETVat with a cutoff value of 35 cm^3 did not show a statistically significant ability to predict PFS. PFS, progression-free survival; WB-SRETV, whole body somatostatin receptor expressing tumor volume.

Fig. 4



The results of the univariate survival analysis of all the WB-TLSRE values derived from all the segmentation methods. WB-TLSRE$_{30\%}$, WB-TLSRE$_{35\%}$, WB-TLSRE$_{40\%}$, WB-TLSRE$_{50\%}$, WB-TLSRE$_{at}$, and WB-TLSRE$_{suv}$ (cutoff value of 801.4, 678.7, 574.3, 421.5, 157, and 243 SUV × ml, respectively) demonstrated statistically significant association with PFS. WB-TLSRE$_{20\%}$, WB-TLSRE$_{45\%}$, WB-TLSRE$_{60\%}$, and WB-TLSRE$_{bgt}$ (cutoff value of 560.5, 477.5, 102.6, and 204.7 SUV × ml, respectively) did not show a statistically significant association with PFS. PFS, progression-free survival; SUV, standardized uptake value; WB-TLSRE, whole body total lesion somatostatin receptor expression.

Table 2 Multivariate cox analysis and c-indices of PET based parameters for PFS

Parameters	*P*-value	Hazard ratio	95% CI of hazard ratio	C-index (95% CI)
WB-SRETV$_{20\%}$	0.009*	3145	1.318–7.506	0.693 (0.604–0.781)
WB-TLSRE$_{20\%}$	0.046*	2308	1.013–5.258	0.658 (0.558–0.758)
WB-SRETV$_{30\%}$	0.026*	2693	1.119–6.478	0.660 (0.567–0.753)
WB-TLSRE$_{30\%}$	0.422	1901	0.395–9.148	0.604 (0.496–0.711)
WB-SRETV$_{35\%}$	0.026*	2693	1.119–6.478	0.660 (0.567–0.753)
WB-TLSRE$_{35\%}$	0.008*	3054	1.326–7.031	0.689 (0.604–0.774)
WB-SRETV$_{40\%}$	0.070	2312	0.931–5.742	0.671 (0.575–0.767)
WB-TLSRE$_{40\%}$	0.008*	3054	1.326–7.031	0.689 (0.604–0.774)
WB-SRETV$_{45\%}$	**0.007***	**3438**	**1.384–8.541**	**0.704 (0.622–0.786)**
WB-TLSRE$_{45\%}$	0.020*	2623	1.160–5.929	0.673 (0.584–0.762)
WB-SRETV$_{50\%}$	0.186	1680	0.778–3.628	0.655 (0.565–0.745)
WB-TLSRE$_{50\%}$	0.008*	3054	1.326–7.031	0.689 (0.604–0.774)
WB-SRETV$_{60\%}$	**0.007***	**3438**	**1.384–8.541**	**0.704 (0.622–0.786)**
WB-TLSRE$_{60\%}$	0.125	1838	0.843–4.010	0.660 (0.558–0.762)
WB-SRETV$_{bgt}$	0.009*	3145	1.318–7.506	0.693 (0.604–0.781)
WB-TLSRE$_{bgt}$	0.077	2229	0.916–5.426	0.662 (0.560–0.763)
WB-SRETV$_{suv}$	0.010*	2896	1.282–6.543	0.700 (0.616–0.784)
WB-TLSRE$_{suv}$	0.077	2229	0.916–5.426	0.662 (0.560–0.763)
WB-SRETV$_{at}$	0.049*	2231	1.001–4.969	0.691 (0.612–0.770)
WB-TLSRE$_{at}$	0.077	2229	0.916–5.426	0.662 (0.560–0.763)

Multivariate analysis was adjusted by age, sex, primary site, metastatic site, and ki-67 index.
The highest C-index values are indicated with bold text.
95% CI, 95% confidence interval; PFS, progression-free survival; WB-SRETV, whole body somatostatin receptor expressing tumor volume; WB-TLSRE, whole body total lesion somatostatin receptor expression..
*$P < 0.5$.

WB-SRETV values. Furthermore, WB-TLSRE$_{20\%}$, WB-TLSRE$_{45\%}$, and WB-TLSRE$_{60\%}$ did not show a statistically significant association with PFS in univariate analysis. These results correlate with previous studies in which WB-TLSRE parameters was not associated with PFS [5,17]. Only Ohlendorf *et al*. reported that WB-TLSRE, which they calculated using a fixed relative threshold of 40%, was associated with PFS [14]. They noted that the difference may be due to different methods used to measure tumor burden and different patient populations. In our study, the WB-TLSRE$_{40\%}$ parameter, which we calculated using a fixed relative threshold of 40%, was associated with PFS in univariate analysis, too. No statistically significant relationship was, however, found between the WB-TLSRE$_{40\%}$ parameter and PFS in multivariate analysis. This finding can be related to tumor heterogeneity between lesions of the same histologic subtype, which may result in heterogeneity of tracer uptake. Tumor heterogeneity cannot be completely represented by a single voxel. Previous studies have shown that SUVmax does not represent tumor heterogeneity and does not affect the prognosis of the NET patients [6]. WB-TLSRE is a parameter that reflects the expression of SSTRs in the lesions in addition to their volume. The predictive power of WB-TLSRE parameters, in contrast to WB-SRETV values, is reduced by the use of non-predictive SUVmax in the calculation of WB-TLSRE values.

We found that WB-SRETV$_{bgt}$ calculated by the background threshold method by taking the liver as the reference region was statistically significantly associated with PFS in univariate analysis. This finding is consistent with the previous studies by Kim *et al*. and Carlsen *et al*. who used the liver as the background reference region [10,17]. Nonetheless, in a recent study by Chen *et al*., the WB-SRETV parameter measured by the threshold method using the liver as the background reference region was not associated with PFS [16]. Differences in liver SUV values between centers might be the main reason for this discrepancy between studies. Besides, the WB-TLSRE$_{bgt}$ parameter calculated by the liver background threshold value method did not show a statistically significant relationship with PFS in univariate analysis, similar to other studies in the literature [16,18].

WB-SRETV$_{suv}$ calculated with the fixed absolute SUV threshold method also showed a statistically significant association with PFS in univariate analysis. Regarding the segmentation methods, there are no studies in the literature using the fixed absolute SUV threshold method in ^{68}Ga-DOTA-peptide PET/CT [6]. Our study reveals that the fixed absolute SUV threshold method can be safely used for segmentation in ^{68}Ga-DOTA-peptide PET/CT. Considering that SUV values may vary among different centers, however, each center should determine an appropriate fixed absolute SUV threshold. This may lead to heterogeneity in the results between centers [19]. Conversely, the WB-TLSRE$_{suv}$ value calculated by the fixed absolute SUV threshold method was not found to have a statistically significant associated with PFS in multivariate analysis.

Comparing four different threshold-based methods with each other, all segmentation methods had high prognostic value in multivariate analysis, but the fixed relative threshold methods (WB-SRETV$_{45\%}$ and WB-SRETV$_{60\%}$ with a cutoff value of 11.8 and 6.3 cm^3, respectively) had the highest C-indices. The fixed relative threshold method also stands out in daily clinical practice thanks to its simpler application than other methods and its high degree of reproducibility. Finally, in all four different threshold-based methods, WB-TLSRE parameters had lower C-indices to predict PFS in multivariate analysis than the corresponding WB-SRETV parameters.

Our study has some limitations, due to its retrospective nature and relatively small sample size. In addition, the optimal threshold value of SUV 5.58, which we used as a fixed absolute SUV threshold value representing the mean physiological liver uptake of ^{68}Ga-DOTATATE, was obtained from the study conducted at our center, which covers the largest number of cases in the literature to date [8]. This value is, however, specific to the center which the study conducted and may not be valid for other centers. SUV values in ^{68}Ga-DOTATATE PET/

CT may vary depending on many technical factors such as differences in equipment, image resolution, correction methods, and reconstruction [20]. Further studies are needed to provide a normalized SUV threshold suitable for multicenter studies. Finally, although we used all threshold-based methods to determine SRETV in ^{68}Ga-DOTATATE PET/CT, algorithm-based methods could not be evaluated. Despite never being used in ^{68}Ga-DOTA-peptide PET/CT, algorithm-based methods have been reported to segment tumors more accurately in tumors with a wide range of uptake and size on FDG PET/CT [21–24]. Further studies with larger patient series are needed to compare threshold and algorithmic methods in ^{68}Ga-DOTA-peptide PET/CT.

Conclusion

Our study demonstrated that the fixed relative threshold method was the most accurate method to determine SRETV on pretreatment ^{68}Ga-DOTATATE PET/CT for predicting prognosis in GEPNET patients. Furthermore, we concluded that the WB-SRETV$_{45\%}$ and WB-SRETV$_{60\%}$ with a cutoff value of 11.8 and 6.3 cm^3, respectively, could be a strong predictor of prognosis in GEPNET patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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