Prognostic value of functional tumor burden on 68Ga-DOTATOC PET/CT in patients with pancreatic neuro-endocrine tumors

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Despite their relative quiescence, pancreatic neuro-endocrine tumors (pNET) can correspond to various presentations and outcomes. Several prognostic factors have been identified, including maximal standardized uptake value of the most intense focus (maxSUV$_{max}$) on Positron Emission Tomography (PET) with a somatostatin analogue. Herein, we investigate the prognostic value on progression free-survival of the total functional tumor volume (TFTV) measured by ^{68}Ga-DOTATOC PET. From patients who underwent ^{68}Ga-DOTATOC PET from 2008 to 2014, we selected consecutive patients with G1 or G2 pNET (2010 World Health Organization classification), at least one abnormal focus on PET and available follow-up data. TFTV was computed by summing the volumes of all pathological foci, delineated use of 41% of its SUV$_{max}$ for each threshold focus. Fifty patients were included. During the follow-up period, 33 patients had stable or responsive disease (66%; median duration 28.5 months; range 6.3–77.7 months) and 17 patients experienced disease progression (34%; median progression time 21 months; range 6.7–44.7 months). Median PFS was 43.5 months. The best TFTV cut-off for predicting progression within 24 months was 13.8 cm³. Multivariate analysis determined that TFTV greater than 13.8 cm³ was the only criterion considered a significant risk factor for tumor progression (HR 2.9; p=0.0003). A significant difference in PFS was observed for TFTV (<13.8 vs. ≥ 13.8 cm³: median not reached vs. 25 months; p=0.0001).

Our study suggests that 68Ga-DOTATOC TFTV measured on PET images is a valuable prognostic biomarker in patients with well-differentiated pNETs of all stages.

Key words: ^{68}Ga-DOTATOC, positron emission tomography, pancreatic neuroendocrine tumors, functional tumor volume, prognostic biomarker

Pancreatic neuro-endocrine tumors (pNET) are rare, with an estimated incidence less than 1 in 100,000 [1]. Compared to cancers of the exocrine pancreas, pNETs are slowly progressive, have relatively good prognosis, and can have a variety of clinical presentations and outcomes [2, 3]. Identifying prognostic markers is therefore crucial for the management of these patients. Tumor grade [4] and disease extent [5] have already been recognized as relevant prognostic factors.

PET imaging using ^{68}Ga-labeled somatostatin analogues is progressively replacing ^{111}In-pentetreotide scintigraphy as first-line imaging method for diagnosis, staging and restaging of pNETs [6, 7]. This recent imaging modality is a powerful tool in the management of patients with well-differentiated neuro-endocrine tumors (NET) [7]. One of its various advantages over scintigraphy and SPECT is the possibility of performing semi-quantitative analysis.

Ambrosini et al. [3] assessed the prognostic value of maximum standardized uptake value of the most intense abnormal focus (maxSUV$_{max}$) on ^{68}Ga-DOTANOC PET in patients with pNETs and a higher SUV$_{max}$ was associated with better outcome.

Recent measurements of tumor burden by metabolic tumor volume (MTV) have been thoroughly reported in the use of ^{18}F-fluorodeoxyglucose (FDG) PET/CT in lymphoma and then in a wide range of solid tumors. The prognostic value on overall survival of MTV at initial staging has been demonstrated [8–10].

The diagnostic target of ^{68}Ga-DOTATOC is not a metabolic pathway, but the pathological over-expression of somatostatin receptors (mainly type 2 and 5). Therefore, we propose the term functional tumor volume (FVT) for the evaluation of tumor volume showing pathologically increased

somatostatin receptor expression and total functional tumor volume (TFVT) for the summed lesion volume at whole body level. To the best of our knowledge, no study has been published on the prognostic value of functional tumor volume measurements in patients with NETs on PET/CT using a 68Ga-labelled somatostatin analogue.

Herein, we investigate the prognostic value on progression-free survival (PFS) of tumor burden in patients with pNETs. This is evaluated by means of the total functional tumor volume (TFTV) which over-expresses somatostatin receptors (SSR), as shown on 68Ga-DOTATOC PET. Our secondary objective is to check whether our series confirm the results of Ambrosini et al. [3] on the prognostic value of maxSUV$_{max}$ on PFS in patients with pNETs.

Patients and methods

Patients. With these objectives, we reviewed the data of the patients referred to our department for 68Ga-DOTATOC PET/CT examination between September 2008 and December 2014 and patients were included in the prospective study from September 2008 to September 2012. The study is "PHRC DOTATOC" EUDRACT 2007-002610-19 and individual authorization was obtained from the French Medicine Agency (ANSM) for each patient from October 2012. All patients gave their informed consent. We selected the data of all consecutive patients with histologically proven G1 or G2 pNET, according to the 2010 World Health Organization classification [4]. The additional inclusion criteria in the present analysis were the detection of at least one abnormal focus on 68Ga-DOTATOC PET/CT and available follow-up data after PET/CT.

All patients underwent physical examination at inclusion by each referring physician in departments specialized in the management of neuroendocrine tumors. Clinical history was recorded to identify the presence of symptoms induced by functioning tumors.

Follow-up visits were performed by the referring physician after 68Ga-DOTATOC PET/CT; imaging follow-up included CT at 6 months (+/– one month) after inclusion. Progression was assessed on CT using the RECIST criteria [11]. If progression was suspected clinically or biologically but not confirmed on conventional imaging, another 68Ga-DOTATOC PET/CT was performed to check for appearance of new pathological foci. This was considered disease progression, similarly to the current RECIST 1.1 criteria using FDG PET [11].

Patient management was decided by each referring physician according to the general status of the patient, the stage of the disease and the results of PET/CT or of liver MRI. The type of management was recorded: surgery, medical therapy (non-radioactive somatostatin analogues, chemotherapy or targeted therapy), somatostatin receptor radionuclide therapy (SRRT), local therapy of a single metastatic site or therapeutic abstention.

The protocol for this ancillary study was approved by the local Ethics Committee and the study was performed in compliance with the Helsinki Declaration for human studies.

PET/CT imaging. 68Ga-DOTATOC was prepared in the radio-pharmacy of our Nuclear Medicine department. 68Ga was eluted from a 68Ge/68Ga generator and DOTATOC was labelled following the Breeman procedure [12]. The 68Ge/68Ga generator and the DOTATOC vials were both purchased from Iason GmbH (Graz, Austria). PET/CT with 68Ga-DOTATOC was performed after an intravenous injection of 2MBq/kg of body mass of the radiotracer followed by an uptake phase of 60 min. No fasting was needed prior administration.

68Ga-DOTATOC PET/CT acquisition covering a field of view from the skull to mid-thighs was performed on a Gemini TF 16 PET/CT machine (Philips Medical System). The CT acquisition was performed first (120 kVp 80 mA.s), and then the PET acquisition in 2 min per bed position in 3D mode with the time-of-flight determination.

Functional tumor volume computation. Any focus with a visual intensity greater than background that could not be explained by physiologic uptake or elimination (pituitary gland, spleen, liver, adrenals, uncinate process, kidneys and urinary tract) was considered pathological somatostatin receptor over-expression.

Total functional tumor volume (TFTV) of all visible lesions at whole body level was measured by a senior nuclear medicine physician on the attenuation-corrected images by summing up the functional volumes of all visible pathological 68Ga-DOTATOC foci. The limit of the functional volume of each focus was determined by applying a threshold of 41% of its SUV$_{max}$, using semi-automatic software (Tumor tracking, IntelliSpace Portal Philips Healthcare). This threshold of 41% was selected arbitrarily, but based on MTV data obtained by FDG [9, 13, 14].

A spherical volume of interest (VOI) was drawn around each pathological uptake focus, and the functional volume was computed by summing all voxels above the threshold within the VOI.

SUV$_{max}$ was calculated by measuring the maximal concentration of 68Ga-DOTATOC in the region of interest corrected for body weight and injected activity (SUV$_{max}$ = maximum activity concentration/[injected activity /body mass]) [15]. The highest SUV$_{max}$, corresponded to the most intense voxel of all VOIs, and the noted maxSUV$_{max}$, was recorded for each patient.

Data collection. Collected data on demographic, clinical and pathological features was recorded on a created computer sheet. The tumors were classified according to the 2010 WHO classification [4] and the TNM classification grading system [5]. The Ki-67 proliferation index was expressed as the percentage of Ki-67-positive cells in 2,000 tumor cells in the most highly immune-staining areas using the MIB1 antibody.

Statistical analysis. Analysis was performed using dedicated software (Medcalc version 11.6.1.0; Windows). Median values and the respective ranges were used to describe the quantitative data. Groups were compared using the Pearson Chi-squared test, the Fisher's exact test for unpaired qualitative variables and the Mann-Whitney U test for unpaired continuous variables.

The number of pathological foci per patients was recorded and a histogram was created.

To evaluate the potential prognostic value of TFTV, we calculated the progression-free survival (PFS) rate by dividing the series of patients, based on disease status (progressive vs. stable disease) at the arbitrarily selected time point of 24 months after the ^{68}Ga-DOTATOC PET/CT [3] . The PFS was defined as the time interval between ^{68}Ga-DOTATOC PET/CT and the time of disease progression. The area under the Receiver-Operating Characteristics curve (AUC) characterized the accuracy of the TFTV at baseline in predicting further disease progression at 24 months after PET/CT. The best prognosis cut-off value was estimated by the maximum-likelihood-ratio method.

PFS was also analyzed by the Kaplan-Meier method according to qualitative variables and the progression-free survival curves were compared using the log-rank test. The predictive risk factors for disease progression were determined by univariate and multivariate analyses using the Cox proportional hazards method. Risk factors were expressed as hazard ratios and 95% confidence intervals were determined.

The multivariate model was constructed using the backward method after all variables had been included and p-value was considered significant when less than 0.05.

Kaplan-Meier, univariate and multivariate analyses for maxSUV$_{max}$ and TFTV were performed on the whole population and on two subgroups of the cohort: localized disease (stages I and II) and advanced disease (stages III and IV). For the maxSUV$_{max}$, the cut-off value of 37.8 was applied because this was previously established in the study of Ambrosini et al. [3]. No published threshold was available for TFTV, so we chose the cut-off values determined by ROC analysis.

Results

Patient characteristics. A total of 50 patients (26 men and 24 women; median age, 51 y; 20–77) with pNETs matched the criteria of the study. ^{68}Ga-DOTATOC PET images were acquired after intravenous injection of an average 127 MBq (51–182 MBq); 1.8 MBq/kg of body mass (0.7–2.4 MBq/kg) and an uptake phase between administration of ^{68}Ga-DOTATOC and average image acquisition of 58 min (40–120 min).

Eight patients (16%) had functioning tumors: 4 insulinomas, 3 gastrinomas, and one glucagonoma; and 42 patients (84%) non-functioning pNET. Eight patients had multiple endocrine neoplasia syndrome type 1 (MEN 1). According to the 2010 WHO classification, the pNET grade was G1 in 26 patients (52%) and G2 in 24 (48%).

Table 1. Patient characteristics in the entire population and stratified according to total functional volume

Patient characteristic	No. of patients	Total functional tumor volume (cm³)			Low tumor burden TFTV <13.8 (n=28)	High tumor burden TFTV ≥13.8 (n=22)
		Median	Range	p-value		
Gender						
Male	26	22	2.1–601		11	15
Female	24	10.9	1.7–370	p=0.25	17	7
Functioning NET						
Yes	8	6.5	2.3–24		7	1
No	42	17.4	1.7–601	p=0.22	21	21
Stage						
I	14	2.2	2.1–22		13	1
IIA	6	7	2.5–25.4		5	1
IIIB	9	3.8	1.7–48		7	2
IV	21	50.4	9.6–601		3	18
Stages I/II	20	3.2	2.1–25.4			
Stages III/IV 2010 WHO classification	30	22.8	1.7–601	p<0.0001		
NET G1	26	9.3	1.7–370		21	5
NET G2	*24*	24	2.3–601	p=0.0062	7	17
Ki67						
<=5%	40	12.1	1.7–6.1		25	15
>5%	10	36.5	2.5–186	p=0.21	3	7
Status at 24mo (40 patients analysed)						
Stable disease	29	26	1.7–271			
Progressive disease	11	165	4.5–601	p<0.001		

The median Ki-67 index of the NET tumor was 2.5% (1–16%); less than or equal to 5% in 40 patients, and greater than 5% in 10 patients (20%). According to the TNM classification, the disease stage was I in 14 patients (28%), IIA in 6 patients (12%), IIIB in 9 patients (18%) and IV in 21 patients (42%). The subgroup of patients with stages III and IV disease included 30 patients and the subgroup of stages I and II 20 patients. The characteristics of all 50 patients are listed in Table 1.

^{68}Ga-DOTATOC foci and total functional tumor volume (TFTV). The number of pathological foci per patient ranged from 1 to 51 (median: 3); the histogram for the distribution of the number of foci per patient is displayed in Figure 1. Data on median TFTV and the respective ranges among the different groups of patients are reported in Table 1. TFTV differed significantly according to the stage (stage III/IV vs. I/II, median: 22.8 cm^3 vs. 3.2 cm^3; p<0.0001), the 2010 WHO classification (NET G2 vs. NET G1: 24 cm^3 vs. 9.3 cm^3; p=0.0062) and the clinical status at 24 months of follow-up (progressive disease vs. stable disease: 165 cm^3 vs. 26 cm^3; p<0.001). There were no significant differences with respect to gender, the presence of tumor syndrome or Ki 67 using a cut-off value of 5%.

Follow-up after ^{68}Ga-DOTATOC PET/CT. The 50 patients were followed up for a median of 25.6 months (6.3–77.7 mo). Of the 50 patients, 19 (38%) received medical therapy alone (non-radioactive somatostatin analogues, chemotherapy or targeted therapy), 2 patients received SRRT (4%), 18 patients (36%) underwent surgery, 6 patients (12%) underwent surgery and received long-lasting somatostatin analogues and 2 patients (4%) had a local treatment (radiofrequency of a single macroscopic metastasis in the liver); therapeutic abstention was decided for 3 patients (6%).

PFS rate at 24 months. PFS rate at 24 months of follow-up was 73% (29/40). Ten patients were not included in this analysis because they had stable disease and a follow-up period of less than 24 months. As reported in Table 1, pre-treatment TFTV was significantly higher (p<0.001) in patients who progressed within 24 months of follow-up (11 patients; median 165 cm^3; range 4.5–601 cm^3) than in patients with stable disease (29 patients; median 26 cm^3; range 1.7–271 cm^3).

The ROC analysis showed that baseline TFTV was quite accurate in predicting whether a patient will progress within 24 months after PET/CT (AUC±SE, 0.88±0.05; p<0.0001); the best cut-off volume was the summed volume of all lesions detected at whole body level with ^{68}Ga-DOTATOC uptake intensity >41% of SUV$_{max}$ in a given lesion. This was 13.8 cm^3 with a sensitivity and specificity to predict further progression within 24 months of 88% and 82%, respectively.

Predictors for tumor progression during the whole follow-up period. During the overall follow-up period, 33 patients had stable or responsive disease (66%; median duration 28.5 mo; range 6.3–77.7 mo; Figure 2) and 17 patients experienced disease progression (34%; median

time for progression 21 mo; 6.7–44.7 mo; Figure 3). Disease progression was assessed on ^{68}Ga-DOTATOC PET/CT for 10 of the 17 patients and on conventional imaging (CT or MRI) for 7 patients.

By univariate analysis, the variables found to be predictive for tumor progression during the whole follow-up period are summarized in Table 2. Risk factors for tumor progression were a NET G2 vs. G1 (HR 1.5; p=0.01), a stage III or IV vs. a stage I or II (HR 1.6; p=0.03), and a TFTV greater than 13.8 cm^3 (HR 2.33; p=0.002).

By multivariate analysis, TFTV greater than 13.8 cm^3 was the only significant risk factor (HR 2.9; p=0.0003). In the subgroup of stage III or IV patients (30 patients), multivariate analysis also showed that TFTV greater than 13.8 cm^3 was the only significant risk factor (HR 1.9 p=0.01).

Gender, functioning status, non-surgical vs. surgical treatment after PET/CT, MEN syndrome, Ki-67 greater than 5%, maxSUV$_{max}$ less than 37.8 were not risk factors for tumor progression; neither in the whole series nor in the subgroup of stage III or IV patients.

We applied TFTV and maxSUV$_{max}$ at baseline for the whole series and combined these to calculate sensitivity, specificity, positive and negative predictive values and accuracy for progressive status prediction (Tables 3 and 4).

Our study confirmed significant differences in PFS with Ki-67, using the cut-off value of 5% established by Panzuto et al. [2] and Ambrosini et al. [3] and the cut-off value of 2% corresponding to the 2010 WHO classification [4].

Analysis of PFS on the whole follow-up period for the entire population. Median PFS was 43.5 months (mo. Figure 4). Significant differences in PFS were observed for TFTV (<13.8 cm^3 vs. ≥13.8 cm^3: median not reached vs. 25 mo; p=0.0001) (Figure 4), Ki-67 (<5% vs. ≥5%: 44.7 mo vs. 33.1 mo; p=0.04), the 2010 WHO classification (NET G1 vs. NET G2: 44.7 mo vs. 32.6 mo; p=0.008).
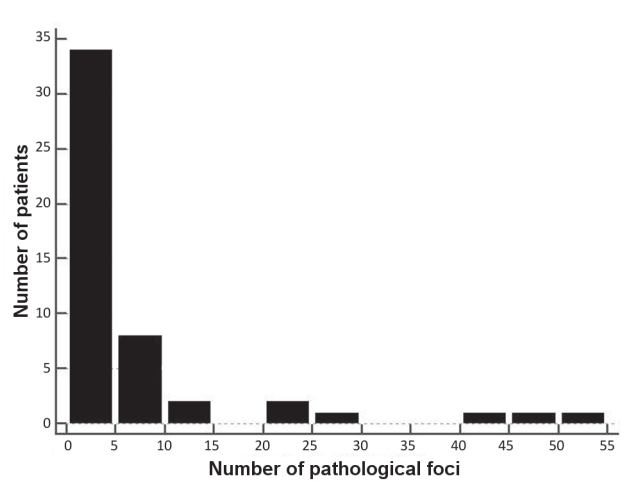

Figure 1. Histogram of the number of pathological foci detected by ^{68}Ga-DOTATOC PET/CT per patient.
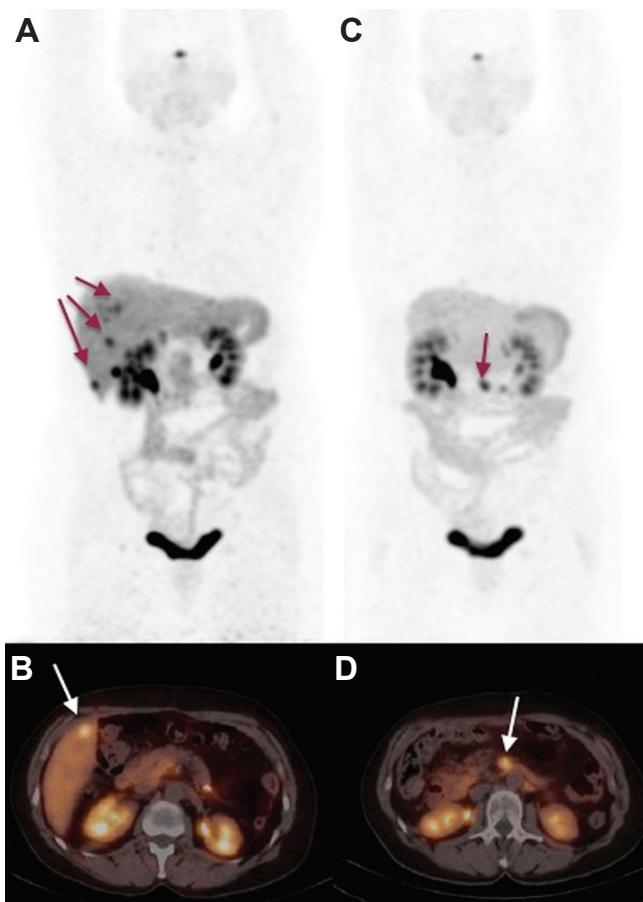
Figure 2. 68Ga-DOTATOC PET/CT of a 37-year-old male patient with pancreatic G1 NET. Maximum intensity projections (A and C) and trans-axial slices (B and D). TFTV was 3.6 cm³ and maxSUV$_{max}$ 22 on baseline PET/CT (A and B). Patient was treated with somatostatine analogues. Disease was stable at 20 mo of follow-up (C and D).
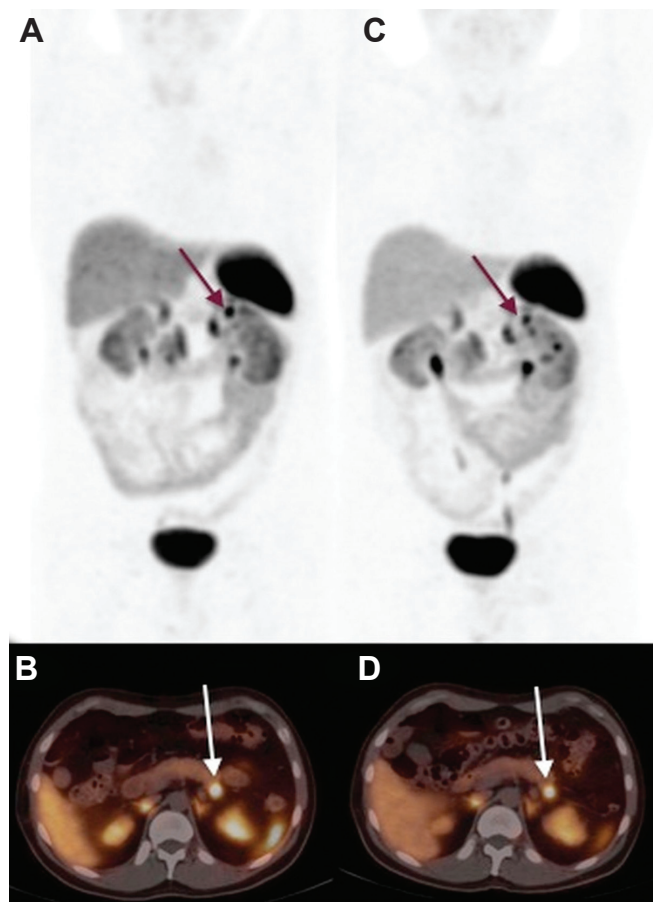
Figure 3: 68Ga-DOTATOC PET/CT in a 57-year-old female patient with pancreatic G2 NET and secondary hepatic lesions. Maximum intensity projections (A and C) and transaxial slices (B and D). TFTV was 50.4 cm³ and maxSUV$_{max}$ 8.8 on baseline PET/CT (A and B). Patient underwent partial hepatectomy. Disease progressed at 19.1 mo of follow-up (C and D) with the detection of a retropancreatic 68Ga-DOTATOC positive lymph node.

Table 2. Risk factors for disease progression at 24 months, univariate and multivariate analyses

Patient characteristics	Univariate			Multivariate		
	HR	95% confidence interval	p-value	HR	95% confidence interval	p-value
Sex (male vs. female)	14	0.34–2.47	p=0.88	–	–	–
Neuro-endocrine syndrome (no vs. yes)	0.89	0.05–3.1	p=0.39	–	–	–
Stage I/II vs. III/IV	1.6	1.1–21.9	p=0.03	–	–	–
NET G2 vs. G1	1.5	1.3– 16.1	p=0.01	–	–	–
Treatment (non-surgical vs. surgery)	0.42	0.55–4.14	p=0.4	–	–	–
MEN vs. no MEN	1.2	0.03–2.2	p=0.24			
Ki67 (>5% vs. ≤5)	1.001	0.96–7.6	p=0.07	–	–	–
Ki67 (continuous)	13.9	33.26–42×10⁹	p=0.008			
TFTV (>13.8 vs. ≤13.8)	2.33	2.3–45.6	p=0.002	2.9	3.7–90.3	p=0.0003
TFTV (continuous)	125	1.004– 1.01	p<0.0001	–	–	–
maxSUV$_{max}$ (>37.8 vs. ≤ 37.8)	0.2	0.22– 1.63	p=0.31	–	–	–
maxSUV$_{max}$ continuous	0.003	0.99–1.01	p=0.61	–	–	–

The following "median not reached" classification indicates that more than half the patients were considered responding or stable at the end of the follow-up period. No significant difference was found by the $maxSUV_{max}$ ($\geq$37.8 vs. <37.8: median not reached vs. 43.6 mo; p=0.35), gender (men vs. women: 43.5 vs. 32.5 mo; p=0.88), the functioning status (functioning vs. non-functioning: 43.5 mo vs. median not reached; p=0.3), disease stage (I and II vs. III and IV: median not reached vs. 32.5 mo; p=0.05), type of treatment (surgery vs. other treatment : median not reached vs. 43.5 mo; p=0.4), the presence of a MEN syndrome (MEN syndrome present vs. absent: median not reached vs. 43.5 mo; p=0.21). The threshold $maxSUV_{max}$ with significant prognostic value for patient's outcome at 24 months was not found.

PFS and multivariate analysis according to the stage of the disease. In the subgroup of 30 stage III or IV patients, 15 patients (50%; median follow-up 28.5 mo; range 6.3–43.8 mo) had stable disease, and 15 patients had disease progression during the overall follow-up period (50%; median time to progression 21 mo; range 6.7–44.7 mo). In this subgroup, as in the overall series, TFTV was quite accurate in predicting if a patient would progress (AUC±SE, 0.85±0.07; p<0.0001). The best cut-off value was 13.8 cm³ with a sensitivity and specificity for the prediction of tumor progression of 93% and 67% respectively.

In this subgroup, the median PFS was 24.5 months, and median not reached means that at the end of the follow-up period, more than half of patients were responding or stable. Significant differences in PFS were observed according to TFTV (<13.8 cm³ vs. $\geq$13.8 cm³: median not reached vs.

22.6 mo; p=0.04) and the 2010 WHO classification (NET G1 vs. NET G2: 44.7 mo vs. 32.5 mo; p=0.02). No significant difference was found according to the $maxSUV_{max}$ (<37.8 vs. $\geq$37.8: 34 mo vs. median not reached; p=0.76), Ki-67 (<5% vs. $\geq$5%: 43.5 mo vs. 32.3 mo; p=0.12), gender (men vs. women: 43.5 vs. 32.5 mo; p=0.88), the functioning status of the NET (functioning vs. non-functioning: 22.6 mo vs. median not reached; p=0.32), type of treatment (surgery
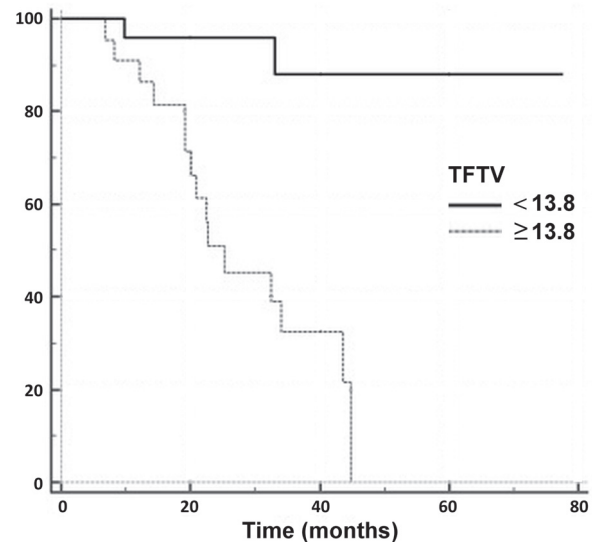

Figure 4. PFS in 50 patients with well-differentiated pNET (G1 and G2) according to baseline TFTV. PFS: progression free survival; total functional tumor volume; Solid line=TFTV <13.8 cm³; dashed line=TFTV $\geq$13.8 cm³; p=0.0001.

Table 3. Number of patients according to the progressive status, TFTV and the $maxSUV_{max}$.

	Progressive disease (positive)			Responsive or stable disease (negative)		
	TTFV	TTFV	$maxSUV_{max}$	TTFV	TTFV	$maxSUV_{max}$
	>13.8 cm³ (positive)	$\leq$13.8 cm³ (negative)		>13.8 cm³ (positive)	$\leq$13.8 cm³ (negative)	
$maxSUV_{max} \leq 37.8$ (positive)	10	2	12	4	23	27
(n=39)	TP both criteria		TP	FP both criteria		FP
$maxSUV_{max} >37.8$ (negative)	4	0	4	4	3	7
(n=11)		FN both criteria	FN		FN both criteria	TN
14		2		8	26	
TP TFTV		FN TFTV		FP TFTV	TN TFTV	
(n=16)					(n=34)	

TP: true positive; TN: true negative

Table 4. Diagnostic performance to predict progressive disease according baseline TFTV, $maxSUV_{max}$ and combination of both criteria.

Parameter	TFTV (positive if > 13.8cm³)	$maxSUV_{max}$ (positive if < 37.8)	TFTV and $maxSUV_{max}$ combined (positive only if both criteria are positive)
Sensitivity	14/16= 88%	12/16=75%	10/16=63%
Specificity	26/34=77%	7/34=21%	30/34=88%
Positive predictive value	14/22=58%	12/39=31%	10/14=71%
Negative predictive value	26/28=93%	7/11=64%	30/36=83%
Accuracy	40/50=80%	19/50=38%	40/50=80%

vs. other treatment: 22.4 mo vs. 33.1 mo; p=0.24), or a MEN syndrome (present vs. absent: 30 mo vs. 29 mo; p=0.33). The threshold $maxSUV_{max}$ with significant prognostic value for patient's outcome at 24 months was not found.

In the stage I and II patient subgroup of 20 patients, 18 had stable disease (90%; median follow-up 28.4 mo; range 6.7–77.5 mo), and the remaining 2 had disease progression during the overall follow-up period (10%; median time for progression 9.8 and 25.2 mo). This subgroup was too imbalanced (only 2 patients with progressive disease) to perform complementary statistical analysis.

Discussion

To the best of our knowledge, this is the first study to establish that a high total functional tumor volume based on ^{68}Ga-DOTATOC uptake can be an independent prognostic biomarker for pNET; and higher volume gives poorer outcome.

In the past two decades, semi-quantitative analysis in FDG PET imaging has helped identify prognostic biomarkers in a wide range of solid tumors and hematology malignancies, including NETs for which a high FDG uptake correlates with poor prognosis [16–18].

Numerous studies have been based on SUV_{max} measurements and this is considered a convenient and reproducible parameter. More recently, volumetric parameters have created great interest in nuclear medicine physicians. Indeed, unlike SUV_{max} or $maxSUV_{max}$, which derive information from one single voxel, the one with the highest radionuclide concentration per focus or in the whole patient, volumetric parameters reflect the entire tumor burden.

In a recent study involving 20 patients with pNET of all grades, Kim et al. [19] suggested that FDG metabolic tumor volume was an independent prognostic factor for overall survival, with high MTV predicting shorter survival.

Herein, we chose progression-free survival, and not overall survival, as the outcome because well-differentiated lower grade NETS frequently over-express somatostatin receptors but they progress slowly and do not show increased glucose metabolism. This choice was proven appropriate because no patients died during a median follow-up period of 25.6 months.

For well-differentiated NETs, which are often FDG-negative, PET with ^{68}Ga-labelled-somatostatin analogue (SRPET) is a powerful tool for diagnosis, staging and restaging [20] and also for selecting patients eligible for somatostatin analogue therapy, including SRRT [21]. SRPET is now part of the diagnostic flowchart for pNET; gradually replacing ^{111}In-pentetreotide scintigraphy and SPECT [6, 7].

The prognostic value of foci $maxSUV_{max}$ on SRPET has recently been investigated by Ambrosini et al. [3] in 43 patients with well-differentiated (WHO G1 and G2) stages III or IV pNETs. These authors found high ^{68}Ga-DOTANOC $maxSUV_{max}$ correlates with better outcome. Our study did not confirm this prognostic value of $maxSUV_{max}$ using the proposed 37.8 cut-off value, even when combined with TFTV to better reflect disease extension. Furthermore, the threshold $maxSUV_{max}$ with significant prognostic value for patient outcome at 24 months was not found in our study.

A further difference between the two studies is that the somatostatin analogue for PET/CT was DOTANOC in Ambrosini [3] and DOTATOC in our work. The different affinity profiles of the two analogues could explain the cut-off value of $maxSUV_{max}$ reported by those authors did not give different outcome in our study cohort. Furthermore, the study populations were not identical because we investigated all stage patients while Ambrosini et al only included stage III and IV patients [3]. Such advanced disease could be consistent with heterogeneous and partly less differentiated tumors. In this population, it is likely that a high $maxSUV_{max}$ reflecting wide over-expression of SSR corresponds to persistent differentiation and better prognosis, but the separate analysis of the subgroup of patients with stages III or IV in our series showed a non-significant trend for a better outcome only in patients with a high $maxSUV_{max}$. Overall, it appears that the cut-off value derived from Ambrosini et al. [3] may not be valid for DOTATOC, even in pNET stages III and IV.

We chose to measure volumes with a threshold of 41%, as in the majority of FDG studies [9], but the pertinence of applying this arbitrary threshold to SRPET should be assessed by further studies. In the same way, in the absence of documented response criteria on SRPET, we used criteria adapted from RECIST to assess disease progression on ^{68}Ga-DOTATOC. In particular, appearance of a new pathological focus meant disease progression. RECIST 1.1 criteria have been validated with FDG PET and their extension to SRPET was an innovation.

Disease progression was assessed on subsequent ^{68}Ga-DOTATOC PET/CTs in 10 patients and on conventional imaging by CT or MRI in 7 patients. Follow-up ^{68}Ga-DOTATOC PET/CTs for disease progression yielded independent information on PET/CT from the prognostic value of ^{68}Ga-DOTATOC uptake by the primary tumor. We evaluated this in our study. The new pathological foci have been accepted as evidence for progression because this examination has a higher detection rate than conventional imaging in the detection of neuroendocrine pathological lesions [20].

To evaluate potential prognostic markers of pNET, we assessed the PFS rate at 24 months for two reasons: the median follow-up period in our series was 25.6 months and Ambrosini et al. [3] evaluated tumor progression at 24 months in the study on the prognostic value of $maxSUV_{max}$. The PFS rate at 24 mo there was 47% compared to our 73%, and this reflects our patients with lower grade.

Limitations to our study require consideration. As the volumetric approach had not been reported in literature for DOTATOC PET/CT in pNET, we had to perform ROC

analyses to evaluate the best prognostic threshold of baseline TFTV to delineate patients who subsequently progress within 24 mo. We then used this cut-off value of 13.8cm^3 in univariate and multivariate analyses and this yielded over-evaluated performance values. The actual prediction values using those cut-off values should be assessed in a validation study on an independent patient sample, because our study was designed to be a pilot study.

In conclusion, our study suggests that ⁶⁸Ga-DOTATOC TFTV measured on PET images is a valuable prognostic biomarker in patients with well-differentiated pNETs in G1 and G2. A validation study is required to assess if a total functional tumor volume greater than 14 cm^3 is indicative of high risk of progression within two years. This would have consequences on scheduling follow-up visits of those patients, as well as provide prognostic biomarkers and optimize the cost-effectiveness of monitoring those pNET patients.

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