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

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], Désirée Deandreis[1]

1. Nuclear Medicine Unit, Department of Medical Sciences, University of 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, Italy
6. Department of Oncology Department of Medical Sciences, University of Turin, Italy
7. Department of Nuclear Medicine, University Hospital of Brest, Brest, France.

Corresponding author: Philippe Thuillier

Department of Endocrinology, University Hospital of Brest

Boulevard Tanguy Prigent

29609 Brest cedex, France

Telephone number: +33 2 98 34 71 20

Fax number: + 33 2 98 34 78 00

E-mail adress: philippe.thuillier@chu-brest.fr

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ABSTRACT (n=248)

Aim: To evaluate the prognostic value of somatostatin receptor tumor burden (SRTB) at ^{68}Ga-DOTATOC positron emission tomography/computed tomography (PET/CT) in patients with well-differentiated neuroendocrine tumors (WD-NETs).

Methods: We retrospectively analyzed ^{68}Ga-DOTATOC-PET/CT of 84 patients with histologically confirmed WD-NETs (51 G1, 30 G2 and 3 G3). For each PET/CT, all DOTATOC-avid lesions were independently segmented by 2 operators using a customized threshold based on the healthy liver maximum standardized uptake value (SUVmax) using LIFEx 5.1. Somatostatin receptor expressing tumor volume (SRETV) and total lesion somatostatin receptor expression (TLSRE=SRETV*SUVmean) were extracted for each lesion and then whole-body SRETV and TLSRE (SRETVwb and TLSREwb) were defined as the sum of SRETV and TLSRE of all segmented lesions in each patient, respectively. 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/metastatic disease (n=74). TTP and overall survival (OS) were calculated by Kaplan-Meier analysis, log-rank test, and Cox's proportional hazard model.

Results: After a median follow-up period of 15.5 months disease progression was confirmed in 35 patients (41.7%) and 14 patients died. Higher SRETVwb (>39.1ml) and TLSREwb (>306.8g) were significantly correlated with shorter median TTP (TTP=12months 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/OS and might have an important clinical utility in the management of in patients with WD-NETs.

Keywords: Neuroendocrine tumors, ^{68}Ga-DOTATOC-PET/CT, Tumor burden, prognosis, somatostatin receptor expressing tumor volume, total lesion somatostatin receptor expression

INTRODUCTION

Neuroendocrine neoplasms (NENs) are a group of tumors of common embryological origin but leading to a variety of clinical presentations and prognosis. The most frequent site is the gastroenteropancreatic tract (GEP–NENs) and the bronchopulmonary system. Although being relatively rare, their incidence has greatly increased in the last 30 years and estimated at approximately 5/100,0000/year (*1*). According to World Health Organization classification (based on Ki67% value and/or number of mitoses/ high power field), NENs range from well-differentiated neuroendocrine tumors (WD-NETs) to poorly differentiated neuroendocrine carcinomas (*2*).

Positron emission tomography/computed tomography (PET/CT) imaging with ^{68}Ga-DOTA-labelled somatostatin analogues (^{68}Ga-DOTA-SSTa) is the mainstay for the "in vivo" evaluation of the somatostatin receptor (SSTR) expression in NENs (*3*,*4*) and almost 90% of primary G1–G2 GEP-NETs are PET-positive due to the high SSTR expression (*5*). In clinical practice ^{68}Ga-DOTA-SSTa-PET/CT plays a major role in tumor characterization of NENs, in the assessment of disease extension and also to select properly the patient candidate for Peptide Receptor Radionuclide Therapy (PRRT), becoming the gold standard in the diagnosis and management of WD-NETs (*6*,*7*). The prognostic value of ^{68}Ga-DOTA-SSTa PET/CT imaging has been widely assessed in the literature, nevertheless mainly focused on semi-quantitative parameters such as standardized uptake value (SUV) (*8*,*9*).

In the last few years, metabolic tumor burden at ^{18}F-FDG-PET has shown a major prognostic value compared to semi-quantitative parameters in several tumor models. Metabolic tumor burden calculation integrates the volume of metabolically active tumor expressed by metabolic tumor volume, and total lesion glycolysis, which is the product of SUVmean and MTV.

Only recently, two studies (*10,11*) have interestingly demonstrated the prognostic utility of the somatostatin receptor tumor burden (SRTB) in patients with WD-NETs through obtained by the measurement of whole-body total lesion somatostatin receptor expression (TLSREwb) and somatostatin receptor expressing tumor volume (SRETVwb) from ^{68}Ga-DOTATATE-PET/CT images.

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

MATERIALS AND METHODS

Population

All the 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 01/01/2017 to 01/04/2020, were retrospectively evaluated and included as follows: (1) histologically proven G1-G3 WD-NETs; (2) GEP or bronchopulmonary NET or unknown primary site; (3) ^{68}Ga-DOTATOC-PET with at least 1 positive lesion; (4) follow-up≥6 months after PET.

Exclusion criteria were: (1) patient<18 years old; (2) incomplete histological data; (3) neuroendocrine carcinoma; (4) concomitant metastatic neoplasia others than NET; (5) negative ^{68}Ga-DOTATOC-PET/CT;

The consort diagram of the study is presented in fig.1.

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

Age, gender, TNM stage at the time of PET imaging, tumor grade according to WHO classification (*12*) (Ki67 for G1<3; G2 3-20; G3>20%, respectively) functional status, previous locoregional and systemic treatments were collected. Patients were considered as “naive-treatment” patients in case of no previous treatments except for surgery of primary tumor.

All patients underwent PET/CT on an analog 3-dimensional (3D) PET scanner (Philips Gemini Dual-slice EXP scanner–PET Allegro^{TM} 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 minutes and following free-breathing CT acquisition for attenuation correction from the vertex to the mid-thigh (5mm slice, 40mAs and 120 kVp), PET data were acquired in 3-dimensional mode, with 2.5 min per bed position and 6-8 bed positions per patient. The PET scans were reconstructed by ordered subset expectation maximization algorithm (3D-RAMLA) and matrix size was 144×144 voxels, resulting in voxels of $4.0\times4.0\times4.0mm^3$. All acquisitions were corrected for attenuation, for scatter and random coincidences.

Image analysis and Somatostatin Receptor Tumor Burden extraction

For each PET/CT, all DOTATOC-avid lesions were segmented independently by 2 nuclear medicine physicians using a semi-automatic method by a free user software LIFEx v.5.1 (IMIV/CEA, Orsay, France) (*13*) and based on SUV threshold method to avoid intra- and inter-operator variability of manual segmentation (*14*,*15*).

For this study, SUVmax threshold based on the healthy liver uptake was chosen. SUVmax value was assessed by placing a spherical VOI of diameter 3 cm 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 with its corresponding

SUVmean value. 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 carried out for each patient by both operators to evaluate reproducibility.

We classified each lesion according to its site: primary tumor, lymph node (ln), liver, bone and others (i.e. peritoneal, lung, and others). Then, whole-body SRETV and TLSRE (SRETVwb and TLSREwb), defined as the sum of all lesions SRETV and TLSRE in each single patient, were calculated respectively (fig.2). When all lesions showed equal or lower than the liver-SUVmax cut-off value, SRETVwb and TLSREwb were defined as equal to 0 as previously mentioned (*17*). We also separate the corresponding SRETVwb (SRETVprimary, SRETVln, SRETVliver, SRETVbone, SRETVother) and TLSREwb (TLSREprimary, TLSREln, TLSREliver, TLSREbone, TLSREother) according to each tumor site. The details of the entire process are described in Supplemental fig.1.

Statistical analysis

Quantitative variables were expressed as median with range. The primary clinical endpoint was the time to progression (TTP) defined as the time between PET/CT imaging to the first event (progression or relapse). Because anatomopathological confirmation of all lesions is no achievable, TTP of the disease was based on morphological imaging criteria and/or functional criteria (*18*). Disease progression was defined as the appearance of new lesion or a significant increase in size of known lesions. The secondary clinical endpoint was the overall survival (OS) defined as the time from the PET/CT until 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. ROC analysis was applied to determine the best cut-off for SRETVwb and TLSREwb parameters to predict patient's outcome using the Youden index (*19*). The area under the curves (AUC), sensitivity, specificity and accuracy were reported.

For TTP, multivariate analysis was performed by Cox proportional hazard regression model to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) including variables with clinical relevance or if $p<0.05$ in univariate analysis. Due to the low number of events, we do not perform multivariate analysis for OS.

We performed a subgroup analysis in patients with metastatic NETs at PET/CT time using the same threshold of SRETVwb and TLSREwb found in the whole cohort. Moreover, an exploratory analysis to assess the repartition of SRTB according to tumor site and progressive vs non-progressive disease during follow-up was performed through the non-parametric Mann-Whitney U test with Bonferroni's adjustment.

Inter-observer agreement for SRETVwb and TLSREwb between the two operators using Intra-class Correlation Coefficients (ICC) was evaluated considering ICC values between 0 and 1 and an ICC>0.9 to define the parameter as robust (*20*).

All statistical tests were two-sided and $p<0.05$ indicated a statistically significant difference. All analyses were performed on XLSTAT 2019.2.2 (Addinsoft, Paris, France).

RESULTS

Among the 322 patients screened, 84 patients (38 male, 46 female; median age at PET of 60.5 (range,25-86) years) were included in the study. The main characteristics of the patients are represented in Table 1. Pancreas was the most frequent site (39/84, 46.4%) and tumors were classified as G1, G2 and G3 in 40.5, 55.9 and 3.6% of case, respectively. Fifty-four (64.3%) patients presented a metastatic disease at the time of PET/CT and 47 patients (55.9%) were defined as treatment-naive.

Somatostatin receptor tumor burden

In the whole cohort, a total of 442 lesions and subsequent VOI 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%), respectively. The median values of SUVmax, SRETV and TLSRE per-lesion were 9.7 [range, 3.3-116.5], 4.0 ml [range, 0.5-1980.3], and 24.8 g [range, 1.8-21819.5], respectively. The median value of SRETVwb and TLSREwb were 32.4 ml [range, 0-3078.7] and 338.3 g [range, 0-22658.6], respectively. In 5 patients, the SRETVwb was equal to zero because the lesions were DOTATOC-avid, but with SUVmax lower than the liver background.

Survival analysis

Progression was detected in 35 patients (41.7%) and 14 patients died after a median follow-up period of 23 months [range, 0-41]. In the entire cohort, the median TTP was 22 months (IQR: 10-Not Reached). Ten patients underwent curative surgery of primary tumor after PET and did not showed disease relapse during the follow-up.

Univariate analysis for TTP/OS

For SRETVwb, the ROC curve showed an AUC of 0.83 (best cut-off=39.1ml) with a sensibility, specificity, and accuracy of 0.86, 0.76 and 0.8, respectively. For TLSREwb, the AUC was of 0.79 (best cut-off=306.8g) with a sensibility, specificity, and accuracy of 0.86, 0.74 and 0.79, respectively). Higher SRETVwb (≥39.1ml) and TLSREwb (>306.8g) were correlated with significantly shorter median TTP (TTP=12months; CI95%[10-23] vs not reached for both; $p<0.001$) and shorter median OS (OS not reached for both; $p<0.001$). SUVmax was not associated with TTP and OS ($p=0.08$ and $p=0.09$, respectively; fig.3)

TNM stage at PET time, Ki67% level, and treatment history (naïve versus previous line of treatment) were also significantly associated with a shorter TTP and OS ($p<0.05$; supplemental fig.2) while age, gender and secretory syndrome were not (p=NS).

Multivariate analysis.

SRETVwb and TLSREwb were highly correlated in our study (R=0.916 in Pearson correlation analysis). Thus, we performed a multivariate analysis using the Cox proportional regression model including only SRETVwb (>39.1ml). SRETVwb was the only independent predictor of TTP (HR=4.8 [1.6-14.5]; p=0.006) regardless of TNM stage, Ki67% and treatment history (p=0.58, 0.85 and 0.39, respectively) (Table 2).

Subgroup analysis in M+ patients.

The diagnostic performance of SRTB parameter to predict TTP and OS was assessed in subgroup of patients with metastatic disease according to lesions site (n=54). Using the same threshold, Kaplan Meier analysis revealed also significant difference with a shorter median TTP and OS for 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 revealed difference between progressive and non-progressive patients (supplemental table 1).

Interobserver agreement

The mean value of liver threshold was of 5.4±2.2 [range, 2.1-12.9] in operator 1, and 5.3±2.0 [range, 2.1-12.2] in operator 2, respectively. The median value of SRETVwb and TLSREwb were of 32.4 ml [range, 0-3078.7] and 338.3 g [range, 0-22658.6] in operator 1, and 32.0 ml [range, 0-3100.0] and 282.0 g [range, 0-22789.0] in operator 2, respectively. Intraclass

correlation coefficient were respectively of 0.963, 0.988 and 0.997 for liver threshold, SRETVwb and TLSREwb.

DISCUSSION

In our study, we investigated the prognostic value of SRTB extracted from ^{68}Ga-DOTATOC-PET/CT in patients with WD-NET. SRETVwb (≥39.1ml) and TLSREwb (≥306.8g) were significantly associated with TTP but at multivariate analysis SRETVwb was an independent prognostic parameter regardless of Ki67% level, TNM stage and treatment.

Previous several studies assessed the prognostic significance of ^{68}Ga-DOTATOC (*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 G1-G3 NETs, Tirosh et al. reported that a SRETV≥7.0mL and ≥35.8mL 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 G1-G2 GEP-NETs, Toriihara et al. found that SRETVwb≥11.1ml and TLSREwb≥146.48g obtained by ^{68}Ga-DOTATATE-PET/CT were associated with PFS but only SRETVwb was independently associated with PFS in survival analysis in accordance with our study (*11*). Kim et al. (*17*) in a retrospective study including 31 patients with unresectable/metastatic WD-GEP-NETs undergoing ^{68}Ga-DOTATOC-PET/CT before receiving lanreotide showed that lower tumor-to-liver ratio (TLR), lower SUVmax and higher SRETVwb (>58.9ml) were significantly associated with shorter PFS in univariate analysis, but only TLR (HR=3.182, p=0.021) remained an independent factor for PFS in multivariate analysis. In our study, SUVmax was not associated with TTP, which is consistent with Tirosh et al. and Toriihara et al. studies (*10*,*11*). One potential explanation is related to the differences in selection criteria. In fact, Kim et al. included a more homogeneous population of patients at an early stage of disease and mostly naive from other types of treatment (87.1% excluding surgery) (*17*). While in ^{18}F-FDG-PET/CT, high SUV is positively associated with prognosis in almost all cancers, including NETs

(*24*), explaining the interest to use total lesion glycolysis, in ^{68}Ga-DOTA-SSTa-PET/CT, low SUVmax values are associated with poorer prognosis in patients with WD-NETs (*8*,*9*,*25*,*26*). Thus, for the same SRETVwb value, patients disclosing lesions with low SUVmean, thus low TLSREwb value, might tend to present less favorable prognosis leading to conflicting results among different studies including different patient population. For this reason SRETVwb seems to be the most prognostic parameter but its use should be validated in further prospective futures studies including more homogeneous populations in term of primary site, disease course and treatment setting.

Furthermore, the proper methodology to evaluate SRTB should be taken into account. In our study a customized threshold based on liver SUVmax has been chosen and to our knowledge, this is the second study in which such a segmentation method is applied in ^{68}Ga-DOTATOC-PET/CT (*17*). This methodology presents the advantage to be fast, hence it could represent a useful tool in clinical practice. Interestingly, we found higher cut-off values of SRETVwb and TLSREwb compared to studies assessing SRTB using ^{68}Ga-DOTATATE while SRETVwb and TLSREwb cut-off values were consistent with Kim et al. study performed with the same radiopharmaceutical ^{68}Ga-DOTATOC (*10*,*11*,*17*). The literature showed that tumor uptake is higher and liver uptake is lower at ^{68}Ga-DOTATOC compared to ^{68}Ga-DOTATATE, leading to 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 terms of segmentation methodology. Toriihara et al. used a 50%-threshold of SUVmax to segment each lesion which leads to lower SRETVwb value, especially in patients with intense radiotracer uptake (*11*). An example of impact on SRTB of different segmentation method is reported in supplemental fig. 4.

In addition, assessing the reproducibility and robustness of SRTB calculation is important. In our study, the reproducibility between the two operators was excellent with ICC>0.9 for both SRETVwb and TLSREwb. To our knowledge, there is no study assessing the reproducibility of SRTB parameters in ^{68}Ga-DOTA-SSTa-PET/CT. Many studies showed that segmentation method can impact the reproducibility of whole-body-metabolic tumor volume between operators in ^{18}F-

FDG-PET/CT imaging, especially in threshold methods based on 41% of SUVmax (*29*,*30*). SRTB parameters in ^{68}Ga-DOTA-SSTa-PET/CT might be more reproducible than whole-body-metabolic tumor volume due to the higher signal-to-noise ratio. This is a crucial point, and it appears important that the reproducibility and the robustness of the whole-body volumetric parameters in ^{68}Ga-DOTA-SSTa-PET/CT should be studied in future, especially between different PET systems.

Beyond the prognostic role, the evaluation of SRETVwb and TLSREwb changes (namely ΔSRETVwb and ΔTLSREwb) after initiation of systemic therapy may offer promising perspectives, especially for patients treated with PRRT (*31*), and need to be assessed in futures studies. However, SSA treatment or PRRT can modify liver uptake as previously reported (*32*), impacting the calculation of SRTB. Therefore, the systematic use of the pre-therapeutic liver SUVmax cut-off value could be a solution to follow the evolution of SRTB parameters (*31*,*33*).

Our work present the following limitations. First, our study was retrospective, includes an heterogenous cohort of patients and was conducted in a single-center on a single PET/CT scanner. Second, we only included patients with DOTATOC-avid lesions and using the liver SUVmax as cut-off, the SRETVwb was equal to zero in 5 patients. This 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 high tumor burden without 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 have an additional value in comparison to conventional clinical prognostic parameters and other standard PET parameters (e.g. SUVmax) to predict patient's prognosis and to guide treatment decisions thus supporting the implementation of these parameters in clinical practice. As previously mentioned, our results remain preliminary and

applicable for ^{68}Ga-DOTATOC-PET/CT but need to be validated in more proper prospective studies and explored with others ^{68}Ga-peptides.

DECLARATION

Abbreviations: ^{18}F-FDG=2-deoxy-2-[18F]fluoro-D-glucose; CT=computed tomography; DFS=disease-free-survival; GEP=gastroenteropancreatic; NENs=neuroendocrine neoplasms; NETs=neuroendocrine tumors; OS=overall survival; PET=positron emission tomography; PFS=progression-free survival; WD-NETs=well-differentiated neuroendocrine tumors; SRETV=somatostatin receptor expressing tumor volume; SRTB=somatostatin receptor tumor burden; ^{68}Ga-DOTA-labelled somatostatin analogues=^{68}Ga-DOTA-SSTa; SUV=standardize uptake value; TLG=total lesion glycolysis; TLSRE=total lesion somatostatin receptor expression; TTP=time to progression

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Key points

Question: Can whole-body volumetric parameters extracted from ^{68}Ga-DOTATOC-PET/CT be usefull to assess the prognosis of well-differentiated neuroendocrine tumors (WD-NETs)?

Pertinent findings: In our cohort, whole-body volumetric 68Ga-DOTATOC-PET/CT parameters (somatostatin receptor expressing tumor volume and total lesion somatostatin receptor expression) were associated with time-to-progression and overall survival. SRETVwb was the only independent prognostic parameter, regardless of Ki67% level, TNM stage at PET time and treatment history (naïve versus previous treatments) before PET scan.

Implication for patients care: In the future, whole-body volumetric 68Ga-DOTATOC-PET/CT parameters could have an additional value in comparison to conventional prognostic parameters to predict 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*. 2011;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 [68Ga]Ga-DOTA-SST Analogues and [18F]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 68Ga-DOTA-conjugated somatostatin receptor targeting peptides and 18F–DOPA. *Eur J Nucl Med Mol Imaging*. 2017;44:1588-1601.

8. Ambrosini V, Campana D, Bodei L, et al. 68Ga-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 68Ga-DOTANOC PET/CT and 18F-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 68Ga-DOTATATE-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 68Ga-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 and Med*. 2014;50:76-96.

15. Liberini V, De Santi B, Rampado O, et al. Impact of segmentation and discretization on radiomic features in 68Ga-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 177Lu-DOTATATE quantification by comparison of SUV-Based parameters measured on both post-PRRT SPECT/CT and 68Ga-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 [68Ga]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(1):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 68Ga-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 68Ga-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*. Epub ahead of print

23. Abdulrezzak U, Kurt YK, Kula M, Tutus A. Combined imaging with 68Ga-DOTA-TATE and 18F-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 18Fluorodeoxyglucose-Positron Emission Tomography and Somatostatin Receptor Scintigraphy for High Ki67 (>=10%) Well-Differentiated Endocrine Carcinoma Staging. *J Clin Endocrinol Metab*. 2010;96:665-671.

25. Campana D, Ambrosini V, Pezzilli R, et al. Standardized uptake values of 68Ga-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;13:7290.2014.00009.

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

28. Poeppel TD, Binse I, Petersenn S, et al. 68Ga-DOTATOC Versus 68Ga-DOTATATE 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. 68Ga-DOTATOC PET/CT-based radiomic analysis and PRRT outcome: A preliminary evaluation based on an exploratory radiomic analysis on two patients. Front Med (Lausanne). 2020;7:601853.

32. Cherk MH, Kong G, Hicks RJ, Hofman MS. Changes in biodistribution on 68Ga-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*. 2020;10:1083.

TABLES

Table 1. Characteristics of patients.

Characteristics	**Value (n=84)**
Sex	**n (%)**
Male	48 (57.1)
Female	36 (42.9)
Age (years) median (range)	60.5 (25-86)
Primary Site	**n (%)**
GEP-NETs (n=72)	72 (85.7)
Pancreas	39
Small intestine	21
Duodenum	3
Caecum/colon	4
Rectum	1
Stomach	4
Lung-NETs	9 (10.7)
Unknown	3 (3.6)
TNM stage	**n (%)**
Only primary tumor	20 (23.8)
Locoregional extension	10 (11.9)
Metastatic	54 (64.3)
Ki67%	**n (%)**
<3%	34 (40.5)
3 and ≤ 20%	47 (55.9)
>20%	3 (3.6)
Functional n (%)	12 (14.3)
Treatment before PET	**n (%)**
Surgery	42 50)
Somatostatin analogs	46 (54.8)
Systemic treatment	16 19.0)
Chemotherapy	13
Everolimus	8
Others	2
Locoregional treatment	12 14.3)
PRRT	5 (6)
Treatment after PET	**n (%)**
Surgery	13 (15.5)
Somatostatin analogs	63 (75.0)
Systemic treatment	16 (19.0)
Chemotherapy	12
Everolimus	8
Others	0
Locoregional treatment	7(8.3)
PRRT	7(8.3)

Table 2. Univariate and multivariate analyses using Cox regression for time to progression according to SRETVwb, TLSREwb and other characteristics of the cohort.

	Univariate analysis		**Multivariate analysis**	
Characteristics	**Hazard Ratio (95%CI)**	**p value**	**Hazard Ratio (95%CI)**	**p value**
Gender		0.31		
Male(ref)	1			
Female	0.70 [0.35-1.39]			
Age		0.58		
≥64 yo(ref)	1			
<64 yo	0.83 [0.43-1.61]			
Ki67%		**0.013**		0.85
<3 (ref)	1		1	
3 to 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 the time of PET		**0.009**		0.58
Local(ref)	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]	
Naive-treatment		**0.001**		0.39
No(ref)	1		1	
Yes	0.20 [0.00-0.515]		0.60 [0.19-1.88]	
SUVmax		0.09		
≥23.4 (ref)	1			
<23.4	0.56 [0.28-1.1]			
SRETV (ml)		**<0.001**		**0.006**
<39.1(ref)	1		1	
≥39.1	8.48 [3.28-21.91]		4.76 [1.56-14.53]	
TLSRE (g)		**<0.001**		
<306.8(ref)	1			
≥306.8	8.41 [3.25-21.74]			

FIGURES

Figure 1. CONSORT diagram of the study

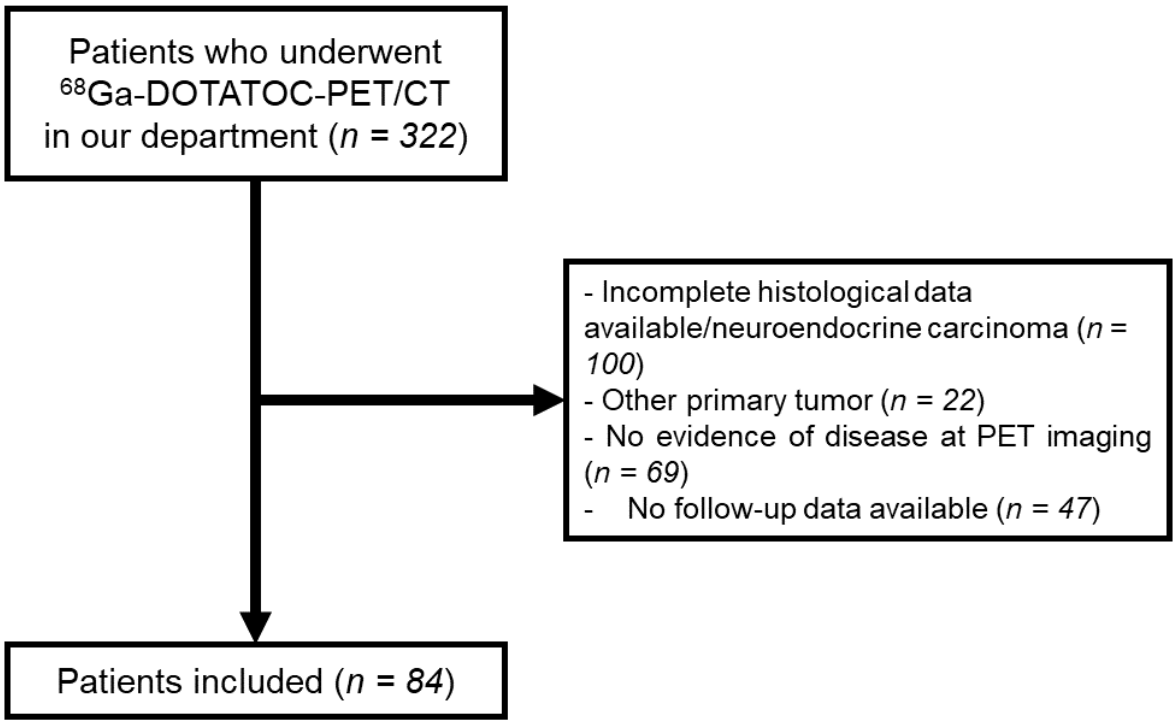


Figure 2. ^{68}Ga-DOTATOC-PET/CT in a well-differentiated pancreatic NET (A: PET/CT, B: PET imaging) showing high uptake in all lesions (highest SUVmax =104.4). SRTB analysis (C: MIP, D: PET/CT, E: PET imaging) highlighted SRETVwb and TLSREwb values of 249ml and 4191g, respectively.

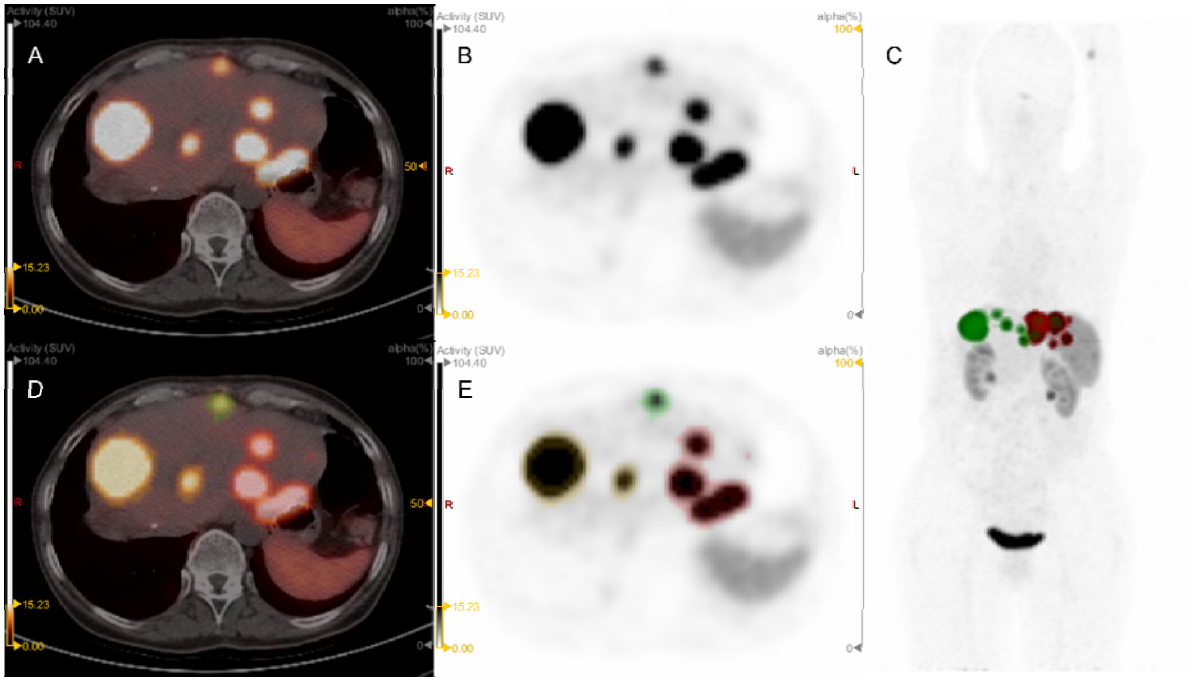
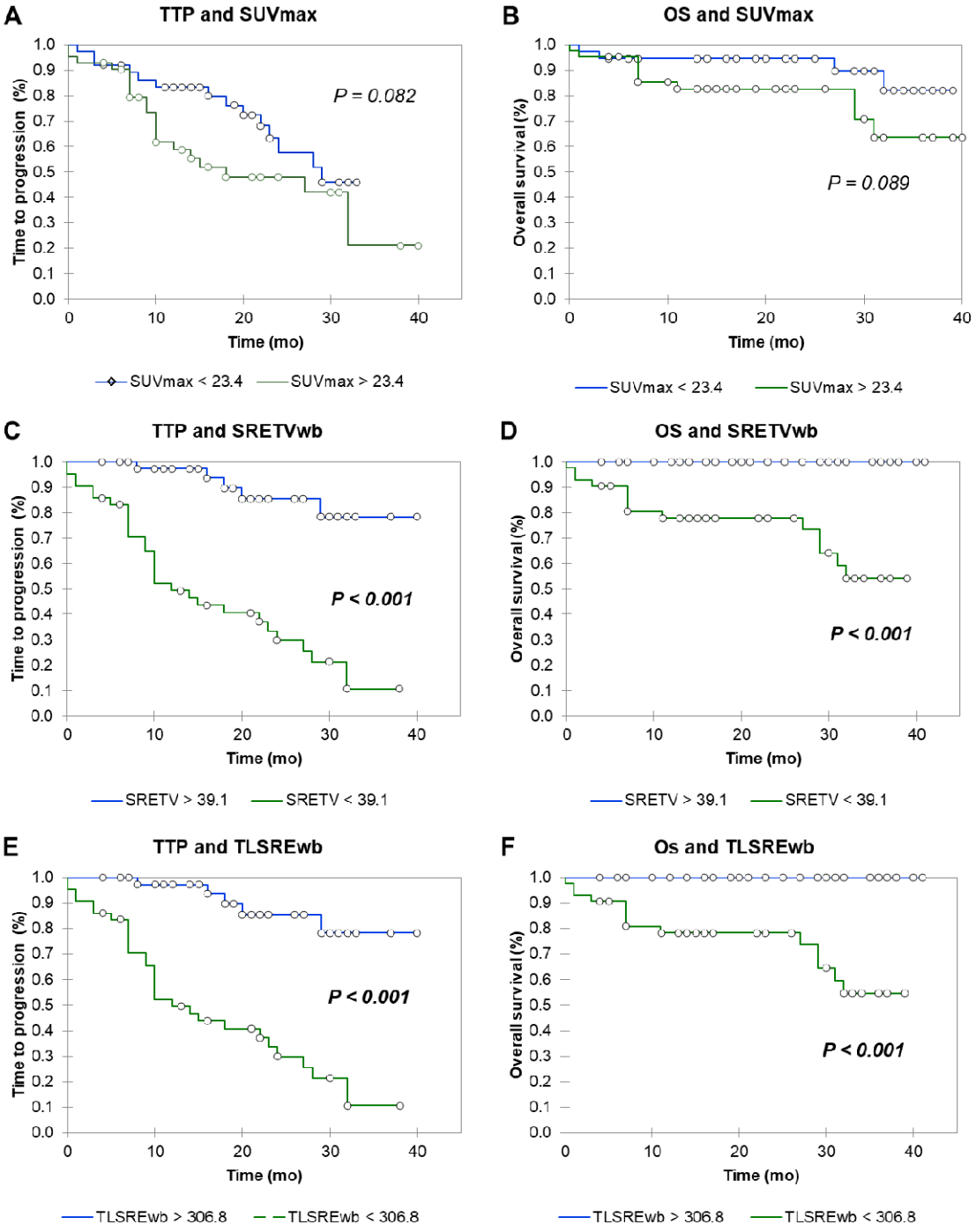
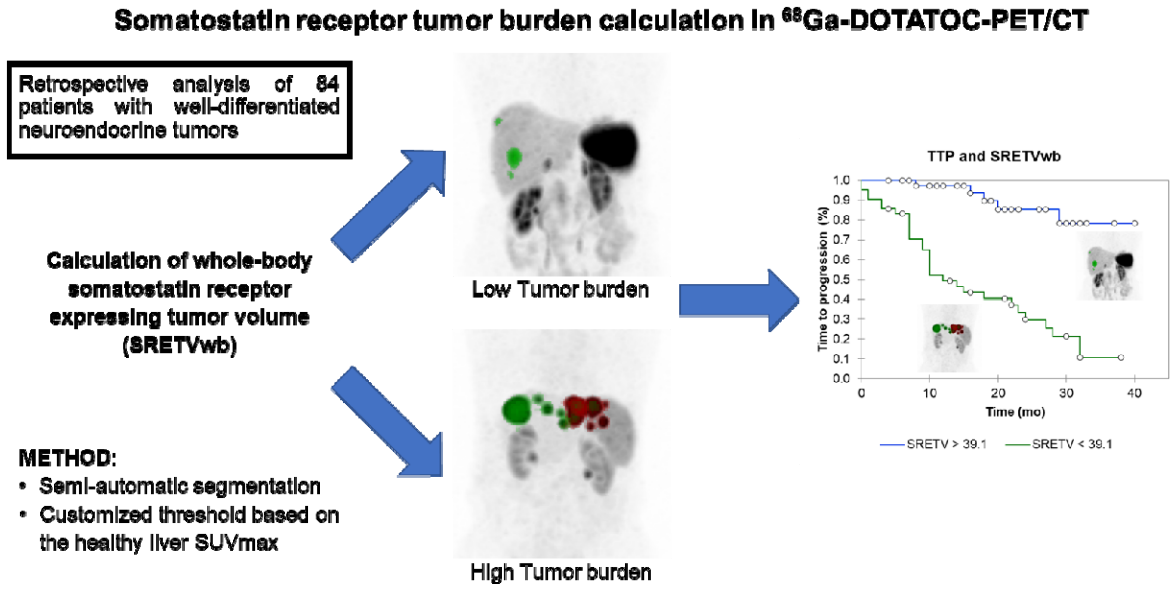
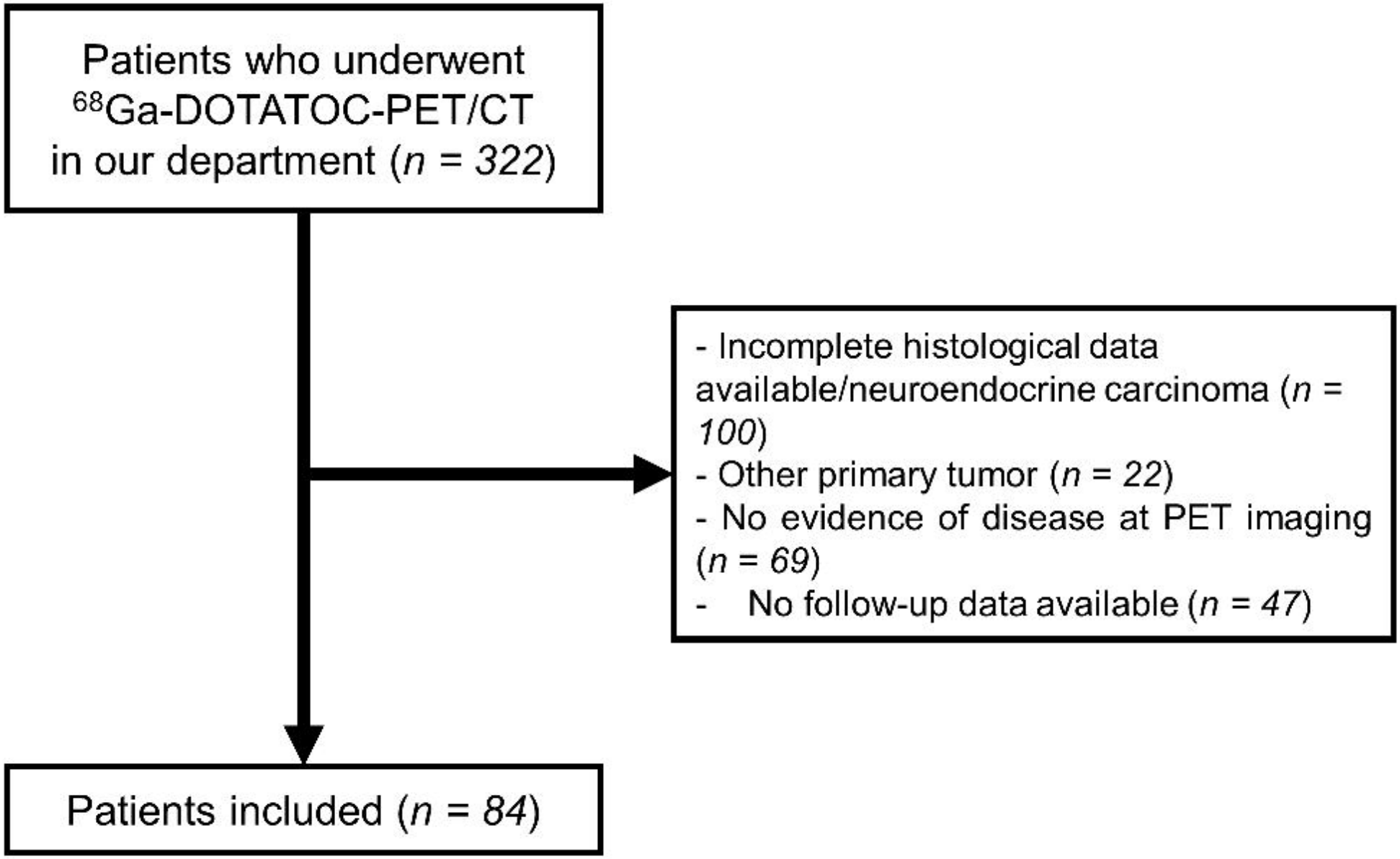


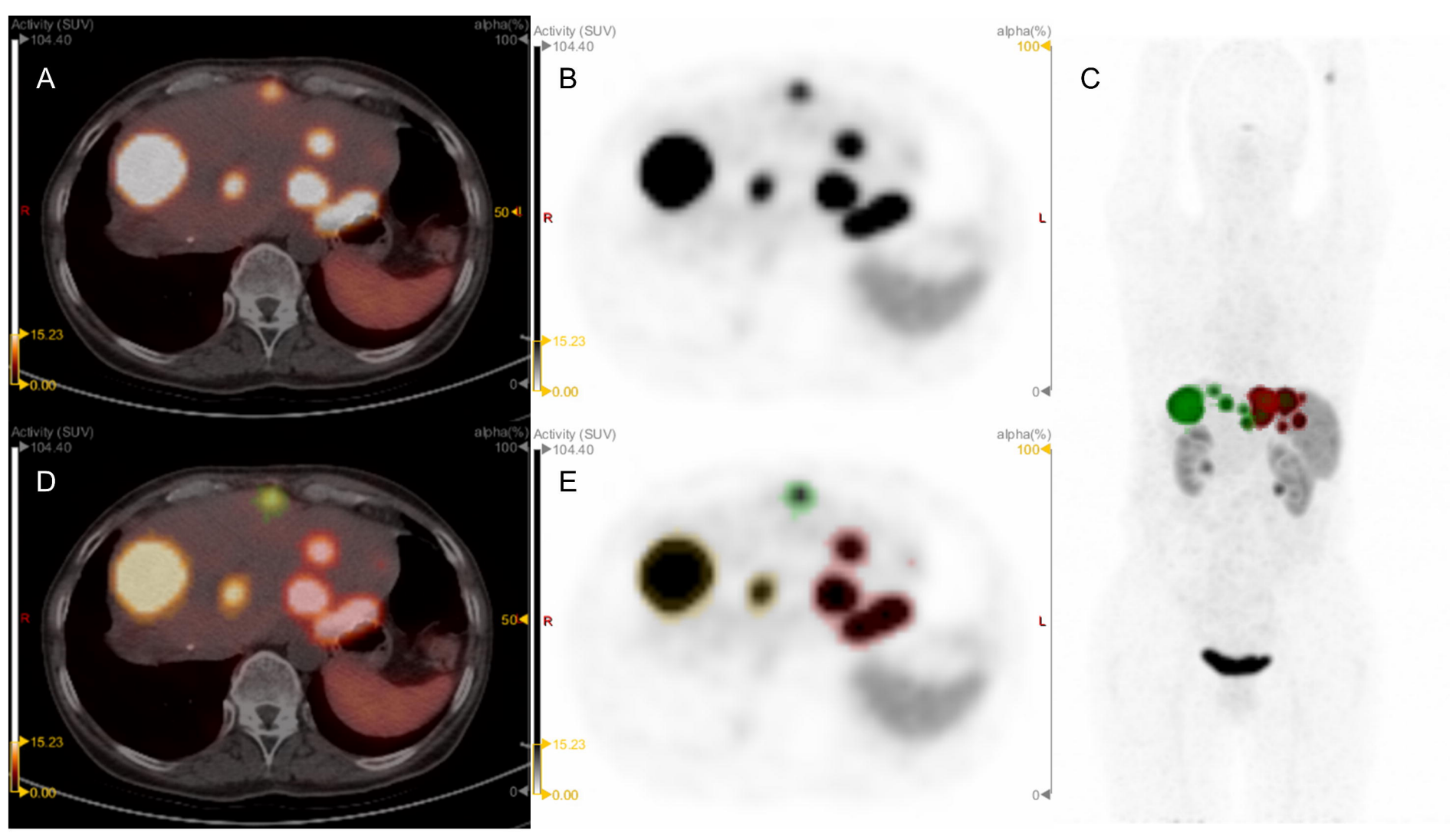
Figure 3. Time-to-progression (left) and overall survival (right) in patients according to SUVmax (A, B), SRETVwb (C, D) and TLSREwb (E, F)

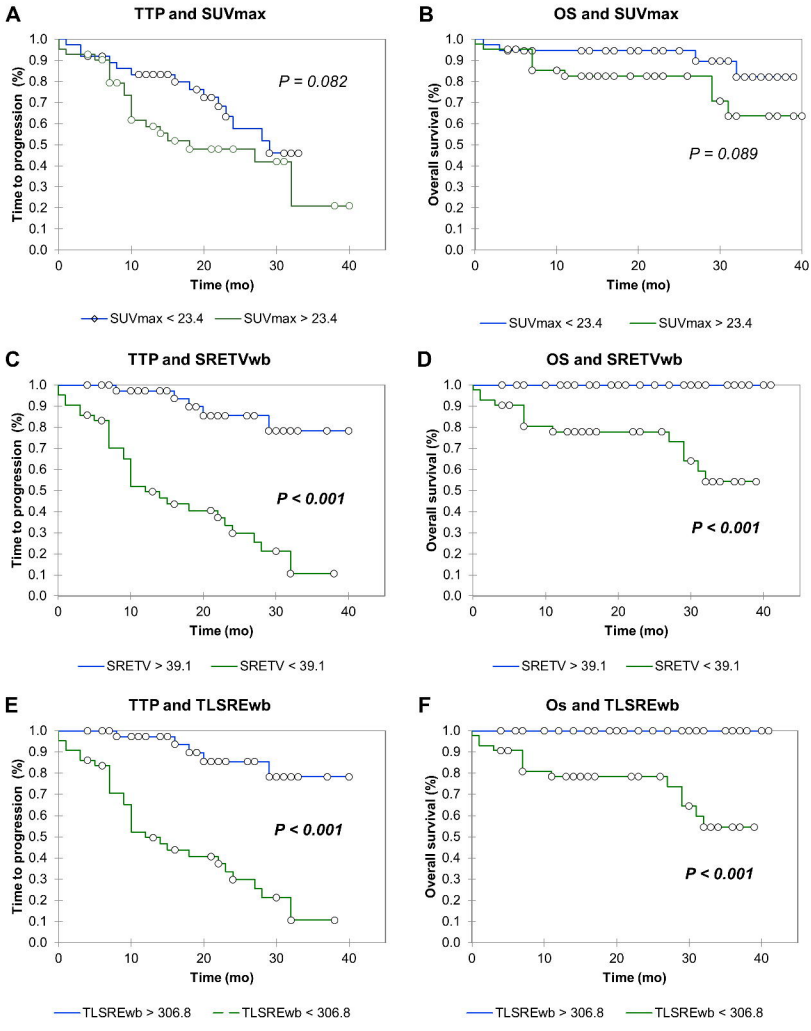


GRAPHICAL ABSTRACT




Patients who underwent
68Ga-DOTATOC-PET/CT
in our department (n = 322)
- Incomplete histological data available/neuroendocrine carcinoma (n = 100)
- Other primary tumor (n = 22)
- No evidence of disease at PET imaging (n = 69)
- No follow-up data available (n = 47)
Patients included (n = 84)

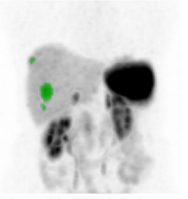

A
B
C
D
E
Activity (SUV)
104.40
15.23
0.00
alpha(%)
100
50
0
R
L


A
TTP and SUVmax
Time to progression (%)
P = 0.082
Time (mo)
SUVmax < 23.4
SUVmax > 23.4
B
OS and SUVmax
Overall survival (%)
P = 0.089
Time (mo)
SUVmax < 23.4
SUVmax > 23.4
C
TTP and SRETVwb
Time to progression (%)
P < 0.001
Time (mo)
SRETV > 39.1
SRETV < 39.1
D
OS and SRETVwb
Overall survival (%)
P < 0.001
Time (mo)
SRETV > 39.1
SRETV < 39.1
E
TTP and TLSREwb
Time to progression (%)
P < 0.001
Time (mo)
TLSREwb > 306.8
TLSREwb < 306.8
F
Os and TLSREwb
Overall survival (%)
P < 0.001
Time (mo)
TLSREwb > 306.8
TLSREwb < 306.8

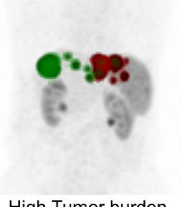
Somatostatin receptor tumor burden calculation in ^{68}Ga-DOTATOC-PET/CT

Retrospective analysis of 84 patients with well-differentiated neuroendocrine tumors

Calculation of whole-body somatostatin receptor expressing tumor volume (SRETVwb)



Low Tumor burden



High Tumor burden

METHOD:

- Semi-automatic segmentation
- Customized threshold based on the healthy liver SUVmax