


Ga-68-Edotreotide Positron Emission Tomography/Computed Tomography Somatostatin Receptors Tumor Volume Predicts Outcome in Patients With Primary Gastroenteropancreatic Neuroendocrine Tumors

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Abstract

Background: We retrospectively aimed to assess the prognostic significance of somatostatin receptor (SSTR) standardized uptake value ($SUV_{max_{SSTR}}$), SSTR representative tumor volume (RTV_{SSTR}) and total lesion SSTR expression (TL_{SSTR}) obtained by [⁶⁸Ga]Ga-edotreotide PET/CT ([⁶⁸Ga]Ga-SSTR PET/CT) in patients with primary gastroenteropancreatic neuroendocrine tumors (GEP-NET) before surgery.

Material and Methods: We analyzed patients who underwent [⁶⁸Ga]Ga-SSTR PET/CT 3-6 weeks before surgery from February 2020 to April 2022. The mean $SUV_{max_{SSTR}}$ value, the RTV_{SSTR} (cm³; 42% threshold) and the TL_{SSTR} (g) were registered. Thereafter the patients were followed up 10.3 months (range 3-27). The PET/CT results were compared to the event free survival (EFS).

Results: Forty-two patients (61 ± 13 years) have been enrolled. At multivariate analysis only RTV_{SSTR} values were predictive. The Kaplan-Meier survival analysis for RTV_{SSTR} showed a significant better EFS in patients presenting lower values as compared to those having greater ($P = .003$, log-rank test). $SUV_{max_{SSTR}}$ was not suitable for predicting EFS, TL_{SSTR} mildly.

Conclusion: RTV_{SSTR} represents a valuable volumetric parameter able to predict the outcome in GEP-NET patients who underwent surgery. The magnitude of the SSTR representative tumor burden holds a predominant value for determining the response to therapy in GEP-NET patients before surgery, rather than the maximal SSTR representation at single voxel.

Keywords

gastroenteropancreatic tumors-neuroendocrine tumors, positron emission tomography/computed tomography, quantitative assessment, volumetric parameters, survival

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Introduction

Neuroendocrine tumors (NETs) represent a group of highly heterogeneous neoplasms that can occur in different organs with an estimated incidence of less than 1/100.000 cases. They

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generally present an indolent growth rate.^{1,2} Gastroenteropancreatic (GEP) NETs constitute the second most common digestive cancer showing low tendency to metastasize but once they diffuse can rapidly progress. Contrarily, those of the small intestine exhibit high malignant potential even if they have a slow grown pattern when in metastatic setting.³ GEP NETs are classified as grade 1 or 2 when well- or moderately differentiated, respectively, with only few cases grade 3, poorly differentiated aggressive, neuroendocrine carcinoma (NEC).^{4,5} The survival and outcome of NET patients with similar stage and grade varies considerably in reason of a significant plethora of prognostic factors, mostly unreliable. Overall, these patients show mainly disease steadiness rather than progression during their long-term follow-up.^{6,7} Several studies have demonstrated that morphological imaging and conventional parameters are useful for assessing both location and extent of NETs as well as for monitoring therapy response, while their role for survival and outcome prediction is still limited.^{8,9} Functional imaging, based on tumor somatostatin receptors (SSTRs) overexpression, constitutes an ideal target for diagnosis and therapy with radiolabeled somatostatin analogues. Over the past decade, [⁶⁸Ga]Ga-SSTR (such as [⁶⁸Ga]Ga-DOTA-TOC/NOC/TATE/EDOTREOTIDE) positron emission tomography-computed tomography (PET/CT) has taken gradually the place of conventional SSTR scintigraphy for assessing NETs due to its superior sensitivity and accuracy.^{10,11} Although [⁶⁸Ga]Ga-SSTR PET/CT is widely employed in this setting, only limited data are currently available concerning the new PET/CT quantitative parameters for the prediction of disease outcome and survival in patients diagnosed with NETs. High maximum standardized uptake (SUVmax) values have been demonstrated to match with a lower grade tumor and a better event-free survival (EFS) whereas it predicts an elevated risk of disease progression when low.^{12,13} Recently, PET/CT volumetric parameters based on SSTR distribution, such as SSTR representative tumor volume (RTV_{SSTR}) and total lesion SSTR expression (TL_{SSTR}) have been implemented for a wide tumor assessment.¹⁴ The aim of this retrospective study is to investigate, at staging, the correlation between the PET/CT functional parameters SSTR-based (SUVmax_{SSTR}, RTV_{SSTR} and TL_{SSTR}) and the EFS in patients complying with primary GEP NETs who shortly will undertake surgery.

Materials and Methods

Patients

We retrospectively reviewed data of two hundred 6 patients with positive biopsy for gastro-entero-pancreatic-neuroendocrine tumor (GEP-NET). Patients were addressed for a baseline [⁶⁸Ga]Ga-edotreotide PET/CT scan from February 2020 to April 2022. The enrolled patients satisfied the inclusion criteria, such as: age at entry above 18 years, primary GEP-

NET with G1 or G2 grading and only locoregional disease, scan performed before surgery. Exclusion criteria were: Patients who previously underwent surgery for GEP-NET, patients with metastatic disease, if any, patient who formerly received radioligand therapy, chemotherapy or somatostatin analogues. Patients with grade 3 NEC, multiple endocrine neoplasia as well as patients with less than 6 months follow-up period after PET/CT (apart from the ones with early tumor progression), constituted additional exclusion criteria. A flowchart of patient selection is shown in Figure 1. Diagnoses were confirmed according to the WHO 5th ed. (2019) classification.

Patients had undergone comprehensive baseline standard assessment including clinical and laboratory data, chest, abdomen, and pelvis CT or MRI. Data as tumor grading, histological specimen, Ki67 values, WHO classification and type of surgery were collected from patients' medical record. Distribution and proliferation rate of cells were determined from Ki-67-stained sections of tissue specimens.

Basilicata Independent Ethics Committee (CEUR) and IRCCS CROB review board gave approval for the study (approval number: #2022-001470; date: February 15, 2022). All patients undergoing PET/CT signed an informed consent form in accordance with the Declaration of Helsinki. The reporting of this study conforms to REMARK guidelines.¹⁵

Imaging Technique

All patients underwent [⁶⁸Ga]Ga-edotreotide PET/CT. The patients received [⁶⁸Ga]Ga-edotreotide intravenously (median:181; range:148-259 MBq; weight-based). Sixty minutes after the tracer injection, PET and modulated low dose CT were carried out with a PET/CT scanner (GE Discovery VCT scanner; Waukesha, WI) that combined a PET scanner and a Light Speed VCT sixty-four row MDCT system. MDCT (pitchx 1.5; 120 mAs; 120 kVp) was performed without contrast medium. The PET scanning was subsequently performed, acquiring 3 minutes per bed position and 6 to eight beds per patient depending on patient height encompassing the whole skeleton. The raw CT data were reconstructed into transverse images with a 3.75-mm section thickness. Sagittal and coronal CT images was generated by reconstruction of the transverse data. Raw PET data were reconstructed with and without attenuation correction into transverse, sagittal, and coronal images. Attenuation correction was based on CT attenuation coefficients, which were determined by iterative reconstruction.

Imaging Evaluation

All images were reviewed by using PET/CT fusion software (Volumetrix for PET-CT and AW volume share 4.5, GE Healthcare, Waukesha, WI, USA). Each PET/CT study was interpreted, in consensus, by three experienced nuclear medicine physicians with 15 years of expertise, one of them

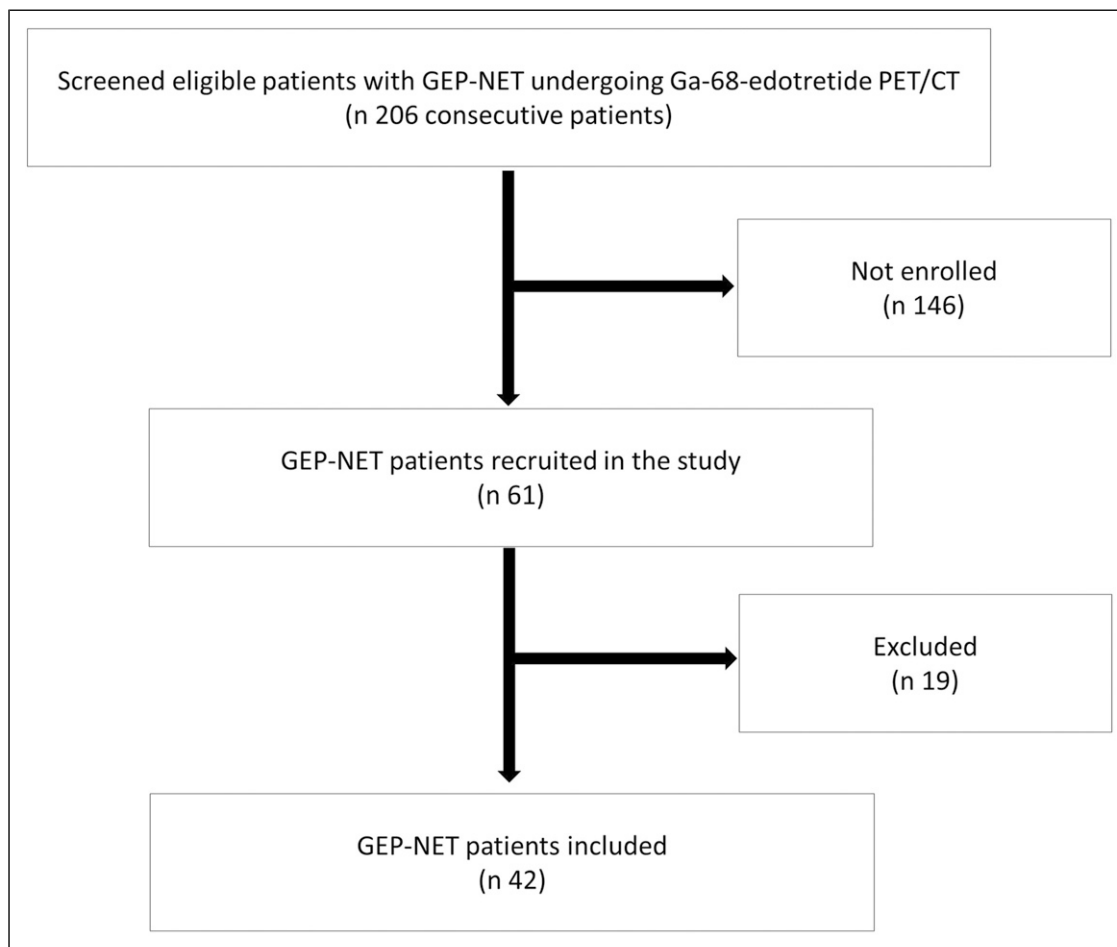


Figure 1. Flowchart of patient selection. Not enrolled: metastatic, previous surgery, radioligand therapy, chemotherapy, somatostatin analogues. Excluded: PET negative, insufficient follow-up, Multi Endocrine Neoplasia.

was a radiologist. The examiners first evaluated only the CT images. Lesion sizes were visually estimated and measured at least in two maximum diameters by using a vendor-provided software (Volumetrix for PET-CT; GE Healthcare, Waukesha, WI, USA). Any lesion ≥ 1.0 cm in maximal transverse or maximal sagittal dimensions, with soft tissue/abdominal window settings, was considered target. The CT volume computation was diameter-based according to the formula: $V = d$ craniocaudal $\times d$ antero-posterior $\times d$ lateral $\times \pi/6$ being the lesions assumed as ellipsoid.

The PET studies were evaluated both visually and semi-quantitatively. Afterward, the maximum standardized uptake values and body weight corrected ($SUV_{max_{sstr}}$) as well as the SSTR expression representative tumor volume (RTV_{sstr} ; cm^3 ; 42% threshold) and total lesion SSTR expression (TL_{sstr} ; g) were determined by using the same vendor-provided software. The RTV_{sstr} was defined as the volume that SUV is more than 42% of $SUV_{max_{sstr}}$. TL_{sstr} was derived from the multiplication of RTV_{sstr} and SUV_{mean} in RTV_{sstr} , as the product of SUV_{avg} multiplied by the number of voxels.

Briefly, focal, or diffuse [^{68}Ga]Ga-edotreotide uptake in a location mismatched with normal anatomy or physiology was interpreted as abnormal and ultimately was considered to be indicative of GEP-NET lesion. A composite score based on RTV_{sstr} and $SUV_{max_{sstr}}$ aggregation was used to further stratify the patients.

Follow-up Assessment

Patients were categorized into two groups according to the cut-off points, determined by receiver-operator-curve (ROC) analysis, for $SUV_{max_{sstr}}$, RTV_{sstr} and TL_{sstr} . The status of disease was followed up 10.3 months thereafter (range 3-27). The evaluation was carried out considering clinical and hematological parameters during scheduled or unscheduled visits, on the basis of diagnostic imaging (i.e. CT, MRI) findings, as well as by phone interview.

Failure to respond without progression (e.g. residual/stable disease and/or indication for therapy changes), progression and/or disease-related death constitute main events. They were considered surrogate endpoints. Clinical parameters and PET/

CT findings were correlated to the disease outcome (event free survival; EFS). EFS was defined as the time from PET/CT until end point occurrence or the time of last censor.

Progression was recognized as evidence of a new lesion or relapse of a previous existing lesion; when there was missing information, the date of unscheduled new somatostatin analogues treatment was considered.

Statistical Analysis

Continuous data are expressed as percentage, means \pm SD, and median as appropriate. Correlation analysis was used to assess the relationship between variables, when requested. Optimal cut-off of $SUV_{max_{sstr}}$, RTV_{sstr} and TL_{sstr} for differentiating patients at high risk of main events were derived from ROC analysis. The ROC analysis was additionally performed for any other parameter, if requested. Event-free survival curves were constructed using the Kaplan-Meier method to account for censored survival times and were compared with the log-rank test. A P value $< .05$ was considered statistically significant. Survival analysis was performed by multivariate Cox proportional hazard regression analysis. The proportional hazard assumption of the Cox model was checked separately for each covariate by a graphical method before performing the regression analysis. Our hypotheses were tested using Bonferroni adjusted alpha levels. The Ki-67 values and age at diagnosis, intended as ordinal variable, were included in the final model.

Results

Patient Characteristics

Forty-two patients (16 women, 26 males; 61 ± 13 years) were included (Figure 1). All patients underwent curative intent surgery after the [^{68}Ga]Ga-edotreotide PET/CT study. Thirty-two pancreatic and 10 gastro-intestinal (stomach, ileum, and large bowel) tissue specimens were collected. Mean Ki-67 was $5.2\% \pm 5.8\%$. Individual data are summarized in Table 1.

Imaging Evaluation

The median $SUV_{max_{sstr}}$ value was 8.55 (range 2.4-37.6), median RTV_{sstr} was 4.94 cm³ (range 1.15-49.2) and median TL_{sstr} was 306.9 g (range 74.0-1928). The ROC curve analysis recognizing cut off values of $SUV_{max_{sstr}}$, RTV_{sstr} and TL_{sstr} for EFS are showed in Figure 2. The area-under-curve (AUC) for $SUV_{max_{sstr}}$ was .585 (95% CI 0.42-.73) and the established cut off value was ≤ 16.3 . The AUC for RTV_{sstr} and TL_{sstr} was .673 (95% CI 0.51-.81) and .590 (95% CI 0.42-.73), respectively whereas RTV_{sstr} and TL_{sstr} cut off values were >2.47 (cm³) and >219.3 (g), respectively.

Table 1. Individual Data of GEP-NET Patients.

Characteristics	Value
Total number of patients	42
Age at diagnosis, year, median (range)	63 (31-86)
Established by referral observer	
Scan positive for NET (%)	42 (100)
NI stage (%)	11 (26)
MI stage (%)	0 (0)
Ki-67	
$\leq 2\%$ (%)	28 (67)
$> 2\%$ (%)	14 (33)
Localization	
Pancreatic (%)	32 (76)
Gastro-enteric (%)	10 (24)
Patient outcome	
No evidence of disease (%)	21 (50)
Progression (%)	5 (12)
Unresponse (%)	11 (26)
Death (%)	5 (12)

GEP-NET, Gastroenteropancreatic-Neuroendocrine Tumor; Ki-67, protein.

Clinical Endpoints, Follow-up, and Correlations

Twenty-one of forty-two patients (50%) reached the endpoint, 5 showed progression, 11 were unresponsive to the therapies, 5 died. Twelve patients had $RTV_{sstr} < 2.47$ (cm³), 11 showed no evidence of disease, 1 died. The median follow up was 10.3 months (range 3-27 months).

The age and Ki-67 values, settled as ordinal variable, were not significantly associated with the outcome (shown in Table 2). The proportional hazard assumption was not rejected for none of the other covariates included in the Cox model ($p = ns$ for all covariates). A better event free survival for patients was associated with lower values of RTV_{sstr} which significantly contributed to the prediction of outcome ($P = .01$, HR 11.7, 95% CI 1.55-87.9). The Kaplan-Meier survival analysis for $SUV_{max_{sstr}}$ did not show a significant difference in EFS ($P = .1$, log-rank test). The survival analysis for TL_{sstr} exhibited a slightly, but significant difference for discriminating patients ($P = .04$, log-rank test) (shown in Figure 3). The composite score allowed the categorization of patients into 4 categories with different survival (shown in Figure 4). A correlation was found between PET- and CT-computed volumes ($r .49$, $P < .001$, 95% CI .22-.69). On a patient basis, all PET/CT parameters did not correlate to Ki67 values.

Discussion

Present treatment approaches are valuable in GEP-NET while the implementation of more precise and timely therapy, tailored to the specific risk stratification, may represent a further

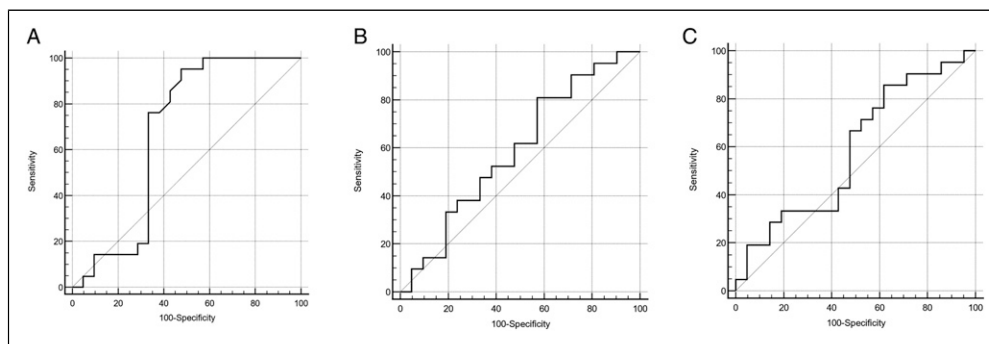


Figure 2. ROC curve analysis establishing the cut off value of RTV_{sstr} , TL_{sstr} and $SUVmax_{sstr}$ for predicting Event Free Survival. The cut off value of RTV_{sstr} (A), TL_{sstr} (B) and $SUVmax_{sstr}$ (C) for stratifying patients was >2.47 (cm^3), >219.3 (g) and ≤ 16.3 , respectively. $SUVmax_{sstr}$, standardized uptake value

Table 2. Univariate Cox Proportional Hazard Regression Analysis.

	HR	95% CI	P-value
$RTVs_{sstr}$ (cm^3) ^a	11.7	1.55-87.9	.01
TLs_{sstr} (g) ^a	3.31	.97-11.3	.05
$SUVmaxs_{sstr}$ ^a	.39	.11-1.36	.14
Ki-67 ^b	1.03	.97-1.11	.25
Age ^b	.99	.96-1.03	.93

^aDichotomized variables on ROC analysis basis.

^bOrdinal variable.

HR, hazard ratio; CI, confidence interval; SSTR, somatostatin receptor; $RTVs_{sstr}$, $sstr$ expression representative tumor volume; TLs_{sstr} , total lesion $sstr$ expression; $SUVmaxs_{sstr}$, $sstr$ maximum standardized uptake value.

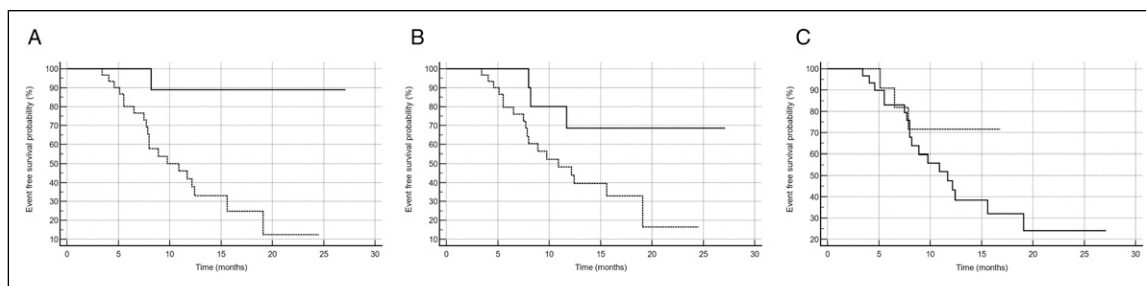


Figure 3. Kaplan-Meier survival graphs indicate a significant difference in EFS between the group of patients categorized by RTV_{sstr} . (A), Kaplan-Meier graph of RTV_{sstr} and EFS showing RTV_{sstr} above (dotted line) and below (solid line) the cut off of >2.47 (cm^3). Low RTV_{sstr} is coupled with prolonged Event Free Survival ($P = .003$, log-rank test). (B), Kaplan-Meier graph of TL_{sstr} and EFS with TL_{sstr} above (dotted line) and below (solid line) the cut off of >219.3 (g); $P = .04$. (C), Kaplan-Meier graph of $SUVmax_{sstr}$ and EFS with $SUVmax_{sstr}$ above (dotted line) and below (solid line) the cut off of ≤ 16.3 ; $P = ns$.

clinical progress. Although, these tumors have a slow growth and a relatively favorable prognosis,^{12-14,16} they can have various clinical features and outcomes. This scenario urges for valid prognostic factors generally missing in the neuroendocrine tumors management. Here, we found that the RTV_{sstr} , a new PET/CT volumetric parameter, may help for stratifying patients with primary GEP-NET undergoing surgery. Increased RTV_{sstr} discriminates subjects with worse prognosis compared to those who did not. RTV_{sstr} had a better prognostic

significance than $SUVmax_{sstr}$ in this setting. Although already described in metastatic and all grades of pancreatic NET,^{14,17-22} the finding is novel since linked to patients with primary GEP-NET complying with loco-regional disease, whose curative intent surgery was shortly performed. Generally, considering the relative quiescence of GEP-NET, it seems appropriate to measure the prognostic potential of different indicators by progression- or event free survival (PFS; EFS) rather than overall survival as partially reported

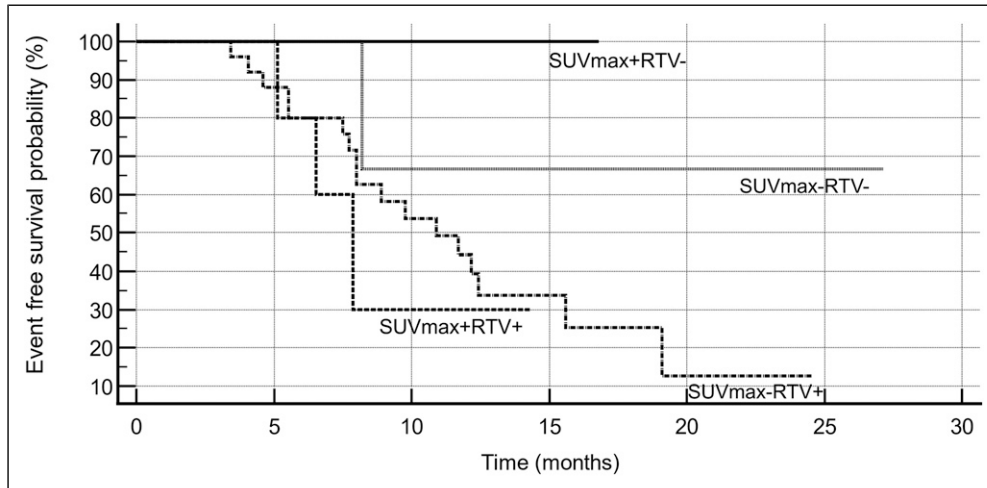


Figure 4. Survival by combination of RTV_{sstr} and $SUVmax_{sstr}$ values. Kaplan-Meier graph of both RTV_{sstr} and $SUVmax_{sstr}$ and Event Free Survival. $RTV_{sstr} +$ and $RTV_{sstr} -$ indicate values of RTV_{sstr} above and below the cut off of >2.47 (cm^3), respectively. $SUVmax_{sstr} +$ and $SUVmax_{sstr} -$ indicate values of $SUVmax_{sstr}$ above and below the cut-off, respectively; ($P = .01$ across categories, log-rank test).

below. Some authors indicated that RTV_{sstr} have prognostic value of progression free survival in well differentiated NET patients.¹⁴ That study enrolled ninety-two surgical or medical patients whose summed values of RTV_{sstr} , calculated in metastatic subjects, were demonstrated to perform better than $SUVmax_{sstr}$. Pauwels et al¹⁸ analyzed pretherapeutic $[^{68}Ga]$ Ga-SSTR PET tumor uptake and the volumetric parameters in patients undergoing ^{90}Y -DOTATOC peptide receptor radionuclide therapy (PRRT). They found that high $[^{68}Ga]$ Ga-DOTATOC-avid tumor volume predicts better outcome in NET patients treated with $[^{90}Y]$ Y-DOTATOC. Similar findings were reported by other authors²² in patients treated with $[^{177}Lu]$ Lu-DOTATATE but, the value of volumetric parameters in predicting outcome was only partially confirmed. Both the latest studies were performed in patients necessitating PRRT hence, a priori, metastatic. Ohlendorf et al¹⁹ also focused their analysis on RTV_{sstr} as predictive factor in advanced-stage GEP-NET showing that this parameter constitutes a valuable imaging biomarker of tumor burden. Some other authors²¹ demonstrated the prognostic value of the volumetric indices in patients with locally advanced, unresectable NETs, in terms of both PFS and disease-specific mortality. Ohnona et al²⁰ indicated the total functional tumor volume measured by $[^{68}Ga]$ Ga-SSTR PET as a relevant prognostic biomarker in patients with all stages of well-differentiated pancreatic NETs. At present, there are still few trials on operable GEP-NET cases at staging time. The same as for volumetric parameters, only few studies focused on $SUVmax$ as a predictive parameter in GEP-NET.^{13,23} Low $SUVmax$ on $[^{68}Ga]$ Ga-SSTR PET was associated with worse prognosis in well-differentiated GEP-NET predicting early failure on SSA monotherapy. In addition, $[^{68}Ga]$ Ga-SSTR PET/CT, via $SUVmax$, impacted on the management of NET patients, leading to a change in treatment decision in about

one-third of patients.²⁴ Ambrosini et al¹² also reported that high $[^{68}Ga]$ Ga-DOTANOC $SUVmax$ correlates with better outcome in stages III or IV pancreatic NETs. In our study a volumetric parameter, the RTV_{sstr} , predicts event free survival being it prognostic of worst outcome when higher, and it appears to work better than $SUVmax_{sstr}$ in operable GEP-NET. Moreover, on a patient basis, lower RTV_{sstr} values seem to be protective also when coupled with $SUVmax_{sstr}$ for prognostic, as patients with low RTV_{sstr} tend to exhibit a longer EFS irrespective of $SUVmax_{sstr}$ (Figure 5).

The $SUVmax$ represents a validated measurement confined to the detection of the hyper-metabolic activity of the tumor at single site (the site most representative of SSTR concentration), which does not consider the whole representative tumor volume. On the other hand, SSTR expression representative tumor volume (RTV_{sstr}) estimates the tumor SSTR representation through the volume of the entire lesion above a minimum threshold designed to exclude background activity.

It is well known that survival time differs among patients with NETs, even those with the same site, stage, and grade of primary tumor. This finding can be partially due to tumor heterogeneity which may translate tracer's uptake heterogeneity between lesions of the same histologic subtype. At present, a variety of imaging-derived parameters have been reported to predict prognosis or treatment outcome, even if none have been translated into routine clinical practice so far. Recently, Paiella et al²⁵ reported that the combined use of $[^{68}Ga]$ Ga-SSTR and $[^{18}F]$ F-FDG PET/CT may be valuable in the diagnostic workup of pancreatic NETs, especially in G2 setting, with an aggregate sensitivity of 99.2%. The PET/CT methodology may help to overcome quantitative and heterogeneous concerns, since the whole tumor burden can be comprehensively assessed both in solid tumors and hematological malignancies.²⁶⁻²⁸ In our study patients

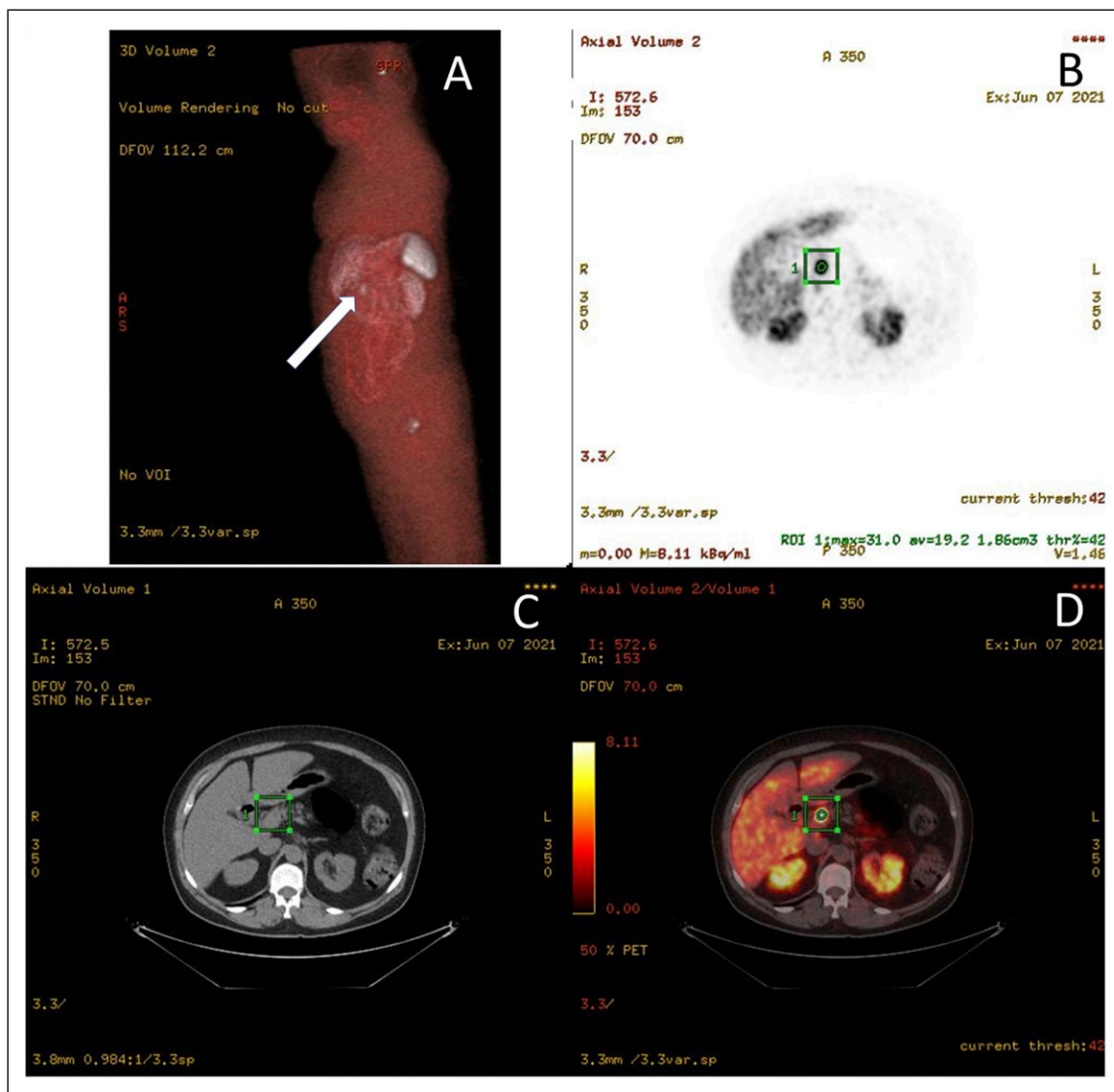


Figure 5. [^{68}Ga]Ga-edotreotide PET/CT in patient with pancreatic GEP-NET. Left anterior oblique surface rendering image of the lesion (arrow) (A), axial PET image with lesion volume computation (box and master region of interest) (B), axial CT image (C), axial PET/CT fused image (D).

presenting higher values of RTV_{sstr} showed a shorter event free survival as compared to those having lower, indicating that the lower the magnitude of tumor volume is -representing SSTR expression- the better the response to subsequent therapy. The SUV_{max} , and the individual features were not predictive, yet we tested the association of SUV_{max} with RTV_{sstr} trying to couple their potentialities in the above-mentioned heterogeneous environment of GEP-NET. Noteworthy, patients with higher RTV_{sstr} worsened irrespective of $\text{SUV}_{\text{max}_{\text{sstr}}}$. Overall, lower RTV_{sstr} values showed tendency to be protective regardless of $\text{SUV}_{\text{max}_{\text{sstr}}}$. It is conceivable that patients with primary tumor and locoregional disease presenting low values of global RTV_{sstr} would respond better since the magnitude of the SSTR representative burden, rather

than the maximal SSTR representation at single voxel, appears to be the key determinant. Tumor heterogeneity cannot be comprehensively depicted by a single “hypermetabolic” voxel. Accordingly, SUV_{max} did not influence the outcome of our patients. Concerning the TL_{sstr} , we noted a prediction tendency like RTV_{sstr} , even barely significant. It was probably due to the preponderant use of non-predictive SUV_{max} in TL_{sstr} computation.

From a patho-physiological point of view, these findings are not surprising since RTV_{sstr} may better represent the real tumor volume in this setting and, the well-known heterogeneous texture of GEP-NET whereas SUV_{max} conveys an index of cell SSTR expression within a well-defined and circumscribed volume. In fact, RTV_{sstr} reflects better than SUV_{max} the aggregated

GEP-NET pathological features such as the degree of cellularity of lesions, the number of neoplastic cells, the degree of SSTR expression and the various histological architecture that may include trabeculae, nests, glandular formation, gyriform, and pseudorosettes.²⁹⁻³¹ Indeed, in this set-up the endoscopic ultrasound holds a prognostic value for stratifying NET patients with solid pancreatic lesions, detecting malignancy-related features as well as identifying the tumor grading reliably.^{32,33}

The abovementioned characteristics of NETs can lead to pitfalls when considering only the SUV_{max}.³⁴⁻³⁶ In this environment the comprehensive volumetric indices, such as RTV_{sstr}, are expected to work better. The prognostic impact of [⁶⁸Ga]Ga-SSTR PET/CT volumetric parameters in GEP-NET patients undergoing surgery remains to be completely established. In view of that, our results demonstrate that RTV_{sstr} was predictive for event free survival in this setting endorsing the use of [⁶⁸Ga]Ga-SSRT PET/CT in daily clinical practice and for tailoring subsequent therapy.

This study included GEP-NET patients that strictly fulfilled inclusion criteria, enrolled at staging, before curative intent surgery. It was performed on a single center basis which gives reason for the small samples size. Additionally, the impact on EFS of subsequent medical therapies, if any, has not been figured.

Conclusion

The quantitative assessment by RTV_{sstr} rather than SUV_{max} on [⁶⁸Ga]Ga-SSTR PET/CT may be helpful to manage patients with GEP-NET before surgery. In this setting, the response to therapy seems to depend upon the tumor burden extent rather than the magnitude of SSTR expression.

Appendix

Abbreviations

EFS	event free survival
GEP-NET	gastroenteropancreatic tumors-neuroendocrine tumors
OS	overall survival
PET/CT	positron emission tomography/computed tomography
SSTR	somatostatin receptors
SUV _{max,sstr}	standardized uptake value
RTV _{sstr}	SSTR representative tumor volume
TL _{sstr}	total lesion SSTR expression

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition

of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; they have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Data Availability Statement

Data that generated the manuscript are guarded in digital form by the corresponding author and are available upon request, if any.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

Basilicata Ethics Committee and IRCCS CROB institutional review board gave approval for the study (approval number: #2022-001470). All patients undergoing PET/CT signed an informed consent form in accordance with the Declaration of Helsinki.

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References

1. Cives M, Strosberg JR. Gastroenteropancreatic neuroendocrine tumors CA cancer. *J Clin*. 2018;68(6):471-487. doi:10.3322/caac.21493.
2. Ahmed M. Gastrointestinal neuroendocrine tumors in 2020. *World J Gastrointest Oncol*. 2020;12(8):791-807. doi:10.4251/wjgo.v12.i8.791.
3. Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis, and recent trend toward improved survival. *Ann Oncol*. 2008;19(10):1727-1733. doi:10.1093/annonc/mdn351.
4. Hendifar AE, Marchevsky AM, Tuli R. Neuroendocrine tumors of the lung: current challenges and advances in the diagnosis and management of well-differentiated disease. *J Thorac Oncol*. 2017;12(3):425-436. doi:10.1016/j.jtho.2016.11.2222.
5. Lloyd RV, Osamura YR, Kloppel G, Rosai J. *WHO Classification of Tumors of Endocrine Organs*. Geneva, Switzerland: WHO Press; 2017.
6. Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer*. 2015;121:589-597. doi:10.1002/ncr.29099.
7. Zandee WT, deHerder WW. The evolution of neuroendocrine tumor treatment reflected by ENETS guidelines. *Neuroendocrinology*. 2018;106:357-365. doi:10.1159/000486096.

8. Sadowski SM, Neychev V, Millo C, et al. Prospective study of ⁶⁸Ga-DOTATATE positron emission tomography/computed tomography for detecting gastro-entero-pancreatic neuroendocrine tumors and unknown primary sites. *J Clin Oncol*. 2016; 34(6):588-596. doi:10.1200/JCO.2015.64.0987.
9. Schmid-Tannwald C, Schmid-Tannwald CM, Morelli JN, et al. Comparison of abdominal MRI with diffusion-weighted imaging to ⁶⁸Ga-DOTATATE PET/CT in detection of neuroendocrine tumors of the pancreas. *Eur J Nucl Med Mol Imaging*. 2013;40(6):897-907. doi:10.1007/s00259-013-2371-5.
10. Deppen SA, Blume J, Bobbey AJ, et al. ⁶⁸Ga-DOTATATE compared with ¹¹¹In-DTPA-octreotide and conventional imaging for pulmonary and gastroenteropancreatic neuroendocrine tumors: a systematic review and meta-analysis. *J Nucl Med*. 2016;57(6):872-878. doi:10.2967/jnumed.115.165803.
11. Bartolomei M, Berruti A, Falconi M, et al. Clinical management of neuroendocrine neoplasms in clinical practice: a formal consensus exercise. *Cancers (Basel)*. 2022;14:2501. doi:10.3390/cancers14102501.
12. Ambrosini V, Campana D, Polverari G, et al. Prognostic value of ⁶⁸Ga-DOTANOC PET/CT SUVmax in patients with neuroendocrine tumors of the pancreas. *J Nucl Med*. 2015;56:1843-1848. doi:10.2967/jnumed.115.162719.
13. Lee DY, Kim YI. Prognostic value of maximum standardized uptake value in ⁶⁸ga-somatostatin receptor positron emission tomography for neuroendocrine tumors: a systematic review and meta-analysis. *Clin Nucl Med*. 2019;44(10):777-783. doi:10.1097/RLU.0000000000002694.
14. Torihara A, Baratto L, Nobashi T, et al. Prognostic value of somatostatin receptor expressing tumor volume calculated from (⁶⁸)Ga-DOTATATE PET/CT in patients with well-differentiated neuroendocrine tumors. *Eur J Nucl Med Mol Imaging*. 2019; 46(11):2244-2251. doi:10.1007/s00259-019-04455-9.
15. McShane LM, Altman DG, Sauerbrei W, et al. REporting recommendations for tumour MARKer prognostic studies (REMARK). *Br J Cancer*. 2005;93(4):387-391.
16. Panzuto FL, Boninsegna L, Fazio N, et al. Metastatic and locally advanced pancreatic endocrine carcinomas: analysis of factors associated with disease progression. *J Clin Oncol*. 2011;29(17): 2372-2377. doi:10.1200/JCO.2010.33.0688.
17. Hou J, Yang Y, Chen N, Chen D, Hu S. Prognostic value of volume-based parameters measured by sstr pet/ct in neuroendocrine tumors: a systematic review and meta-analysis. *Front Med (Lausanne)*. 2021;8:771912. doi:10.3389/fmed.2021.771912.
18. Pauwels E, Van Binnebeek S, Vandecaveye V, et al. Inflammation-based index and (⁶⁸)Ga-DOTATOC PET-derived uptake and volumetric parameters predict outcome in neuroendocrine tumor patients treated with (⁹⁰)Y-DOTA-TOC. *J Nucl Med*. 2020;61(7):1014-1020. doi:10.2967/jnumed.119.236935.
19. 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*. 2020;66:361-371. doi:10.23736/S1824-4785.20.03238-0.
20. Ohnona J, Nataf V, Gauthé M, et al. Prognostic value of functional tumor burden on ⁶⁸Ga-DOTATOC PET/CT in patients with pancreatic neuro-endocrine tumors. *Neoplasma*. 2019;66(1):140-148. doi:10.4149/neo_2018_180328N209.
21. Tirosh A, Papadakis GZ, Millo C, et al. Prognostic utility of total (⁶⁸)Ga-DOTATATE-avid tumor volume in patients with neuroendocrine tumors. *Gastroenterology*. 2018;154(4):998-1008. e1. doi:10.1053/j.gastro.2017.11.008.
22. Ortega C, Wong RK, Schaefferkoetter J, et al. Quantitative ⁶⁸Ga-DOTATATE PET/CT parameters for the prediction of therapy response in patients with progressive metastatic neuroendocrine tumors treated with ¹⁷⁷Lu-DOTATATE. *J Nucl Med*. 2021;62(10):1406-1414. doi:10.2967/jnumed.120.256727.
23. Lee H, Eads JR, Pryma DA. ⁶⁸Ga-DOTATATE positron emission tomography-computed tomography quantification predicts response to somatostatin analog therapy in gastroenteropancreatic neuroendocrine tumors. *Oncologist*. 2021; 26(1):21-29. doi:10.1634/theoncologist.2020-0165.
24. Virgolini I, Gabriel M, Kroiss A, et al. Current knowledge on the sensitivity of the (⁶⁸)Ga-somatostatin receptor positron emission tomography and the SUVmax reference range for management of pancreatic neuroendocrine tumours. *Eur J Nucl Med Mol Imaging*. 2016;43(11):2072-2083. doi:10.1007/s00259-016-3395-4.
25. Paiella S, Landoni L, Tebaldi S, et al. Dual-tracer (⁶⁸Ga-DOTATOC and ¹⁸F-FDG)-PET/CT scan and G1-G2 nonfunctioning pancreatic neuroendocrine tumors: a single-center retrospective evaluation of 124 nonmetastatic resected cases. *Neuroendocrinology*. 2022;112(2):143-152. doi:10.1159/000514809.
26. Storto G, Nicolai E, Salvatore M. [¹⁸F] FDG-PET-CT for early monitoring of tumor response: when and why. *Q J Nucl Med Mol Imaging*. 2009;53(2):167-180.
27. Nappi A, Gallicchio R, Simeon V, et al. [¹⁸F] FDG-PET/CT parameters as predictors of outcome in inoperable NSCLC patients. *Radiol Oncol*. 2015;49(4):320-326. doi:10.1515/raon-2015-0043.
28. Storto G, De Renzo A, Pellegrino T, et al. Assessment of metabolic response to radioimmunotherapy with ⁹⁰Y-ibritumomab tiuxetan in patients with relapsed or refractory B-cell non-Hodgkin lymphoma. *Radiology*. 2010;254(1): 245-252. doi:10.1148/radiol.09090603.
29. Şentürk M, Acar B, Yildirim MA, Çakır M, Küçükkartallar T, Vatansav C. Clinicopathological characteristics of gastroenteropancreatic neuroendocrine tumors: 10 years of experience from a single center. *Pancreas*. 2022;51(2):159-163. doi:10.1097/MPA.0000000000001981.
30. Riss P, Scheuba K, Strobel O. Endocrine and neuroendocrine tumors. *Chirurg*. *Der Chirurg*. 2021;92(11):996-1002. doi:10.1007/s00104-021-01512-8.
31. Watanabe H, Fujishima F, Komoto I, et al. Somatostatin receptor 2 expression profiles and their correlation with the efficacy of

- somatostatin analogues in gastrointestinal neuroendocrine tumors. *Cancers (Basel)*. 2022;14(3):775. doi:[10.3390/cancers14030775](https://doi.org/10.3390/cancers14030775).
32. Crinó SF, Brandolese A, Vieceli F, et al. Endoscopic ultrasound features associated with malignancy and aggressiveness of nonhypovascular solid pancreatic lesions: results from a prospective observational study. *Ultraschall Med*. 2021;42(2):167-177. doi:[10.1055/a-1014-2766](https://doi.org/10.1055/a-1014-2766).
 33. Tacelli M, Bina N, Crinó SF, et al. Reliability of preoperative pancreatic neuroendocrine tumors grading on endoscopic ultrasound specimens: a systematic review with meta-analysis of aggregate and individual data. *Gastrointest Endosc*. 2022; S0016-5107(22)01831-4. doi:[10.1016/j.gie.2022.07.014](https://doi.org/10.1016/j.gie.2022.07.014).
 34. Hope TA, Bergsland EK, Bozkurt MF, et al. Appropriate use criteria for somatostatin receptor PET imaging in neuroendocrine tumors. *J Nucl Med*. 2018;59(1):66-74. doi:[10.2967/jnumed.117.202275](https://doi.org/10.2967/jnumed.117.202275).
 35. Binderup T, Knigge U, Loft A, Federspiel B, Kjaer A. 18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. *Clin Cancer Res*. 2010;16(3):978-985. doi:[10.1158/1078-0432.CCR-09-1759](https://doi.org/10.1158/1078-0432.CCR-09-1759).
 36. Binderup T, Knigge U, Mogensen AM, Hansen Kjaer CPA. Quantitative gene expression of somatostatin receptors and noradrenaline transporter underlying scintigraphic results in patients with neuroendocrine tumors. *Neuroendocrinology*. 2008;87(4):223-232. doi:[10.1159/000113128](https://doi.org/10.1159/000113128).