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Semi-automatic tumor delineation for evaluation of ^{64}Cu-DOTATATE PET/CT in patients with neuroendocrine neoplasms: prognostication based on lowest lesion uptake and total tumor volume

Esben Andreas Carlsen[1, 2], Camilla Bardram Johnbeck[1, 2], Mathias Loft[1, 2], Andreas Pfeifer[1,2], Peter Oturai[1, 2], Seppo W. Langer[2, 3], Ulrich Knigge[2, 4], Claes Nøhr Ladefoged[1, 2, *] and Andreas Kjaer[1, 2, *, †]

[1]Dept. of Clinical Physiology, Nuclear Medicine & PET and Cluster for Molecular Imaging, Dept. of Biomedical Sciences, Rigshospitalet and University of Copenhagen, Denmark

[2] ENETS Neuroendocrine Tumor Center of Excellence, Rigshospitalet, Copenhagen, Denmark

[3]Dept of Oncology, Rigshospitalet and University of Copenhagen, Denmark

[4]Depts. of Clinical Endocrinology and Surgical Gastroenterology, Rigshospitalet, Denmark

[*] Shared last author

[†] Correspondence to Prof. Andreas Kjaer, MD, PhD, DMSc, Dept. of Clinical Physiology, Nuclear Medicine & PET, KF-4011, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. Orcid: https://orcid.org/0000-0002-2706-5547 . e-mail: akjaer@sund.ku.dk

First author: Esben Andreas Carlsen, MD, Dept. of Clinical Physiology, Nuclear Medicine & PET, KF-4011, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. Orcid: https://orcid.org/0000-0002-5231-4197. e-mail: esben.a.carlsen@gmail.com

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ABSTRACT

Patients with neuroendocrine neoplasms (NEN) have heterogeneous somatostatin receptor expression with highly differentiated lesions having higher expression. Receptor expression of the total tumor burden may be visualized by somatostatin receptor imaging, e.g. ^{64}Cu-DOTATATE PET/CT. Assessment of maximal lesion uptake is associated with progression-free survival (PFS), but not overall survival (OS). We hypothesized that the lesion with lowest, rather than highest, ^{64}Cu-DOTATATE uptake would be more prognostic and developed a semi-automatic method for evaluating this.

Methods

Patients with NEN underwent ^{64}Cu-DOTATATE PET/CT. A standardized semi-automatic tumor delineation method was developed and used to identify the lesion with the lowest uptake, i.e. lowest of lesion mean standardized uptake values $(SUV)_{mean}$. Additionally, we assessed total tumor volume derived from the semi-automatic tumor delineation. Kaplan-Meier and Cox regression analyses were used to determine association with OS and PFS.

Results

In 116 patients with NEN, median PFS (95% confidence interval) was 23 (20-31) months and median OS was 85 (68-113) months. Minimum SUV_{mean} and total tumor volume were significantly associated with PFS and OS in univariate Cox regression analyses, while SUV_{max} was only significant for PFS. In multivariate Cox analyses, both minimum SUV_{mean} and total tumor volume remained statistically

significant. Minimum SUV_{mean} and total tumor volume were then dichotomized by their median, and patients were categorized into 4 groups: High/low total tumor volume and high/low minimum SUV_{mean}. Patients with low total tumor volume and high minimum SUV_{mean} had a hazard ratio (95% confidence interval) of 0.32 (0.20-0.51) for PFS and 0.24 (0.13-0.43) for OS, both $P<0.001$ (reference: high total tumor volume and low minimum SUV_{mean}).

Conclusion

We propose a standardized semi-automatic tumor delineation method to identify the lesion with lowest ^{64}Cu-DOTATATE uptake and total tumor volume. Assessment of lowest, rather than highest lesion uptake greatly increases prognostication by ^{64}Cu-DOTATATE PET/CT. Combing lesion uptake and total tumor volume, we derived a novel prognostic classification of patients with NEN.

Keywords

Neuroendocrine neoplasms; ^{64}Cu-DOTATATE PET; semi-automatic tumor delineation; minimum SUV_{mean}; total tumor volume

INTRODUCTION

Patients with neuroendocrine neoplasms (NEN) have a disease course and survival span that varies considerably. In recent years, several treatment options have been validated for patients with NEN. One criterion that can be used for selection of different treatment strategies is the expected prognosis of a patient, i.e. more aggressive treatment in patients with a rapid and aggressive disease course. In patients with NEN, the World Health Organization (WHO) grading scheme based on the proliferation marker Ki-67 determined either in a biopsy or surgically resected tumor at present plays a crucial role in this regard. Currently, NEN patients are graded according to Ki-67 and tumor differentiation (*1*). However, a known limitation hereof is interlesional tumor heterogeneity between primary tumor and metastatic lesions (*2-5*). Furthermore, with disease progression, increase of Ki-67 is seen (*4*). By sampling of the entire tumor and/or several lesions, increase in Ki67 and WHO grade is frequently seen (*2-5*). Hence, prediction of prognosis may be enhanced by assessing the total tumor volume to identify the most dedifferentiated lesion. This, as well as longitudinal monitoring, is possible using whole body positron emission tomography (PET) assessment.

PET is widely used in patients with NEN, especially somatostatin receptor imaging (SRI) by radiolabeled somatostatin analogues, e.g. ^{64}Cu-DOTATATE, ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC, in patients with low grade NEN, and glucose uptake imaging by ^{18}F-FDG in patients with high grade NEN. We have previously reported the ability of ^{64}Cu-DOTATATE PET to predict overall survival (OS) and progression-free survival (PFS) in patients with NEN (*6*). Whilst unable to identify a cutoff to predict OS, we showed that patients with a maximal tumor SUV_{max} >43.3 had half the risk of progressive disease, compared to patients with a maximal $SUV_{max} \leq 43.3$. The highest tumor SUV_{max} for a patient is easy to obtain, however, it reflects the greatest somatostatin receptor density and

therefore the prediction is likely based on the most differentiated, and least aggressive, tumor area. For ^{18}F-FDG PET both metabolic tumor volume and total lesion glycolysis have been reported (*7-9*), which has also been adopted to SRI (*10*). Total tumor volume based on SRI tumor segmentation has been shown to have prognostic implications (*11-14*). Besides volumetric information, lowest lesion SUV_{mean} would also be available with total tumor segmentation and thus the most dedifferentiated lesion could be used for prognostication.

The aim of the paper is to propose a scheme for semi-automated tumor delineation in ^{64}Cu-DOTATATE PET for patients with NEN and to use this to improve the prognostic value of ^{64}Cu-DOTATATE. To do so, measures of lowest lesion SUV_{mean} and total tumor volume extracted from tumor delineation were used. We hypothesized that this could increase the prognostic value of ^{64}Cu-DOTATATE PET compared with the previously reported method based on SUV_{max}.

METHODS

Patients

Between November 2009 and March 2013 our group recruited patients with NEN in two prospective clinical studies with ^{64}Cu-DOTATATE PET/CT (*15,16*), approved by the Regional Scientific Ethical Committee (reference no. H-D-2008-045). Written informed consent was obtained from all participants. Included patients had histopathologically confirmed gastroenteropancreatic or lung NEN or NEN of unknown primary and were referred for PET/CT for staging, restaging or follow-up. All scans were reviewed for inclusion in the present follow-up study. If more than one ^{64}Cu-DOTATATE PET/CT was available for a patient, the earliest scan was used. We excluded patients with no signs of

NEN due to previous radical surgery. Patients were followed and treated with standard of care at the ENETS Neuroendocrine Tumor Center of Excellence, Rigshospitalet, Copenhagen, Denmark. Treatment decisions were made in multidisciplinary tumor boards blinded to the ^{64}Cu-DOTATATE PET/CT but guided by ^{111}In-Octreotide scintigraphy (clinical routine throughout the inclusion period), Ki-67, WHO grade and tumor location. Patient characteristics collected at baseline were age, sex, site of primary tumor, Ki-67 index (%), grade and treatment. The patients were assessed at regular follow-up visits and with diagnostic CT performed according to guidelines (*17*). At the discretion of the treating physician, SRI, magnetic resonance imaging and/or ultrasound were also performed during follow-up.

Radiotracer and Image Acquisition

Radiotracer production, PET/CT image acquisition and reconstruction methodology has been published previously (*15,16,18*). In short, patients had a whole-body PET/CT scan performed 61 ± 1 min (range, 43-99 min) after injection of 202 ± 1 MBq (range, 174-245 MBq) ^{64}Cu-DOTATATE. A Siemens Biograph 40 or 64 TruePoint PET/CT was used. All images were reconstructed with the same algorithm (TrueX; Siemens Medical Solutions) using 3 iterations, 21 subsets and smoothed by 2 mm Gaussian filter (full width at half maximum), on 336x336 matrices (2x2x3 mm^3 voxels). CT-based attenuation correction was applied. A diagnostic quality CT scan with iodine intravenous contrast was performed before the PET. If contraindicated, iodine contrast was not used. To ensure quantitatively accurate measurements between the different PET/CT scanners, we perform a quality control every 2 weeks, testing they are calibrated to measure within our acceptance range (5%).

Image Analysis

All PET/CT scans were analyzed using Mirada DBx 1.2.0 software package (Mirada Medical Ltd., Oxford, UK) blinded to the patients PFS and OS. A nuclear medicine physician in training (EAC) analyzed all scans and a subgroup (n=12) was additionally assessed by a board certified nuclear medicine physician (CBJ) blinded to results of the former. To the best of our knowledge, no standardized method for semi-automatic tumor delineation using somatostatin receptor imaging PET has been proposed. We therefore adapted the method proposed in PERCIST for ^{18}F-FDG PET to obtain a standardized patient-specific threshold = 1.5*liver SUV_{mean} + 2*standard deviation (SD) (*19*). Lower thresholds increase the delineation of lesions with a low tracer uptake but also of physiologic tracer uptake, which would substantially limit the semi-automatic approach. According to PERCIST, if no normal liver is available (e.g. full cancer involvement), the blood value should be used. However, in SRI PET, the blood value is markedly lower than the liver. We therefore chose to use normal spleen uptake in cases where normal liver tissue could not be assessed. In each patient, a 3 cm sphere was placed in normal liver tissue (or in normal spleen tissue). SUV_{mean} and SD was extracted and used to calculate the patient-specific threshold by the formulas below:

$$Liver: 1.5*SUV_{mean} + 2*SD$$

The formula was adapted for spleen SUV_{mean} based on normal data available in (*20*):

$$Spleen: 0.67*SUV_{mean} + 2*SD$$

SUV was calculated as decay-corrected measured radioactivity concentration/(injected activity/body weight). Hereafter a region encompassing all lesions was drawn manually and voxels with a SUV above the threshold delineated automatically. Delineated noise (i.e. non-pathological tracer uptake) and physiological tracer uptake (pituitary gland, liver, spleen, kidneys, adrenal glands, urinary tract, uncinate process of pancreas) was manually deleted.

Data Extraction

Partial volume effect results in underestimation of SUV in small lesions. We therefore defined a minimum lesion size of 1 mL based on that partial volume effect typically occurs in lesions smaller than 3 times the full width at half maximum (*21*). To obtain the minimum SUV_{mean} (i.e. the lesion with the lowest SUV_{mean}), data were extracted for each lesion individually. Confluent lesions were considered as one if the lesions were not separated based on the patient-specific threshold. Furthermore, total tumor volume (i.e. the sum of all lesions) was derived based on ^{64}Cu-DOTATATE PET.

Endpoints

Follow-up was performed on July 13th 2020. CT routine images and or magnetic resonance imaging were used for evaluation of PFS in accordance with Response Evaluation Criteria in Solid Tumors v. 1.1 (*22*). PFS was calculated as time from ^{64}Cu-DOTATATE PET/CT to, if any, progression or death from any cause. If no progression or death from any cause occurred within the follow-up, the patient was censored at the time of last available diagnostic imaging. OS was calculated as time from ^{64}Cu-

DOTATATE PET/CT to death by any cause. Patients alive at follow-up were censored to the day of follow-up, i.e. July 13th 2020.

Statistics

Continuous variables are reported as mean and standard error of mean (SEM) or median and minimum-maximum. Kaplan-Meier analysis was used for estimation of median time with 95% confidence interval (CI) to endpoint. Uni- and multivariate Cox regression analyses for outcome were performed for derived PET parameters as continuous and dichotomized (by median) parameters. Use of median of total tumor volume and minimum SUV_{mean} as suitable cutoffs were investigated using the R-package 'Cutoff Finder' (*23*). A p-value<0.05 was considered statistically significant. R statistical software, version 4.0.0. (R Foundation for Statistical Computing, Vienna, Austria) was used for the analyses.

RESULTS

In total, 128 patients with ^{64}Cu-DOTATATE PET/CT were assessed by the semi-automatic tumor delineation method. A median of 5 lesions were delineated per patient (min-max: 1-78). We excluded 12 patients due to no lesions above the minimum tumor volume threshold of 1 mL. Patient characteristics of the final population (n=116) are given in Table 1.

Semi-automatic Tumor Delineation

The time spent on the entire process of tumor delineation including manual deletion of physiological uptake was 20 (min-max: 5-35) minutes. The volume threshold 1 mL was not applied when the tumor

delineation was performed, but in the following post-processing. Shortest time was spent in patients with few lesions, where the drawn region of interest encompassing all lesions did not include foci with physiological uptake. The median patient-specific SUV threshold was 8.58 and defined from normal liver tissue in the majority of patients (108/116; 93%). In 11 of 12 patients the inter-reader comparison showed concordance regarding categorization according to total tumor volume and minimum SUV_{mean} (see below). In one patient the physiological uptake of the bladder had mistakenly not been removed, hence the volume was overestimated leading to discordant classification.

PET Parameters

The derived total tumor volume and SUV parameters are shown in Table 2. Minimum SUV_{mean} and total tumor volume were both statistically significantly associated with PFS and OS in univariate Cox regression analyses, whereas SUV_{max} was only for PFS (Table 3). In multivariate analyses of minimum SUV_{mean} and total tumor volume as continuous parameters both remained statistically significantly associated with PFS and OS (Table 4).

Progression-Free Survival and Overall Survival

Median PFS (95% CI) was 23 (20-31) months and median OS was 85 (68-113) months for the entire patient cohort (n=116). During follow-up 103 (89%) had disease progression and 68 died (59%). Total tumor volume and minimum SUV_{mean} were dichotomized at median values based on analyses of optimal cutoff for each parameter (Supplemental Figure 1). Patients were divided into 4 possible groups: High total tumor volume + low minimum SUV_{mean} (VhSl), high total tumor volume + high minimum SUV_{mean} (VhSh), low total tumor volume + low minimum SUV_{mean} (VlSl) and low total

tumor volume + high minimum SUV_{mean} (VlSh). Representative patient examples from the 4 groups are shown with and without semi-automatic tumor segmentation in Figure 1. Patients in the VhSl group (n=43) had a median PFS (95% CI) of 13 (7-21) months and median OS of 31 (18-53) months. For patients in the VlSh group (n=43), median PFS was 42 (25-80) months and median OS was not reached (lower limit of median: 95 month). Using VhSl as reference group, patients in the VlSh group had a HR (95% CI) of 0.32 (0.2-0.51) for PFS and 0.24 (0.13-0.43) for OS, both $P<0.001$ (Table 5/Figure 2). Although not powered for this purpose, exploratorily we assessed the categorization separately in patients with small intestine and pancreatic primary tumors and found similar prognostic performance (Supplemental Table 1). In comparison no significant differences were observed for patients with Ki67 <3% (n=27) vs. Ki67 3-20% (n= 79) in regard to PFS and OS (Supplemental Table 2/ Supplemental Figure 2).

DISCUSSION

The major finding of our study was that the prognostic value of ^{64}Cu-DOTATATE PET could be greatly improved by evaluating lowest lesion uptake rather than highest in patients with NEN. This is in accordance with our hypothesis and fits well into somatostatin receptor density being a surrogate of differentiation, i.e. lower density in more dedifferentiated and aggressive tumors. We furthermore present a novel combined classification of total tumor volume and lowest lesion uptake from ^{64}Cu-DOTATATE PET to incorporate previous reports that tumor volume derived from SRI (*10-14*) is associated with prognosis in patients with NEN. Applying the combination of total tumor volume and lowest lesion uptake, we classified patients into 4 groups, where patients in the group VhSl had the poorest prognosis in regards to PFS and OS.

We and others have reported on the prognostic ability of lesion SUV_{max} from either ^{64}Cu-DOTATATE (*6*) or ^{68}Ga-DOTATATE/DOTANOC (*24-26*). A limitation to that metric, besides concerns about the influence of image noise on single-pixel SUV_{max} (*27*), is the fact that prognostication then is based on the lesion with the highest uptake, i.e. greater somatostatin receptor density. One previous study of 30 patients with NEN investigating prognostication based on the lesion with lowest uptake did however fail to show an association between low uptake and higher risk of progressive disease (*26*). Furthermore, total lesion somatostatin receptor expression (the product of total tumor volume and overall SUV_{mean}) has been proposed (*10*). However, the results we present contradict this concept. The effect of total tumor volume and SUV_{mean} have opposite direction, and a high "total lesion activity" in SRI may be seen in patients with low tumor burden and high SUV_{mean} or high tumor burden and low SUV_{mean}. As presented, two such patients would be expected to have different prognosis.

A prerequisite to analyzing total tumor volume and minimum SUV_{mean} is tumor segmentation. A standardized semi-automatic method for PET-guided segmentation in patients with NEN has not been reported previously. We therefore employed a standardized patient-specific cutoff to delineated lesions based on the method described for ^{18}F-FDG (*19*). Recently, a number of papers have described the prognostic implications of tumor volume derived from ^{68}Ga-DOTATATE (*10-12*) or ^{68}Ga-DOTATOC (*13,14*), but not for ^{64}Cu-DOTATATE. In order to obtain tumor volume, different strategies were utilized; manual delineation of lesions including areas with either 41% or 50% of lesion SUV_{max} or semi-automatic delineation with individual SUV_{max} threshold based on agreement between anatomical and functional lesion delineation. However, none of the studies reported time spent on segmentation of tumors (*8-14*). In the present study, the time spent was approximately 20 minutes per patient, although less time (down to 5 minutes) was needed when areas of physiological uptake

(kidney, urinary bladder and spleen) could be avoided due to tumor location. Patients were concordantly grouped by the total tumor volume/minimum SUV_{mean} classification in all but one patient in the interreader analysis. The presented semi-automatic segmentation scheme may be feasible for clinical translation; however, faster segmentation is desirable. One approach would be to minimize the need for manual deletion of physiological uptake by use of anatomical data gained from the CT scan. This has been demonstrated for prostate cancer using ^{68}Ga-PSMA PET (*28*). An added gain would be that of organ-specific tumor burden, e.g. tumor burden in liver or bone. Subclassification according to tumor location may further enhance the prognostic implication of total tumor volume, e.g. it could be speculated that patients with mainly liver metastases have a different prognosis from patients with mainly bone metastases.

Limitations

The threshold used to delineate lesions was based on the PERCIST criteria, as no standardized semi-automated criteria have been suggested for SRI PET. To limit partial volume effect, only lesions greater than 1 mL were used for analysis of SUV. A larger required lesion size could have further limited partial volume effect, but at the cost of excluding a larger proportion of the lesions, hence potentially excluding more patients due to small lesions. Using the 1 mL cutoff, 12 of 128 patients were excluded, which is a limitation to the general use. The results may not translate directly to SRI PET with ^{68}Ga due to better resolution of ^{64}Cu-based imaging (4-fold shorter positron range) (*29*).

CONCLUSIONS

A standardized semi-automatic tumor segmentation scheme was applied to obtain total tumor volume and minimum lesion SUV_{mean} from ^{64}Cu-DOTATATE PET in patients with NEN. By use of lowest lesion uptake, rather than highest, results from ^{64}Cu-DOTATATE PET were significantly associated with both PFS and OS. Furthermore, patients could be classified into 4 groups with high/ low total tumor volume and high/low minimum SUV_{mean}, where patients with high total tumor volume and low minimum SUV_{mean} had the poorest prognosis.

DISCLOSURE

Andreas Kjaer and Ulrich Knigge are inventors on a patent application: “PET tracer for imaging of neuroendocrine tumors” (WO 2013029616 A1). No other potential conflicts of interest relevant to this article exist.

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KEY POINTS

Question

Is the prognostic capability of ^{64}Cu-DOTATATE PET in patients with neuroendocrine neoplasms improved by using total tumor segmentation to identify the lesion with lowest uptake compared to maximal uptake?

Pertinent Findings

Minimum SUV_{mean} as a measure of lowest lesion uptake was strongly associated with both overall and progression-free survival. This was not the case for maximal lesion uptake. We present a standardized semi-automatic tumor segmentation scheme and use it to define a novel classification combining total tumor volume and minimum SUV_{mean}. Patients with a high total tumor volume and low minimum SUV_{mean} have a significantly worse prognosis than other patients do.

Implications for Patient Care

Based on the combination of total tumor volume and minimum SUV_{mean} in ^{64}Cu-DOTATATE PET, patients with NEN may be classified into four groups and stratified with different risks of progressive disease and death. The classification may aid in clinical treatment decisions.

FIGURES AND TABLES

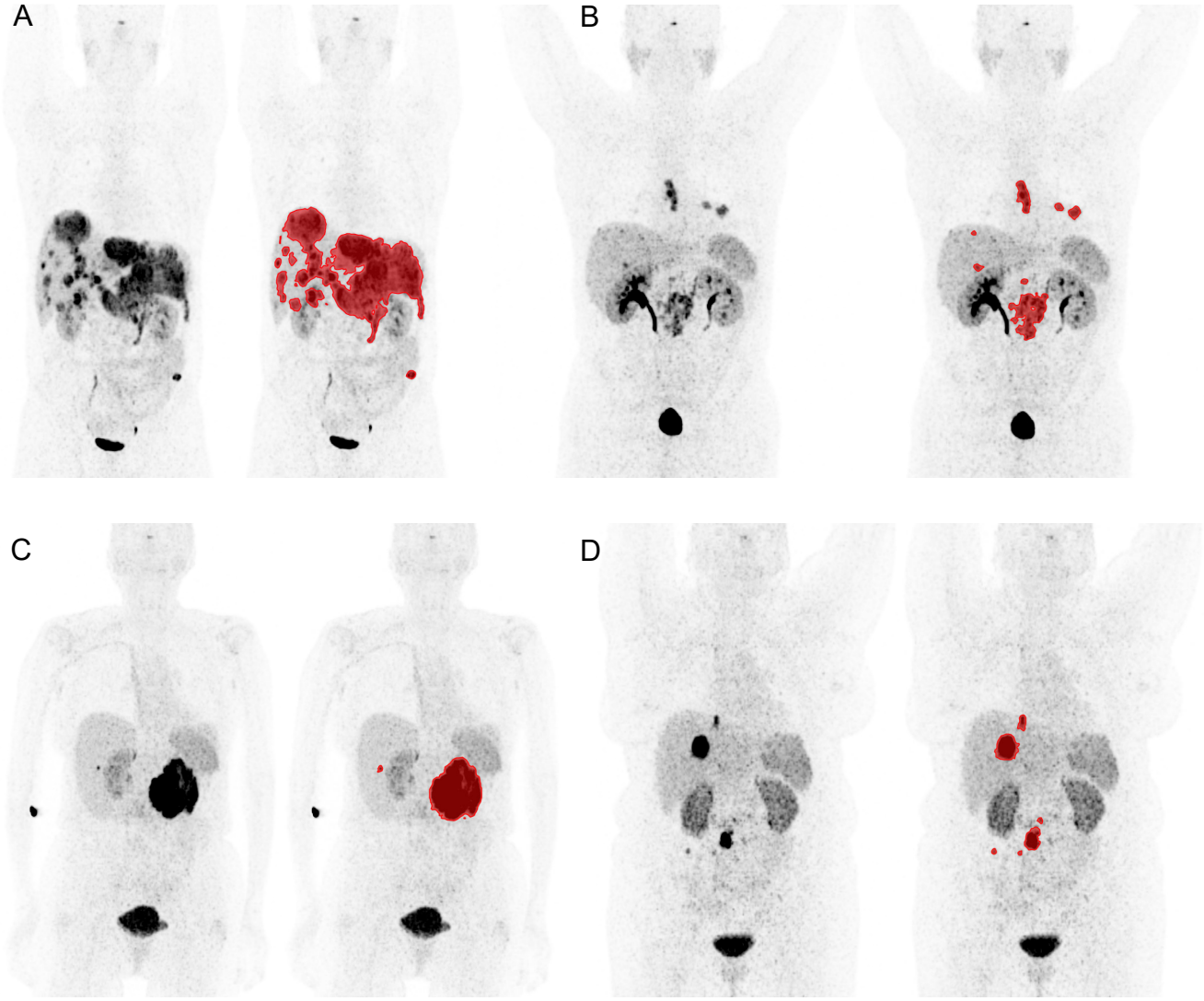


FIGURE 1. Patient examples of classification based on lowest lesion uptake combined with total tumor volume. Maximum intensity projections are shown without and with delineated tumor volume. Window setting for all images was 0-30. All separate lesions were analyzed individually to obtain minimum SUV_{mean}. A: VhSl, total tumor volume: 1041 mL/minimum SUV_{mean}: 9.6. OS: 17 mo./PFS: 11 mo. B: VlSl, total tumor volume: 54 mL/minimum SUV_{mean}: 13.1. OS: 51 mo./PFS: 42 mo. C: VhSh, total tumor volume: 415 mL/minimum SUV_{mean}: 25.3. OS: 68 mo./PFS: 34 mo. D VlSh, total tumor volume: 45 mL/minimum SUV_{mean}: 15. OS: 118 mo./PFS: 80 mo. OS = overall survival. PFS = progression-free survival.

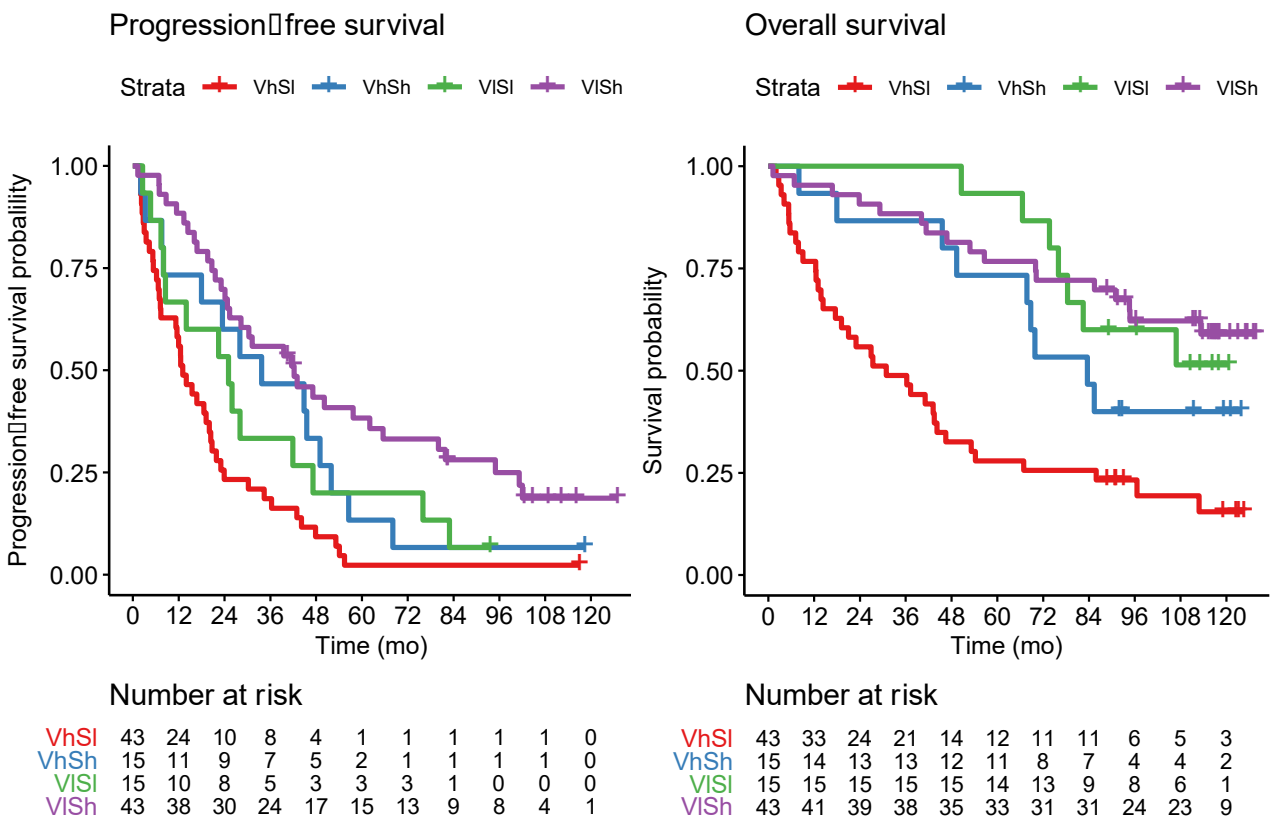


FIGURE 2. Kaplan-Meier plots of progression-free and overall survival for patients grouped by total tumor volume and minimum SUV_{mean}. High total tumor volume + low minimum SUV_{mean} (VhSl), high total tumor volume + high minimum SUVmean (VhSh), low total tumor volume + low minimum SUV_{mean} (VlSl) and low total tumor volume + high minimum SUV_{mean} (VlSh)

TABLE 1. Baseline Characteristics of 116 Patients with NENs.

		***n*=116**
Age, mean (SD)		62.2 (10.8)
Sex (%)		
	Male	64 (55)
	Female	52 (45)
Ki67*, median (min, max)		5 (1, 100)
WHO† (%)		
	G1	27 (23)
	G2	79 (68)
	G3	4 (3)
	Missing	6 (5)
Site of primary (%)		
	Small intestine	66 (57)
	Pancreas	25 (22)
	Cecum	7 (6)
	Extrahepatic biliary tract	2 (2)
	Gastric	1 (1)
	Lung	5 (4)
	Unknown primary NEN	10 (9)
Treatment before ^{64}Cu-DOTATATE PET/CT (%) ‡		
	No treatment	15 (13)
	Localized treatment(s)	10 (8)
	Systemic treatment(s)	43 (37)
	Localized and systemic treatment(s)	48 (41)

Percentages were rounded and may not add up to 100%. NEN: neuroendocrine neoplasms. WHO: World Health Organization. SD: Standard deviation. *Missing for 6 patients. † Patients with lung NEN had Ki67 < 10% and were accordingly placed in G1 and G2. ‡ Localized treatment for NEN: Surgery (n=52), hepatic artery embolization (n=7), radiofrequency ablation (n=7) and/or external radiation (n=2). Systemic treatment for NEN: Interferon (n=52), somatostatin analogue (n=47), chemotherapy (n=48) and/or peptide receptor radionuclide therapy (n=36).

TABLE 2. Parameters Obtained by Semi-automatic Total Tumor Delineation in ^{64}Cu-DOTATATE PET.

	***n*=116**
SUV_{max}	58.6 (13.4, 195)
Minimum SUV_{mean}	14.2 (5.6, 56.8)
Total tumor volume (mL)	54.9 (1.1, 3840)
Threshold for delineation	8.52 (4.7, 14.9)

All parameters reported as median (min, max). SUV = standardized uptake value.

TABLE 3. Univariate Cox Regression Analyses for Progression-Free Survival and Overall Survival.

Progression-free survival		
Parameter	**HR (95% CI)**	***P***
SUV_{max}	0.99 (0.99-1.00)	0.049
Minimum SUV_{mean}	0.94 (0.90-0.98)	<0.001
Total tumor volume	1.001 (1.00-1.001)	<0.001
Overall survival		
Parameter	**HR (95% CI)**	***P***
SUV_{max}	0.99 (0.99-1.00)	0.12
Minimum SUV_{mean}	0.91 (0.86-0.96)	<0.001
Total tumor volume	1.001 (1.001-1.001)	<0.001

All parameters are continuous. *n*=116. HR = hazard ratio. CI = confidence interval. SUV = standardized uptake value

TABLE 4. Multivariate Cox Regression Analyses for Progression-Free Survival and Overall Survival.

Progression-free survival		
Parameter	**HR (95% CI)**	***P***
Minimum SUV_{mean}	0.96 (0.92-1.00)	0.03
Total tumor volume	1.001 (1.00-1.001)	<0.01
Overall survival		
Parameter	**HR (95% CI)**	***P***
Minimum SUV_{mean}	0.94 (0.89-1.00)	0.045
Total tumor volume	1.001 (1.00-1.001)	<0.001

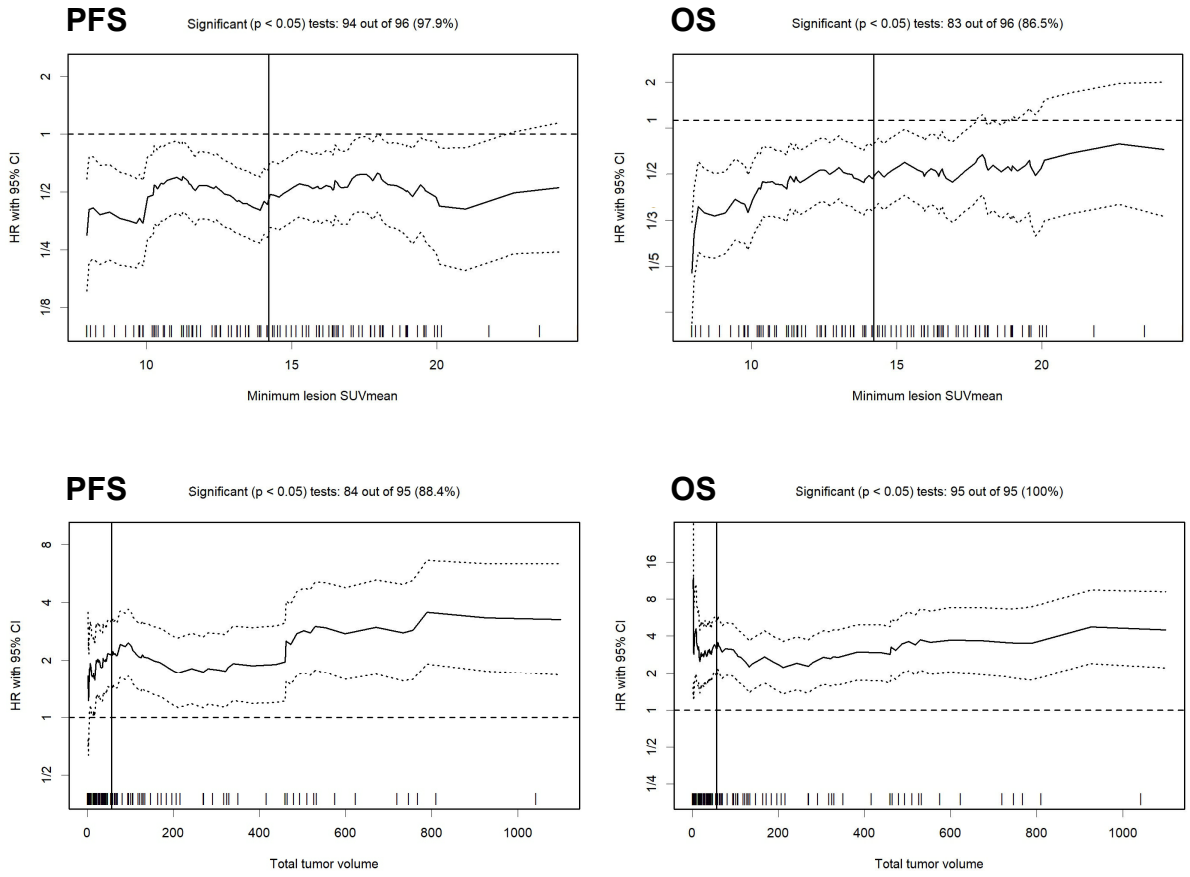
Both parameters are continuous. *n*=116. HR = hazard ratio. CI = confidence interval. SUV = standardized uptake value.

TABLE 5. Univariate Cox Regression Analyses for Progression-Free Survival and Overall Survival.

Progression-free survival		
Group	**HR (95% CI)**	***P***
VhSl (n=43)	Reference	-
VhSh (n=15)	0.51 (0.28-0.94)	0.03
VlSl (n=15)	0.58 (0.32-1.08)	0.08
VlSh (n=43)	0.32 (0.20-0.51)	<0.001
Overall survival		
Group	**HR (95% CI)**	***P***
VhSl (n=43)	Reference	-
VhSh (n=15)	0.43 (0.21-0.90)	0.02
VlSl (n=15)	0.27 (0.12-0.61)	<0.01
VlSh (n=43)	0.24 (0.13-0.43)	<0.001

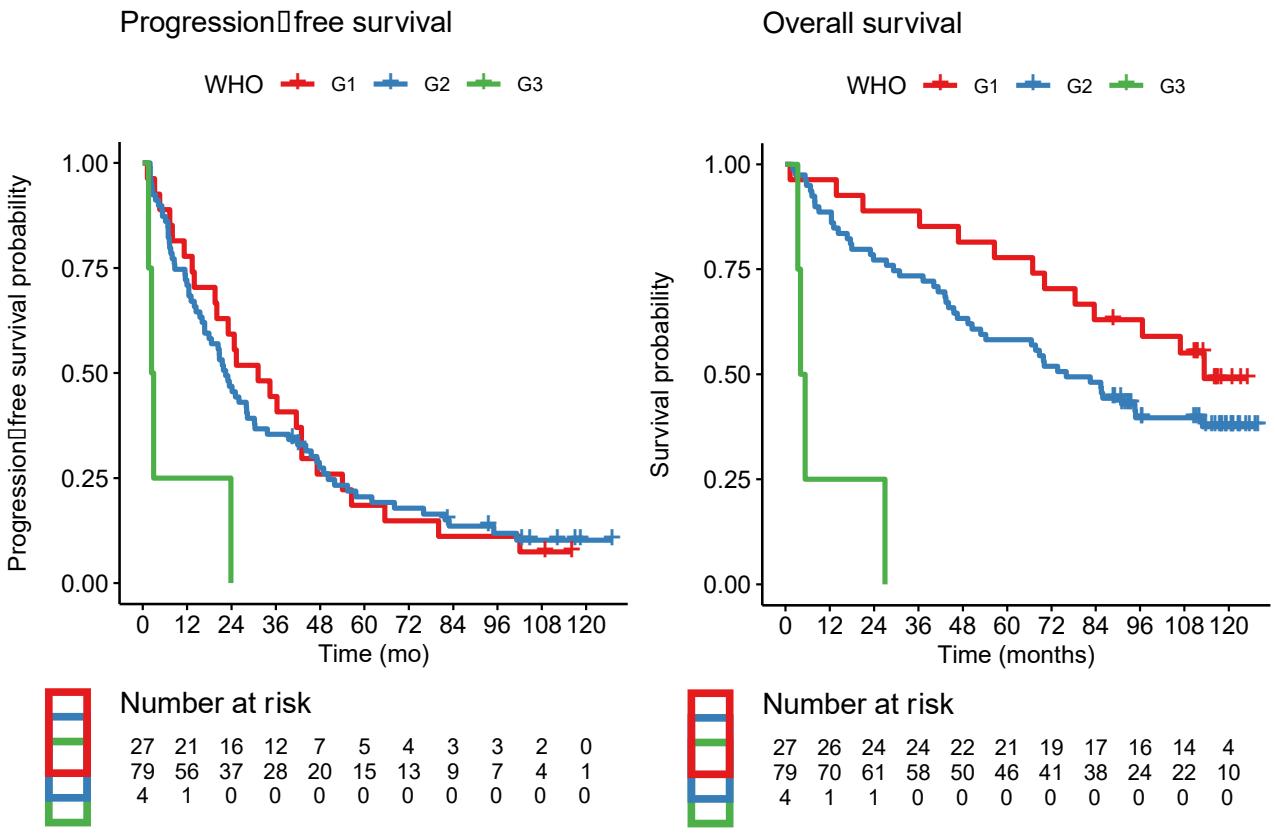
Patients with high total tumor volume and low minimum SUV_{mean} are reference. *n*=116. HR = hazard ratio. CI = confidence interval. SUV = standardized uptake value. VhSl = high total tumor volume + low minimum SUV_{mean}. VhSh = high total tumor volume + high minimum SUVmean. VlSl = low total tumor volume + low minimum SUV_{mean}. VlSh = low total tumor volume + high minimum SUV_{mean}.

Supplementary



SUPPLEMENTAL FIGURE 1. HR (solid line) and corresponding 95% CI (dotted lines) at every possible cutoff of minimum SUV_{mean} and total tumor volume in regards to PFS and OS. Distribution of observations is shown along the x-axis. Vertical solid line is placed at median values. Horizontal dotted line at HR = 1. For total tumor volume and minimum SUV_{mean}, the plots show that the median is a reasonable cutoff. HR: hazard ratio. CI: confidence interval. PFS: progression-free survival. OS: overall survival. SUV: standardized uptake value.

SUPPLEMENTAL FIGURE 2. Kaplan-Meier plots of progression-free survival and overall survival for patients grouped by WHO classification.



SUPPLEMENTAL TABLE 1. Univariate Cox Regression Analyses for Progression-Free Survival and Overall Survival.

Progression-free survival						
	Small intestine			***Pancreas***		
Group	**n**	**HR (95% CI)**	***P***	***n***	**HR (95% CI)**	***P***
VhSl	20	Reference	-	11	Reference	-
VhSh	10	0.63 (0.28-1.42)	0.26	3	0.31 (0.08-1.19)	0.09
VlSl	11	1.2 (0.56-2.55)	0.63	0	NA	-
VlSh	25	0.47 (0.24-0.90)	0.02	11	0.22 (0.08-0.61)	<0.01
Overall survival						
	Small intestine			***Pancreas***		
Group	**n**	**HR (95% CI)**	***P***	***n***	**HR (95% CI)**	***P***
VhSl	20	Reference	-	11	Reference	-
VhSh	10	0.61 (0.23-1.60)	0.31	3	0.41 (0.09-1.89)	0.25
VlSl	11	0.48 (0.18-1.25)	0.13	0	NA	-
VlSh	25	0.29 (0.12-0.68)	<0.01	11	0.23 (0.08-0.69)	<0.01

Patients with high total tumor volume and low minimum SUV_{mean} are reference. HR = hazard ratio. CI = confidence interval. SUV = standardized uptake value. VhSl = high total tumor volume + low minimum SUV_{mean}. VhSh = high total tumor volume + high minimum SUVmean. VlSl = low total tumor volume + low minimum SUV_{mean}. VlSh = low total tumor volume + high minimum SUV_{mean}.

SUPPLEMENTAL TABLE 2. Univariate Cox regression analyses for progression-free survival and overall survival. WHO Grade 1 as reference. N=110. HR: hazard ratio. CI: confidence interval

Progression-free survival		
Group	**HR (95% CI)**	**p-value**
Grade 1 (n=27)	Reference	
Grade 2 (n=79)	1.05 (0.66-1.65)	0.84
Grade 3 (n=4)	4.88 (1.66-14.32)	<0.01
Overall survival		
Group	**HR (95% CI)**	**p-value**
Grade 1 (n=27)	Reference	
Grade 2 (n=79)	1.60 (0.87-2.96)	0.13
Grade 3 (n=4)	18.08 (5.42-60.26)	<0.001

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