Prognostic Utility of Total ^{68}Ga-DOTATATE-Avid Tumor Volume in Patients with Neuroendocrine Tumors

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Abstract

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Background & Aims—Survival times vary among patients with neuroendocrine tumors (NETs) —even among those with the same site, stage, and grade of primary tumor. This makes it difficult to select treatment for patients with unresectable NETs, because some patients can survive decades without treatment. ^{68}Gallium-DOTATATE positron emission tomography with computed tomography (^{68}Ga-DOTATATE PET/CT) is a sensitive imaging technique for detection of NETs. We investigated the prognostic accuracy of ^{68}Ga-DOTATATE PET/CT analysis of tumor volume in patients with NETs.

Methods—We performed a prospective study of 184 patients with NETs (128 [69.6%] with metastases and 11 patients [6.0%] with locally advanced disease) at the National Institutes of Health Clinical Center from 2013 through 2017. All patients underwent ^{68}Ga-DOTATATE PET/CT image analysis and total ^{68}Ga-DOTATATE-Avid tumor volume (^{68}Ga-DOTATATE TV) was determined. We also measured fasting serum chromogranin A, neuron-specific enolase, gastrin, glucagon, vasoactive intestinal peptide, pancreatic polypeptide, and 24-hour urinary 5-hydroxyindoleacetic acid levels in all patients. Disease progression was defined as a new lesion or a growth of a known lesion, during the interval between baseline ^{68}Ga-DOTATATE PET/CT scan and follow-up imaging (14.0±6.1 months; range 1–35 months). The primary outcomes were progression-free survival (PFS) and disease-specific mortality during a median follow-up time of 18 months (range 4–35 months).

Results—We found an inverse correlation between quartiles of ^{68}Ga-DOTATATE TV and PFS (*P*=.001) and disease-specific survival (*P*=.002). A ^{68}Ga-DOTATATE TV of 7.0 mL or more was associated with higher odds of disease progression (hazard ratio, 3.0; *P*=.04). A ^{68}Ga-DOTATATE TV of 35.8 mL or more was associated with increased risk of disease-specific death (hazard ratio, 10.6) in multivariable analysis (*P*=.01), as well as in subgroup analysis of patients with pancreatic NETs.

Conclusions—In a prospective study, we demonstrated the prognostic utility of ^{68}Ga-DOTATATE TV in a large cohort of patients with NETs, in terms of PFS and disease-specific mortality.

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies arising from neuroendocrine cells that are dispersed throughout the human body. About two-thirds of NETs originate from the gastrointestinal tract and pancreas, 25% from the bronchopulmonary tract, and the remaining are from other sites.[1] The incidence of NETs is increasing and is estimated to exceed 5 cases per 100,000 people per year.[2] Although most NETs have an indolent course, a subset of patients with NETs have aggressive disease, and a substantial number of patients with NETs present with distant metastases at initial diagnosis. [3–5]

Many treatment options have been developed over the last decade for patients with locally advanced and metastatic NETs. Such new treatments include medical therapy with

somatostatin analogs,[6,7] everolimus,[8,9] sunitinib,[10,11] liver-directed therapies,[12] and peptide receptor radionuclide therapy (PRRT).[13] However, the optimal timing of treatment interventions for NETs is unknown, as the disease course of patients with locally advanced and metastatic NETs is highly variable, even when patients have the same tumor stage and grade. Thus, new clinical prognostic tools are required in order to select the population of patients that are at risk of disease-progression and disease-specific mortality. Such prognostic tools could determine which patients with NETs would benefit from treatment intervention, the type and timing of treatment, and whether the treatment-associated side effects are justified in light of the estimated life expectancy and their impact on quality of life.

Positron emission tomography (PET)/computed tomography (CT) imaging has been shown to improve the management of patients with both solid and hematological malignancies. For example, in patients with non-small cell lung cancer preoperative ^{18}Fluoro-deoxy-glucose (^{18}FDG) PET/CT scanning reduced the number of thoracotomies,[14] and its use for surveillance of advanced head and neck cancer reduced the intervention rate.[15] In patients with Hodgkin's lymphoma, the use of ^{18}FDG-PET/CT might avert further radiotherapy in patients with early disease[16] and lead to reduced treatment toxicity among those with advanced disease.[17] The clinical utility of measuring total ligand-avid tumor volume (TV) based on PET/CT scanning has been evaluated in patients with cancer in small cohort and/or retrospective studies. For example, ^{18}FDG-PET/CT based volume measurements predicted shorter progression-free survival (PFS) in follicular lymphoma[18] and breast cancer,[19] and total ^{11}C-Methionine-avid volume predicted PFS in high-grade glioma.[20] Furthermore, ^{18}FDG-PET/CT TV in multiple myeloma[21], adrenocortical carcinoma[22] and non-small cell lung cancer[23] were associated with patient survival, as was ^{18}F-fluoroethyl-tyrosine (^{18}F-FET) PET/CT in patients with gliomas[24]. A large prospective study has shown that a high SUVmax (>3) derived from ^{18}F-FDG PET/CT was independently associated with shorter PFS in patients with NETs.[25] Furthermore, the combined use of ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT scans was found to be beneficial in the clinical management of patients with poorly differentiated NET.[26]

Radiolabeled somatostatin receptor (SSR)–binding molecules with PET/CT imaging are commonly used to stage patients with NETs.[27] This imaging approach is highly sensitive for detecting sites of NETs because these tumors express SSR. Among the new-generation radiolabeled high-affinity SSR ligands (DOTATATE, DOTATOC, DOTANOC) developed and evaluated in studies, ^{68}Ga-DOTATATE PET/CT imaging is one of the more sensitive and specific imaging modalities for detecting NETs.[28] To our knowledge, no study has utilized this quantitative imaging measurement approach in patients with NETs who had ^{68}Ga-DOTATATE PET/CT imaging to determine if it has any prognostic utility.

In this prospective study, we evaluated the prognostic utility of ^{68}Ga-DOTATATE TV as a marker for PFS and disease-specific mortality in a large cohort of patients with NETs. In addition, we performed multivariable analyses of other clinical and biochemical variables associated with PFS and disease-specific mortality.

METHODS

Study Population

Patients known to have NETs based on imaging (CT, magnetic resonance imaging [MRI], and ^{18}F-FDG PET) and biochemical evidence, and/or a pathologically confirmed NET, were enrolled in the study. This was a single center prospective study, conducted at the National Institutes of Health Clinical Center between the years 2013 and 2017 and focused on mostly patients with gastrointestinal and pancreatic NETs. The current analysis included only subjects with ^{68}Ga-DOTATATE-avid disease and who had yearly follow up in order to assess survival rates.

NETs were classified according to the primary tumor location based on anatomical imaging, ^{68}Ga-DOTATATE PET/CT localization, and/or pathological diagnosis. Primary tumor locations were subdivided into pancreatic NETs (PNETs) or small intestine NETs (SINETs), whereas subjects with NETs of gastric, duodenal, rectal, lung, or appendiceal subtypes were grouped as "other NET" due to their small numbers. Subjects with metastatic NETs, with pathological ^{68}Ga-DOTATATE uptake but no clear primary lesion, were defined as NET of unknown primary. Tumor grade was determined according to the 2010 World Health Organization (WHO) classification.[30] All patients underwent testing for fasting serum chromogranin A (CGA), neuron-specific enolase (NSE), gastrin, glucagon, vasoactive intestinal peptide (VIP), and pancreatic polypeptide (PP), as well as 24-hour urinary 5-hydroxyindoleacetic acid (5HIAA) levels.

The study was performed under an Investigational New Drug approval from the United States Food and Drug Administration, and was approved by the National Cancer Institute Institutional Review Board and the National Institutes of Health Radiation Safety Committee. Written informed consent was obtained from all study participants.

^{68}Ga-DOTATATE PET/CT Studies—For ^{68}Ga-DOTATATE PET/CT imaging, 185 MBq (5 mCi) of ^{68}Ga-DOTATATE was administered intravenously through a peripheral vein. After approximately 60 minutes, the patient was positioned supine in a PET/CT scanner, and images were obtained from mid thighs to the skull. A low-dose, non-contrast–enhanced CT was used for attenuation correction and anatomic localization. SUVmax was measured based on patient total body weight. Patients treated with long-acting octreotide were scanned before the next scheduled monthly dose, while those on short-acting octreotide discontinued treatment for 24 hours before imaging.

Quantification Analysis of ^{68}Ga-DOTATATE PET/CT Studies—Disease burden was assessed by quantifying ^{68}Ga-DOTATATE uptake using the MIM Vista workstation (version 6.5.9). A volume of interest (VOI) encompassing the entire body were drawn, and subsequently an SUVmax threshold–based approach[29] customized per patient was applied in order to include all ^{68}Ga-DOTATATE avid lesions (Figure 1). The software enables automatic generation of individual VOIs encircling each separate lesion. Per each scan, a well demarcated ^{68}Ga-DOTATATE-avid lesion was selected. The automatic demarcation by the software was compared with the lesion anatomic cross-sectional image, and the

SUVmax threshold was then set, so there will be a maximal overlap between the anatomic and functional measurements, with <5% qualitative difference between the images.

Discrete ^{68}Ga-DOTATATE avid lesions with clear delineation of the tumor were used for tumor volume calculations (Supplementary Figures 1 and 2). This involved visual inspection of the automated volume segmentation, to avoid incomplete segmentation of pathologic avidity (Supplementary figures 1C and 2C) and inclusion of background physiologic uptake (Supplementary figures 1D and 2D).

After setting the SUVmax threshold and encircling all lesions, areas of physiologic ^{68}Ga-DOTATATE uptake or uptake not related to disease were manually removed by an experienced nuclear medicine physician who was blinded to the clinical patient data, and then SUVmax and total volume of all ^{68}Ga-DOTATATE-avid lesions (^{68}Ga-DOTATATE TV) were automatically determined. The study cohort was grouped into four quartiles: Q1 [range, 0·1–2·9 ml], Q2 [3·0–9·9 ml], Q3 [9·9–43·1 ml], and Q4 [43·6–1136·6 ml]) by ^{68}Ga-DOTATATE TV and Q1 [8–32], Q2 [33–55], Q3 [56–90], and Q4 [92–307]) by SUVmax.

Disease progression analysis—Only patients with either locally advanced or metastatic disease (n=139) were included in the disease progression analysis. In addition to an annual ^{68}Ga-DOTATATE PET/CT scan, patients underwent annual anatomic imaging (CT/MRI) per protocol, and additional scans and/or ^{18}F-FDG PET/CT as clinically justified. Among patients included in the PFS analysis, all patients had in average more than one scan per year, with a mean rate of 3.1±1.1 (range 1.3–5.5). No difference in the number of scans performed during follow-up was found between patients in the different ^{68}Ga-DOTATATE TV quartiles (3.6±1.8, 3.8±1.5, 3.4±1.5, 3.7±2.3, in quartiles 1, 2, 3 and 4, respectively, p=0.8), or for any specific imaging modality among patients included in the analysis.

Disease progression was defined as a new lesion or a growth of a known lesion, during the interval between baseline ^{68}Ga-DOTATATE PET/CT scan and follow up imaging (14.0±6.0 months, range 1–35 months). Among 51 patients with disease progression during follow-up, 44 were defined as having disease progression based on ^{68}Ga-DOTATATE PET/CT showing new disease, four based on CT, two based on MRI, and one – based on ^{18}F-FDG PET/CT scan.

Statistical Analyses

Statistical calculations were performed using the SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). Results are expressed as mean ± standard deviation (SD) unless otherwise indicated. For group comparisons, the independent Student's t-test or one-way analysis of variance (ANOVA) was used to analyze differences in parametric variables, and the chi-square test was used to analyze differences in categorical variables. Non-parametric tests were used as appropriate. The Kaplan–Meier estimator with a log-rank (Mantel–Cox) test was used to estimate and compare PFS and disease-specific mortality rates by PET/CT indices and biochemical biomarkers levels. Multivariable analysis was used to assess the prognostic utility of ^{68}Ga-DOTATATE TV in terms of disease-specific mortality and PFS after controlling for confounding factors (Supplementary Tables 1 and 2). The joint effects of variables were analyzed by Cox proportional hazards models, using the enter method, to

estimate hazard ratios (HR) and 95% confidence intervals (CI) for PFS and disease-specific mortality during follow-up.

After validating the association between ^{68}Ga-DOTATATE TV and PFS and disease-specific mortality in our cohort, we aimed to generalize these findings. Thus, optimal cut-offs for predicting PFS and disease-specific mortality were defined using the receiver operating characteristic (ROC) curve. The discriminative performance of ^{68}Ga-DOTATATE TV was assessed by calculating the Harrell *c*-statistic, which corresponds to the area under the ROC curve. The P value for statistical significance was set at <0.05.

RESULTS

One hundred and eighty-four patients had ^{68}Ga-DOTATATE PET/CT imaging with a median follow-up time of 18 months (range of 4–35 months) and with a mean time from diagnosis of 5.3±6.0 years. The mean age of the study cohort was 55·3±14·2 years, and 95 (51·6%) were women. Ninety-nine subjects (53·8%) had primary PNETs, 57 (31·0%) had primary SINETs, and 13 patients (7·1%) had metastatic NETs with unknown primary tumors. Fifteen subjects had other NET subtypes: gastric (n=3), duodenal (n=7), rectal (n=1), appendiceal (n=1), large intestine (n=2), and bronchial (n=1) NETs. Metastatic disease was present in 128 subjects (69·6%) with 24 patients (13·0%) having only lymph node metastases and 84 subjects (65·6%) having liver metastases. Additional eleven patients (6·0%) had locally advanced disease. Eighty-six patients were treated medically following study enrollment: 47 received octreotide, 24 received lanreotide, 6 received everolimus, 7 received sunitinib and 2 patients were treated with systemic chemotherapy. In addition, 42 patients underwent surgical intervention following their inclusion, ten patients underwent PRRT and 4 patients had liver directed therapy. The clinical characteristics by ^{68}Ga-DOTATATE TV quartiles are summarized in Table 1 and Figure 2.

Eleven patients died of their disease during follow-up, with no significant difference in age (57·4±17·5 vs. 55·2±14·0 years, P=0·6) or gender (63·6% vs. 50·9% women, P=0·4). Among patients who died of their disease, 6 had PNETs, 4 had SINETs, and 1 had an unknown primary. As expected, patients who died of their disease had higher rates of metastatic disease (100% vs. 61·3%, P=0·01): liver (81·8% vs. 42·2%, P=0·01), lymph nodes (81·8% vs. 43·4%, P=0·01) and bone (45·5% vs. 15·6%, P=0·01). They also had higher WHO tumor grade (G2 or G3, 100% vs. 48%, P=0·001, Supplementary Figure 3), and higher plasma CGA (3,366±4,838 vs. 2,121±19,675, P=0·001) and NSE levels (20·6±11·5 vs. 9·7±3·5, P=0·001).

The optimal ^{68}Ga-DOTATATE TV cutoff points for PFS and disease-specific mortality were 7·0 mL (*c*-statistic 0·683, p<0.001) and 35·8 mL (*c*-statistic 0·844, p<0.001), respectively. These cut-offs points identified 78·9% of patients who developed disease progression, and 81·8% of patients died of their disease during the follow-up.

^{68}Ga-DOTATATE TV and progression-free survival

Patients with disease progression during follow-up (n=51) had higher rate of metastases to the liver (72·5% vs. 50·8%, P=0·02), and/or bones (35·3% vs. 11·1%, P=0·002), and received

more medical treatment (72·0% vs. 44·4%, P=0·003) and PRRT (18·0% vs. 1·6%, P=0·002) compared to patients with stable disease (n=88). ^{68}Ga-DOTATATE TV 7·0 ml was associated with higher risk for disease progression both on univariate (P=0·02, Table 2 and Figure 3A) and multivariable analyses (HR 3·0, 95% CI 1·1–8·7, P=0·04). In order to control for the effect of treatment on disease progression, we performed a subgroup analysis according to medical therapy during follow-up. A trend for lower PFS among patients with ^{68}Ga-DOTATATE TV 7 mL was found among patients with no treatment during follow-up (Log-rank test, p=0.05), with a similar trend among patients receiving medical treatment (p=0.086).

^{68}Ga-DOTATATE TV and disease-specific mortality

There was no significant difference in disease-specific mortality by mean SUVmax values (63·3±46·4 vs. 69·3±51·3, P=0·7). However, disease-specific mortality was significantly different by ^{68}Ga-DOTATATE TV (301·7±349·3 vs. 54·4±117·7, dead vs. alive, respectively, P<0·001). Moreover, survival analysis revealed a significant difference when compared by ^{68}Ga-DOTATATE TV quartiles, but not by SUVmax quartiles (Supplementary figures 5A and 5B).

On univariate analysis (Table 2), tumor WHO G3 grade, presence of liver, lymph node and/or bone metastases, elevated urinary 5HIAA (>8 mg/24h), and high ^{68}Ga-DOTATATE TV (35·8 mL) were associated with higher disease-specific mortality in patients with NETs (Figure 3B). On multivariable analysis, only high ^{68}Ga-DOTATATE TV 35·8 mL was associated with a higher disease-specific mortality (HR 10·6, 95% CI 1·6–68·9, P=0·014).

Subgroup Analysis

^{68}Ga-DOTATATE TV 35·8 mL was associated with a high disease-specific mortality rate in patients with PNETs (Log-Rank test, P=0·001, HR 16·4, 95% CI 1·9–140·2, P=0·01; Figure 3C), with a trend in patients with SINETs (HR 5·4, 95% CI 0·6–51·8, P=0·1, Figure 3D). High ^{68}Ga-DOTATATE TV was associated with disease-specific mortality even when excluding patients with no metastases both on univariate (HR = 8·5, 95% CI 1·8–39·4, P=0·006) and multivariable analyses (HR = 11·2, 95% CI 1·2–107·7, P=0·04).

We performed subgroup analysis in patients with PNETs, comparing the utility of tumor markers used mostly in PNETs. We did not find increased risk for DSM among patients with high plasma levels of gastrin (Log-rank test, p=0.99), glucagon (p=0.68), VIP (p=0.62) or pancreatic polypeptide (p=0.68).

DISCUSSION

In this prospective study, we assessed the prognostic utility of ^{68}Ga-DOTATATE PET/CT imaging indices in a large cohort of patients with NETs. ^{68}Ga-DOTATATE TV was significantly higher among subjects who had disease progression and among those who died of their disease. Survival analysis demonstrated a stepwise increase in cumulative risk for disease progression and for disease-specific mortality by increasing ^{68}Ga-DOTATATE TV quartiles. Cut-offs for ^{68}Ga-DOTATATE TV and PFS (7·0 mL) and disease-specific mortality (35·8 mL) were calculated, with high c-statistic (0·844) for disease specific

mortality and moderate (0·683) for PFS. In multivariable analysis, ^{68}Ga-DOTATATE TV was associated with lower PFS and higher disease-specific mortality. Furthermore, there was an inverse association between ^{68}Ga-DOTATATE TV levels and survival rates in patients with PNETs with a similar trend in patients with SINETs.

A number of retrospective studies have assessed radiolabeled SSR–binding ligands as prognostic markers for NETs. In these studies, a low SUVmax was reported to be associated with poor prognosis in patients with NETs.[31–33] In our cohort we did not find any association between SUVmax and the prognosis of patients with gastrointestinal and pancreatic NETs, but when utilizing SUV for setting the threshold for volumetric measurements, ^{68}Ga-DOTATATE TV was associated with prognosis. The fact that SUVmax only reflects the expression of SSR in the tumor tissue, whereas ^{68}Ga-DOTATATE TV utilizes both volumetric tumor measurements and SSR expression,[29] may explain this difference. In addition, although ^{68}Ga-DOTATATE detection of NET is high, ranging between 79–96% in different studies[28,34,35], we included only patients with ^{68}Ga-DOTATATE-avid NETs, possibly excluding patients harboring poorly-differentiated NET, with higher risk for disease-specific mortality.

The presence of NET liver metastases was associated with higher disease-specific mortality by univariate analysis as expected.[36–39] However, by multivariable analysis, presence of metastases was not associated with disease-specific mortality, whereas ^{68}Ga-DOTATATE TV was significantly associated, suggesting a more accurate assessment of tumor burden. Interestingly, although ^{68}Ga-DOTATATE SUVmax was reported as a potential prognostic marker in NET,[33] it was not associated with disease-specific mortality in the current study. This may be due to SUVmax measurement being representative of a single region of the tumor and thus not representative of the total tumor burden. Moreover, the known heterogeneity in SSR-based ligand uptake, even within the same individual's scan, might further limit its utility.[40] Finally, WHO tumor grade is an important prognostic factor in NETs,[38] as was also found in the current study. However, in practice data on tumor grade is often incomplete as not all patients have resection of their tumor or biopsy of all tumor sites and analysis of the tumor grade, and patients may have different tumor grade depending on the tumors site[41].

The incidence of PNETs in the general population accounts for 7–10% of all gastrointestinal and pancreatic NETs,[2,42] whereas in our cohort PNETs accounted for the majority of the NETs (53.4%). The high proportion of PNETs in our study may be due to the focus of the clinical protocol on gastrointestinal and pancreatic NETs and the referral of many patients with PNETs to our center.

In our analysis, ^{68}Ga-DOTATATE TV was an independent prognostic factor for disease-specific mortality in patients with PNETs with a trend in patients with SINETs. This finding is expected, as patients with PNETs have a worse survival as compared to patients with other NET subtypes.[38,43] Furthermore, several studies have observed lower survival rates among patients with foregut tumors[39] and among patients with liver metastases from PNETs vs. other gastrointestinal NETs.[38]

The ^{68}Ga-DOTATATE TV optimal cut-off value for disease-specific mortality had high accuracy, thus suggesting it could be useful for selecting patients for closer follow-up and early intervention. Also, the c-statistic calculated for PFS identified most patients at risk for progression and thus could help guide the need for treatment before disease progression occurs.

Our study findings have several important clinical implications in patients with NETs. First, analysis of ^{68}Ga-DOTATATE TV could help identify which patients are likely to progress or die of their disease. Second, measurement of ^{68}Ga-DOTATATE TV can be used to identify patients who should have treatment intervention because of a higher-risk of disease progression or disease-specific mortality. This is important because most newly developed therapies, when evaluated in clinical trials in patients with unresectable NETs, have used disease-progression on anatomic imaging (within 6–18 months) as a criterion for treatment intervention and as the primary endpoint to evaluate treatment efficacy. Therefore, the application of ^{68}Ga-DOTATATE TV measurement could more precisely identify those patients likely to have progressive disease early or die of their disease. Third, given the ever-expanding treatment options available to patients with unresectable NETs—including active surveillance, as some patients could have indolent metastatic disease for decades that does not require intervention—the use of ^{68}Ga-DOTATATE TV measurement can stratify patients into low- and high-risk groups for which treatment intervention should be considered. Such an approach could represent the potential of ^{68}Ga-DOTATATE TV as a method to implement precision medicine in patients with NETs. Our findings are likely to be generalizable and can be applied by other medical centers as ^{68}Ga-DOTATATE was recently approved by the United States Food and Drug Administration for NET imaging.

Our study limitations include the heterogenous study cohort, which consisted of patients with various primary NET locations, and of different disease stages and grades. In addition, our results need to be validated in future studies.

In conclusion, ^{68}Ga-DOTATATE TV is independently associated with PFS and disease-specific mortality in patients with NETs, with higher TV values associated with a lower PFS and higher disease-specific mortality. This new data could be used to determine the need for treatment intervention, frequency of follow up and ultimately lead to precision medicine in patients with NET.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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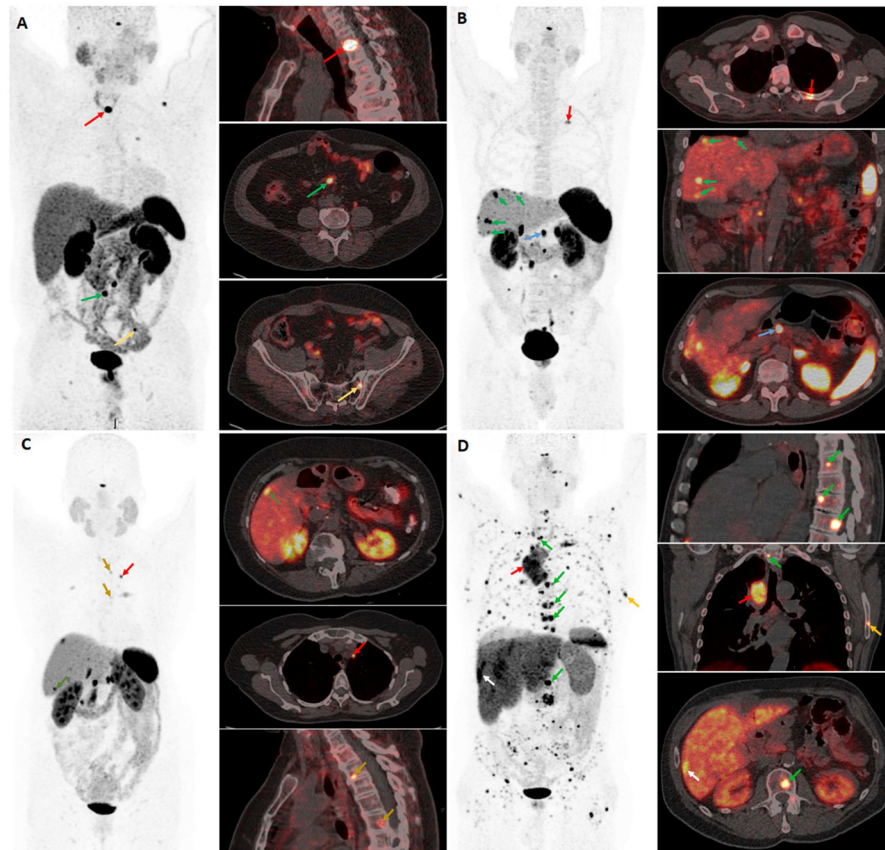
Figure 1.
^{68}Ga-DOTATATE positron-emission tomography (PET)/computerized tomography (CT) of patients with metastatic neuroendocrine tumors (NETs) from each total ^{68}Ga-DOTATATE-avid volume (^{68}Ga-DOTATATE TV) quartile: (A) small-intestine NET (SINET) with metastases to the spine, mesenteric lymph-node and sacrum (red, green and yellow arrows, respectively) and ^{68}Ga-DOTATATE TV of 2·2 mL (first quartile range); (B) pancreatic NET (PNET, blue arrow) with metastases to the left 4th rib (red arrow), liver (green arrows), retroperitoneal and mesenteric lymph nodes (^{68}Ga-DOTATATE TV 6·2 mL, second quartile range); (C) PNET metastases to the liver, mediastinum, spine (green, red and yellow arrows respectively) and pleura (^{68}Ga-DOTATATE TV of 10·8 mL, third quartile range); and (D) PNET with metastases to the spine (green arrows), left scapula (yellow arrow), mediastinum (red arrow) and liver (white arrows) with a ^{68}Ga-DOTATATE TV of 127·8 mL (forth quartile).
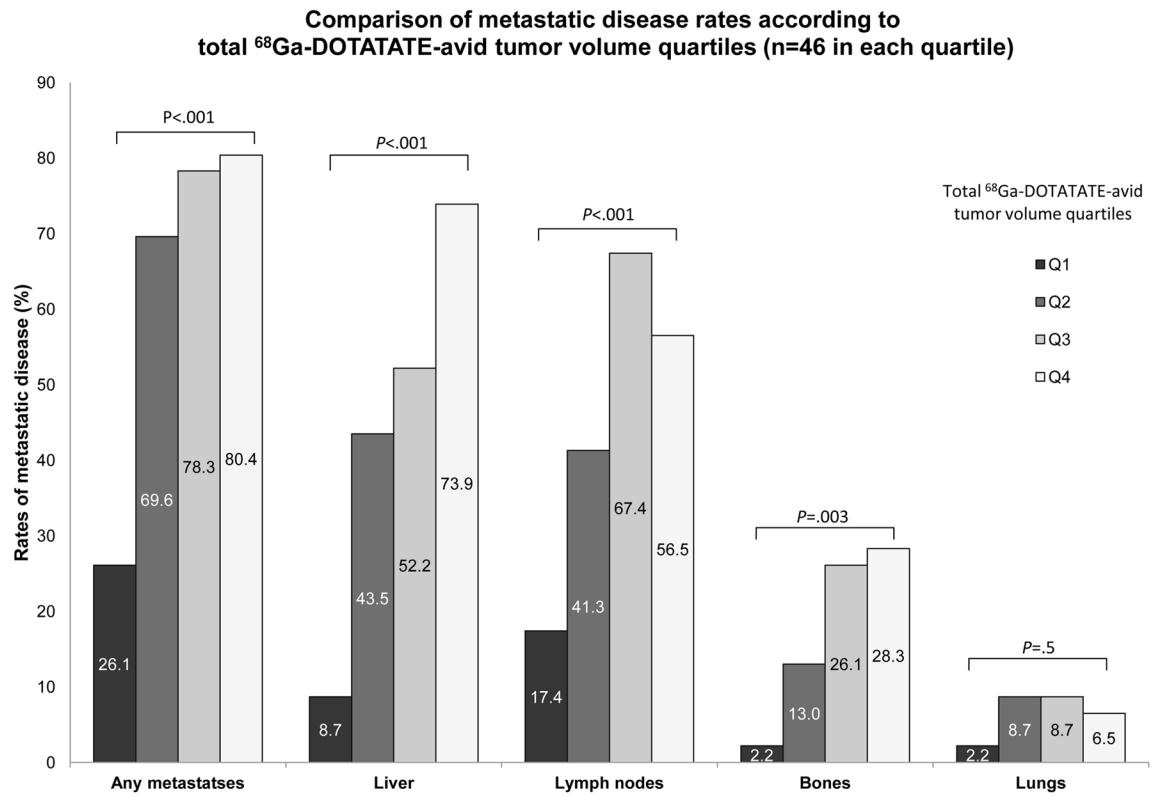
Figure 2.

Comparison of metastatic disease rates according to total ^{68}Ga-DOTATATE-avid tumor volume quartiles (n=46 in each quartile)
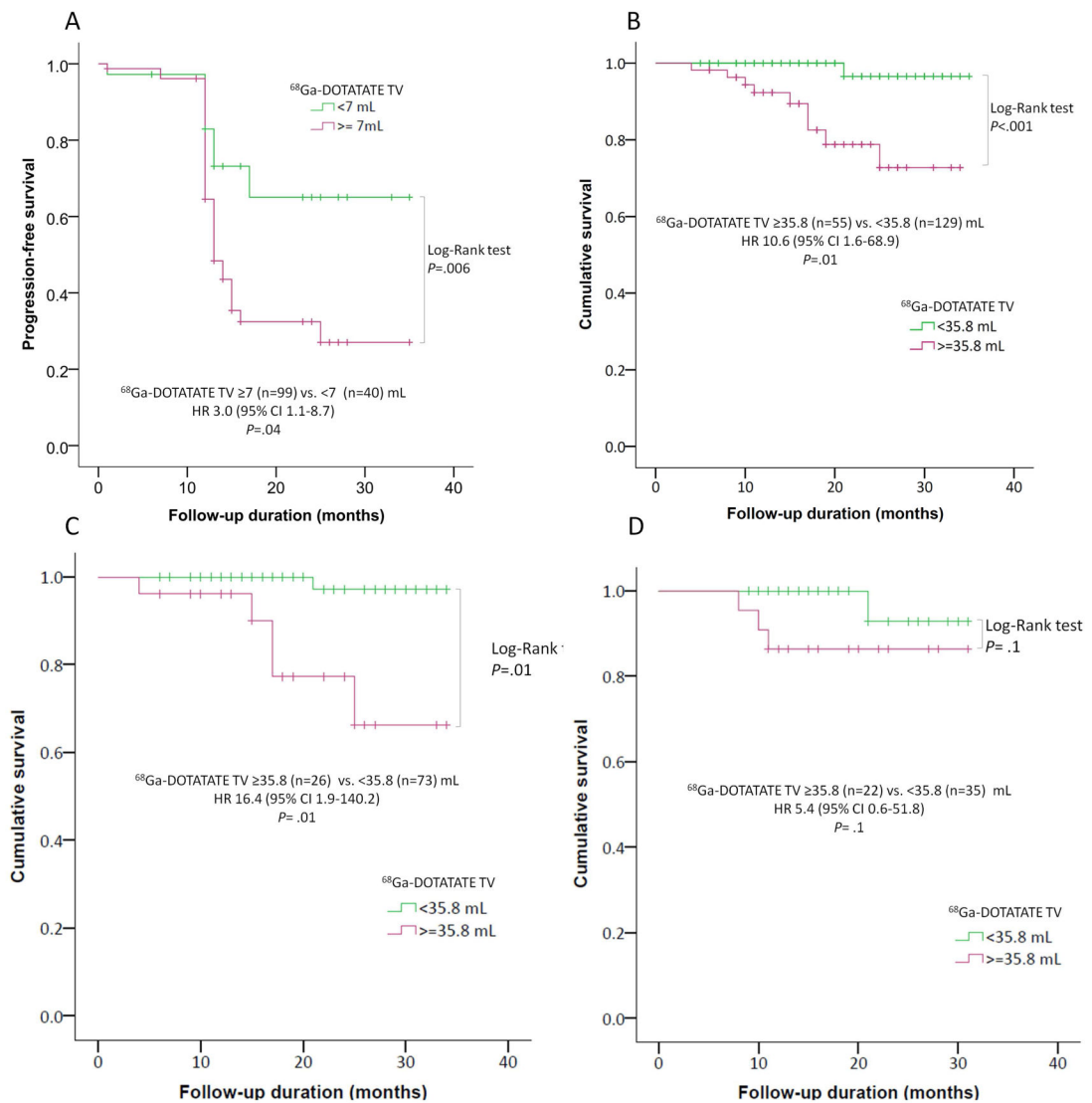
Figure 3.
Survival analysis in patients with neuroendocrine tumors. Progression-free survival by ^{68}Ga-DOTATATE-avid tumor volume (n=139, A). Kaplan-Meier survival analysis by ^{68}Ga-DOTATATE-avid tumor volume in the entire cohort (n=184, B), and among patients with pancreatic (n=99, C) and small-intestine neuroendocrine tumors (n=57, D).

HR, hazard ratio; CI, confidence interval

Table 1

Study cohort clinical characteristics by total ^{68}Ga-DOTATATE avid tumor volume quartiles

|	Q1 n=46	Q2 n=46	Q3 n=46	Q4 n=46	P value
Age (years)	52·7±16·1	54·7±14·6	56·9±13·3	56·8±12·4	NS
Female n (%)	23 (50·0%)	29 (63·0%)	24(52·2%)	19 (41·3%)	NS
Disease progression during follow-up n(%)	3 (8·8%)	18 (53·9%)	18 (47·4%)	18 (54·5%)	0·001
Died of disease during Follow-up n (%)	0	1 (2·2%)	2 (4·3%)	8 (17·4%)	0·002
Time since diagnosis (months)	3·2±3·7	6·2±6·4	7·9±7·7	3·8±4·5	0·001
F/u duration (months)	18·4±8·4	21·4±8·0	19·7±7·8	17·0±7·4	0·05
NET subtype					NS
PNET	24 (52·2%)	27 (58·7%)	23 (50·0%)	25 (54·3%)	
SINET	11 (23·9%)	12 (26·1%)	17 (37·0%)	17 (37·0%)	
Unknown primary	4 (8·7%)	5 (10·9%)	1 (2·2%)	3 (6·5%)	
Other	7 (15·2%)	2 (4·3%)	5 (10·9%)	1 (2·2%)	
SUVmax	32·7±22·3	70·2±52·4	83·4±46·9	90·3±55·5	<0·001
^{68}Ga-DOTATATE TV (mL)	1·2±0·8	6·4±2·0	24·1±10·6	245·1±227·1	<0·001
Treatment after inclusion					
Medical n (%)	14 (31·1%)	23 (50·0%)	18 (39·1%)	31 (68·9%)	0·002
Surgical n (%)	11 (24·4%)	10 (21·7%)	12 (26·1%)	9 (20·0)	NS
PRRT n(%)	0	3 (6·5%)	2 (4·3%)	5 (11·1%)	NS
LDT n(%)	0	2 (4·3%)	0	2 (4·3%)	NS
WHO 2010 grading					NS
G1	11 (64·7%)	6 (40·0%)	11 (45·8%)	11 (44·0%)	
G2	5 (29·4%)	9 (60·0%)	13 (54·2%)	11 (44·0%)	
G3	1 (5·9%)	0	0	3 (12·0%)	
Disease stage n (%) *					<0·001
I	21 (45·7%)	10 (21·7%)	3 (6·5%)	0	
II	7 (15·2%)	1 (2·2%)	3 (6·5%)	1 (2·2%)	
III	10 (21·7%)	10 (21·7%)	9 (19·6%)	5 (10·9%)	
IV	8 (17·4%)	25 (54·3%)	31 (67·4%)	40 (87·0%)	
Plasma CGA (ng/mL)	213±374	627±1242	693±1353	7220±37446	NS

	Q1 n=46	Q2 n=46	Q3 n=46	Q4 n=46	P value
Urinary 5HIAA (mg/24h)	4·8±1·8	5·7±3·7	7·6±5·3	30·6±47·0	<0·001
Plasma NSE (ng/mL)	9·4±3·8	28·6±59·4	10·8±7·4	14·3±10·9	NS
Plasma gastrin (pg/mL)	81±126	125±241	461±1398	159±454	NS
Plasma glucagon (pg/mL)	37·9±20·4	42·2±36·9	40·4±33·3	55·8±73·1	NS
Plasma PP (pg/mL)	147±84	240±293	198±248	427±995	NS
Plasma VIP (pg/mL)	33·3±13·3	37·9±15·9	36·8±12·8	47·7±53·0	NS

NS, non-significant; f/u, follow-up; NET, neuroendocrine tumor; PNET, pancreatic neuroendocrine tumor; SINET, small intestine neuroendocrine tumor; SUVmax, maximal standardized uptake values in 68Ga-DOTATATE PET/CT; 68Ga-DOTATATE TV, total 68Ga-DOTATATE-avid tumor volume; SSA, somatostatin analogs; LDT, liver-directed therapy; WHO, World Health Organization; CGA, chromogranin A; 5HIAA, 5-hydroxyindoleacetic acid; NSE, neuron-specific enolase; PP, pancreatic polypeptide; VIP, vasoactive intestinal peptide

Continuous variables are presented as mean±standard deviation

*
Tumor staging was determined according to the American Joint Committee on Cancer, 8th edition.

Table 2

Results of univariate analysis for progression-free survival and disease-specific mortality in patients with neuroendocrine tumors

Variable	Progression-free survival			Disease-specific mortality		
	HR	95% CI	P value	HR	95% CI	P value
Female	1·1	0·6 – 2·0	0·7	1·7	0·5 – 5·8	0·4
PNET vs. other subtypes	0·7	0·4 – 1·2	0·2	0·9	0·3 – 3·1	0·9
WHO 2010 grade G3 vs. G1/G2	1·2	0·2 – 8·9	0·8	66·5	6·0 – 743·0	0·001
Presence vs. absence of metastases						
Liver	2·0	1·1 – 3·7	0·03	6·3	1·4 – 29·4	0·02
Lymph nodes	1·5	0·8 – 2·8	0·2	5·4	1·2 – 25·0	0·03
Bone	2·7	1·5 – 4·8	0·001	4·9	1·5 – 16·1	0·009
Lung	0·6	0·2 – 1·9	0·4	1·3	0·2 – 10·5	0·8
Hereditary vs. sporadic	0·4	0·2 – 0·9	0·02	0·3	0·1 – 1·4	0·1
Functional vs. non-functional tumor	0·6	0·4 – 1·1	0·1	0·9	0·3 – 2·9	0·8
Treatment after inclusion						
Surgery	1·5	0·8 – 2·8	0·3	0·4	0·04 – 2·8	0·3
Medical	2·4	1·3 – 4·5	0·006	0·9	0·2 – 3·1	0·8
PRRT/LDT	2·2	1·1 – 4·4	0·02	2·3	0·5 – 10·8	0·3
SUVmax 55·9[+]	1·0	0·6 – 1·8	0·9	0·6	0·2 – 1·9	0·4
Total ^{68}Ga-DOTATATE volume 7·0 ml	2·4	1·2 – 4·9	0·02	NA[*]	NA	NA
Total ^{68}Ga-DOTATATE volume 35·8 ml	1·4	0·8 – 2·5	0·2	12·5	2·7 – 57·7	0·001
Biochemical biomarkers						
Elevated plasma NSE (>15 ng/mL)	2·2	1·02 – 4·7	0·04	3·6	0·6 – 21·0	0·1
Elevated plasma CGA (>73 ng/mL)	1·4	0·8 – 2·8	0·3	NA[*]	NA	NA
Elevated urinary 5HIAA (>8 mg/24h)	1·7	1·0 – 3·0	0·07	5·2	1·5 – 18·8	0·01

HR, hazard ratio; CI, confidence interval; PNET, pancreatic neuroendocrine tumors; WHO, World Health Organization; SSA, somatostatin analogues; PRRT, peptide receptor radionuclide therapy; LDT, liver-directed therapy; SUVmax, maximum standardized uptake value; NA, not applicable.

[+] Median values,

[*] Cox regression analysis was not performed as one of the groups had no events.