Downloaded from jnm.snmjournals.org by on March 14, 2017. For personal use only.

Prognostic Value of ^{68}Ga-DOTANOC PET/CT SUV_{max} in Patients with Neuroendocrine Tumors of the Pancreas

Valentina Ambrosini[1], Davide Campana[2], Giulia Polverari[1], Chiara Peterle[1], Stefania Diodato[1], Claudio Ricci[2], Vincenzo Allegri[1], Riccardo Casadei[2], Paola Tomassetti[2], and Stefano Fanti[1]

[1]*Nuclear Medicine, Department of Experimental Diagnostic and Specialized Medicine, University of Bologna and S. Orsola–Malpighi Hospital, Bologna, Italy; and* [2]*Department of Medical and Surgical Sciences, S. Orsola–Malpighi University Hospital, Bologna, Italy*

This study was performed to investigate the role of ^{68}Ga-DOTANOC SUV_{max} as a potential prognostic factor in patients with pancreatic neuroendocrine tumor (pNET). **Methods:** Among the patients who underwent ^{68}Ga-DOTANOC PET/CT, we retrospectively collected the data of those who had G1 or G2 pNET (2010 World Health Organization classification), presented with disease on PET/CT and CT, and had at least 6 mo of follow-up. Patients with multiple endocrine neoplasia were excluded. **Results:** Overall, 43 patients were included. No significant differences in SUV_{max} were observed with respect to sex, tumor syndrome, stage, World Health Organization classification, or Ki-67. During follow-up (median, 20 mo), 11 patients (35.6%; median, 33 mo; interquartile range, 20–48 mo) had stable disease and 32 (74.4%; median, 19 mo; interquartile range, 14–26 mo) had progressive disease. SUV_{max} at 24 mo of follow-up was significantly higher ($P = 0.022$) in patients with stable disease than in patients with progressive disease. The best SUV_{max} cutoff ranged from 37.8 to 38.0. The major risk factors for progression included an SUV_{max} of no more than 37.8 (hazard ratio, 3.09; $P = 0.003$), a Ki-67 of more than 5% (hazard ratio, 2.89; $P = 0.009$), and medical therapy alone (hazard ratio, 2.36; $P = 0.018$). Advanced stage (IV) ($P = 0.026$), an SUV_{max} of less than 37.8 ($P = 0.043$), and medical therapy alone ($P = 0.015$) were also confirmed at multivariate analysis. Median progression-free survival was 23 mo. Significant differences in progression-free survival were observed in relationship to Ki-67 (median, 45 mo for Ki-67 $\leq$ 5% and 20 mo for Ki-67 $>$ 5%; $P = 0.005$), SUV_{max} ($<$37.8 vs. $>$38.0: 16.0 vs. 27.0 mo; $P = 0.002$), and type of therapy (medical vs. peptide receptor radionuclide therapy: 16.0 vs. 26.0 mo; $P = 0.014$). **Conclusion:** ^{68}Ga-DOTANOC SUV_{max} is a relevant prognostic factor in patients with G1 and G2 pNET, and its routine use will improve disease characterization and management in these patients, who may present with atypical cases showing heterogeneous clinical behavior.

Key Words: ^{68}Ga-DOTA-NOC; PET/CT; SUV_{max}; NET; pancreas

J Nucl Med 2015; 56:1843–1848
DOI: 10.2967/jnumed.115.162719

Pancreatic neuroendocrine neoplasms (pNETs) are considered rare, with a wide spectrum of clinical presentation. Their real incidence is quite controversial: although they are found in about 1% of autopsies, their clinical incidence is reported to be only about 0.5–1/100,000 (*1,2*). Although pNETs are characterized by an overall better prognosis than other forms of solid tumor, patient outcome can vary greatly depending on tumor grade (*3*) and disease extent (*4*). However, the improved diagnostic and therapeutic management of these patients has led to an increase in prevalence of the disease, and in turn, atypically presenting cases showing heterogeneous clinical behavior have increased, either at diagnosis or during the course of the disease. Therefore, the possibility of identifying prognostic parameters that may help clinicians stratify patients into different risk groups is extremely relevant.

The diagnostic flowchart for pNETs currently includes several imaging modalities, both morphologic (sonography, CT, MRI) and functional (somatostatin receptor scintigraphy, PET/CT with ^{68}Ga-DOTA-peptides) (*5–7*). In the past 5 y, PET/CT with ^{68}Ga-DOTA-peptides has been increasingly used for its high accuracy in detecting lesions (at both primary and metastatic sites), safety, contained costs (*5–7*), and ability to select patients for whom peptide receptor radionuclide therapy (PRRT) is appropriate.

Once the tumor is detected, the possibility of identifying accurate prognostic factors for disease progression is crucial to the management of these patients. Studies have investigated the role of grading, staging, functioning status, and somatostatin receptor density as potential prognostic factors in pNETs (*8*). Two studies indicated that SUV_{max} measured in the lesion with the highest ^{68}Ga-DOTANOC uptake was a prognostic parameter in heterogeneous populations of neuroendocrine tumors with different primary sites (including gastroenteropancreatic and lung tumors) (*9,10*).

However, since pNETs may present a clinical course different from that of NETs with other primary sites (*8,11*), the aim of the present study was to investigate whether SUV_{max} measured at ^{68}Ga-DOTANOC PET/CT may be used as a prognostic factor in NET patients with a pancreatic primary.

MATERIALS AND METHODS

Among the patients who underwent ^{68}Ga-DOTANOC PET/CT at our PET center from September 2006 to October 2014, we retrospectively collected the data of those with pathologically proven G1 or G2 pNET (2010 World Health Organization [WHO] classification) (*3*). The additional two inclusion criteria were the presence of disease at both ^{68}Ga-DOTANOC PET/CT and CT (performed within a month of each other) and at least 6 mo of clinical follow-up.

Patients with multiple endocrine neoplasia syndrome type 1, a condition well known to present with clinical behavior different from that of other gastroenteropancreatic NETs, were excluded from the analysis.

All patients underwent physical examination, and their clinical history was taken with the aim of investigating the putative clinical

Received Jun. 25, 2015; revision accepted Sep. 14, 2015.
For correspondence or reprints contact: Valentina Ambrosini, Nuclear Medicine, Pad 30, Azienda Ospedaliero Universitaria di Bologna, Policlinico S. Orsola-Malpighi, Via Massarenti 9, 40138 Bologna, Italy.
E-mail: valentina.ambrosini@unibo.it
Published online Sep. 24, 2015.
COPYRIGHT © 2015 by the Society of Nuclear Medicine and Molecular Imaging, Inc.

Downloaded from jnm.snmjournals.org by on March 14, 2017. For personal use only.

features of the functioning tumors. Laboratory and radiologic examinations were performed to evaluate the location of the tumor and to stage the disease. According to recent literature on pNETs, patients were divided into two groups according to a Ki-67 cutoff of 5% (*8,12,13*).

The presence of clinical symptoms associated with an increase in serum peptide levels was used to identify patients with functioning tumors.

Clinical follow-up was performed at the internal medicine outpatient service dedicated to pNET patients and included a CT scan every 3 mo during the first year and every 6 mo afterward.

Treatment after PET/CT with everolimus (10 mg daily of Afinitor [Novartis]), cold somatostatin analogs alone every 28 d (30 mg of octreotide acetate [Sandostatin LAR; Novartis] or 120 mg of lanreotide acetate [Somatuline Autogel; Ipsen]), or cold somatostatin analogs in association with PRRT was recorded.

All patients gave written informed consent to participate in the study. The study protocol was approved by the local Ethical Committee of the S. Orsola–Malpighi Hospital and was performed according to the Helsinki Declaration for human studies.

PET/CT with ^{68}Ga-DOTANOC was performed following current international guidelines (intravenous injection of 120–185 MBq followed by an uptake time of 60 min [range, 45–90 min], without specific examination preparation) (*14*). ^{68}Ga-DOTANOC was synthesized by the Radiopharmacy of the Nuclear Medicine Unit of S. Orsola–Malpighi Hospital. ^{68}Ga was eluted from a ^{68}Ge/^{68}Ga generator, and DOTANOC was labeled with ^{68}Ga following the procedure described by Zhernosekov et al. (*15*). ^{68}Ga-DOTANOC PET scans were obtained using a dedicated PET/CT scanner (Discovery LS; GE Healthcare). PET emission images were recorded for 4 min per bed position; CT images were used for nonuniform attenuation correction (acquisition parameters, 140 kV, 90 mA, 0.8-s tube rotation, 5-mm thickness). All images were corrected for scatter, randoms, dead time, and decay. Images were reconstructed with a 2-dimensional ordered-subset expectation maximization iterative algorithm (2 iterations, 28 subsets).

PET/CT images were acquired from the skull base to the middle of the thigh. PET/CT results were evaluated by 2 skilled nuclear medicine specialists unaware of the results of the other imaging modalities, and the definitive report was reached by consensus. Any localization with an intensity greater than background that could not be explained by physiologic activity (pituitary gland, spleen, liver, adrenals, kidneys, or urinary bladder) was considered to indicate somatostatin receptor expression.

SUV_{max} was calculated by measuring the maximal concentration of the labeled tracer in the region of interest corrected for body weight and injected dose (SUV_{max} = maximum activity concentration/[injected dose/body weight]) (*16*). For each PET scan, SUV_{max} was measured by choosing the region of interest in the lesion with the highest tracer uptake. For large tumors, the region of interest was moved over several sites within the mass to ensure that the true SUV_{max} was obtained.

All data were collected, and a computerized data sheet was created. Data on demographic, clinical, and pathologic features were retrospectively analyzed. The tumors were classified according to the 2010 WHO classification (*3*), and the novel TNM classification/G grading system (*4*). The Ki-67 proliferation index was expressed as the percentage of Ki-67–positive cells in 2,000 tumor cells in the most highly immunostaining areas using the MIB1 antibody (DBA). The tumors were measured and scored according to RECIST (*17*).

Median values and the respective interquartile range (IQR, 25th–75th percentile) were used to describe the data. Groups were compared using the Pearson χ^2 test (the Fisher exact test was used when necessary) or the Mann–Whitney *U* test for continuous variables. The area under the receiver-operating-characteristic curve was evaluated to determine the accuracy of SUV_{max} at diagnosis in predicting disease progression. The best prognostic cutoff was estimated by a maximum-likelihood-ratio method.

Progression-free survival (PFS) was defined as the interval between ^{68}Ga-DOTANOC PET/CT and the time of disease progression. PFS was measured using the Kaplan–Meier method, and the results were compared using the log-rank test. The predictive risk factors for progressive disease were analyzed by univariate and multivariate analysis using the Cox proportional-hazards method. Risk factors were expressed as hazard ratios and 95% confidence intervals. The multivariate model was constructed using the forward-stepwise method after all variables had been included. All analyses performed for risk factors are listed in the tables.

The *P* value was considered significant when less than 0.05. Statistical analysis was performed using dedicated software (SPSS, version 19.0; IBM).

To evaluate the potential role of SUV_{max} on prognosis, we divided the patients on the basis of disease status (progressive disease vs. stable disease) at an arbitrarily selected follow-up time point. A 24-mo time point was chosen for three reasons: about half our patients underwent PRRT; PFS in patients treated with PRRT was 23 mo in the pancreatic subgroup of a recent multicenter trial (*18*); and our follow-up schedule included a radiologic evaluation at 24 mo (CT every 3 mo during the first year and every 6 mo afterward).

RESULTS

Patient Characteristics

Overall, 43 patients (22 men and 21 women; median age, 58 y; IQR, 48–64 y) with pNETs were included in the study. Eight patients (18.6%) had functioning tumors: 5 gastrinomas, 1 insulinoma, 1 VIPoma (vasoactive intestinal peptide–secreting tumor), and 1 ACTHoma (adrenocorticotropin hormone–secreting tumor). In the remaining 35 patients (81.4%), the tumor was nonfunctioning. According to the 2010 WHO classification, 14 patients (32.3%) had a G1 pNET and 29 (67.7%) a G2 pNET.

The median Ki-67 index was 6.1% (IQR, 2.0%–8.9%); 22 of 43 patients (51.2%) had a Ki-67 of 5% or less, and 21 of 43 patients (48.8%) had a Ki-67 of more than 5%. According to the TNM classification, 7 patients (16.3%) had stage IIIB disease and 36 (83.7%) stage IV.

The characteristics of all 43 patients are listed in Table 1.

^{68}Ga-DOTANOC SUV_{max}

Data on median SUV_{max} and the respective IQRs (25th–75th percentiles) among the different groups of patients are reported in Table 1. There were no significant differences with respect to sex, presence of tumor syndrome, stage, and 2010 WHO classification.

Follow-up

All patients were evaluated for a median of 20 mo (IQR, 15–33 mo). Twenty of the 43 patients (46.5%) were treated with medical therapy: 13 with long-acting somatostatin analogs alone (Sandostatin LAR [30 mg] every 28 d or Somatuline Autogel [120 mg] every 28 d), 2 with long-acting somatostatin analogs plus everolimus (Afinitor [10 mg] every day), and 5 with everolimus alone. Twenty-three (53.5%) had combined treatment with both long-acting somatostatin analogs and PRRT.

During follow-up, 11 patients (35.6%; median, 33 mo; IQR, 20–48 mo) had stable disease and 32 (74.4%; median, 19 mo; IQR, 14–26 mo) had disease progression.

To evaluate the potential role of SUV_{max} on prognosis, we divided the patients on the basis of disease status (progressive vs. stable) at 24 mo of follow-up. As reported in Table 1, SUV_{max} was significantly

Downloaded from jnm.snmjournals.org by on March 14, 2017. For personal use only.

TABLE 1
SUV_{max} Median and IQR (25th–75th Percentiles) Among Different Groups of Patients

Patient characteristic	No. of patients	SUV_{max} Median	SUV_{max} IQR	*P*
Sex				
Male	22	45.9	36.3–58.2	0.875
Female	21	37.8	35.7–69.3	
Syndrome				
Yes	8	33.9	19.8–95.6	1.000
No	35	45.5	38.6–57.4	
Stage				
IIIB	7	34.3	25.2–62.2	0.687
IV	36	48.9	39.9–62.1	
2010 WHO classification				
NET G1	14	57.7	42.4–79.3	0.092
NET G2	29	36.2	33.2–55.7	
Ki-67				
≤5%	22	53.3	42.5–68.6	0.132
>5%	21	36.0	29.1–58.5	
Follow-up at 24 mo				
Stable disease	18	49.8	44.9–78.8	0.022
Progressive disease	20	33.4	26.1–52.4	

higher ($P = 0.022$) in patients with stable disease (Fig. 1) (18 patients; median, 49.8; IQR, 44.9–78.8) than in patients with progressive disease (20 patients; median, 33.4; IQR, 26.1–52.4; Fig. 2). Five patients were not included in the analyses because they had stable disease and less than 24 mo of follow-up.

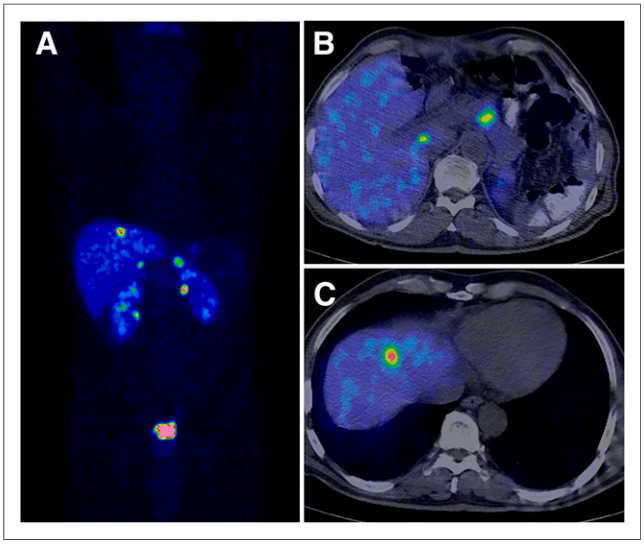


FIGURE 1. ^{68}Ga-DOTANOC PET/CT maximum-intensity-projection (A) and transaxial images (B and C) of patient with G2 pNET (A and B) and liver metastasis (A and C). Measured SUV_{max} was 56. Patient had stable disease at follow-up.

The receiver-operating-characteristic curve of SUV_{max} was quite accurate in predicting patients who had progressive disease after 24 mo of follow-up (area under the curve ± SE, 0.715 ± 0.084; $P = 0.023$), and the best cutoff ranged from 37.8 to 38.0. The sensitivity and specificity obtained using the best cutoff were 72.2% and 70.0%, respectively.

Predictors for Tumor Progression

The variables found by univariate analysis to be risk factors for tumor progression are summarized in Table 2. Risk factors for tumor progression were an SUV_{max} of no more than 37.8 (HR, 3.09; $P = 0.003$), medical therapy alone (HR, 2.36; $P = 0.0148$), and a Ki-67 of more than 5% (HR, 2.89; $P = 0.009$). The variables found by multivariate analysis to be risk factors for tumor progression were a Ki-67 of more than 5% (HR, 3.24), stage IV (HR, 3.31), medical therapy alone (HR, 2.70), and an SUV_{max} of no more than 37.8 (HR, 2.37).

PFS

Median PFS was 23 mo (Fig. 3). Significant differences in PFS were observed in relationship to Ki-67 (median, 45 mo for Ki-67 ≤ 5% and 20 mo for Ki-67 > 5%; $P = 0.005$; Fig. 3A), SUV_{max} (<37.8 vs. >38.0: 16.0 vs. 27.0 mo; $P = 0.002$; Fig. 3B), and type of therapy (medical vs. PRRT: 16.0 vs. 26.0 mo; $P = 0.014$; Fig. 3C). No significant difference was found according to the 2010 WHO classification (NET G1 vs. NET G2: 30.0 vs. 23.0 mo; $P = 0.097$), disease stage (IIIB vs. IV: 46.0 vs. 20.0 mo; $P = 0.195$), or functioning status (functioning vs. nonfunctioning: 26.0 vs. 20.0 mo; $P = 0.191$).

DISCUSSION

In the past decade, both optimization of diagnostic algorithms (especially after the advent of ^{68}Ga-DOTA-peptide PET/CT) and use of novel therapeutic strategies (mainly PRRT and biologic target drugs) determined an increase in NET prevalence. Correspondingly, clinicians witnessed an increment of atypical cases that did not fit the classic paradigm that NETs are always indolent. Therefore, identification of easily assessable prognostic parameters is crucial for an accurate evaluation both at baseline and during the course of the disease, since an initially indolent tumor may become aggressive. SUV_{max} is an optimal parameter because it can easily be assessed in a relatively noninvasive way. Moreover, being a whole-body procedure, PET/CT provides a functional evaluation of the whole tumor burden that is not feasible with the commonly used Ki-67.

There is much literature on ^{68}Ga-DOTA-peptide PET/CT focused on assessing diagnostic accuracy (*5,7*) and comparing the performance of one tracer with another (*19,20*).

Unlike the potential prognostic role of ^{18}F-FDG SUV_{max} (*21,22*), that of ^{68}Ga-DOTA-peptide SUV_{max} has, to our knowledge, scarcely been investigated. Two papers reported how the ^{68}Ga-DOTANOC SUV_{max} correlates with somatostatin receptor expression (*9,23*), and two investigated the potential prognostic role of SUV_{max} in patients with neuroendocrine tumors with different primary sites (*9,10*). However, pNETs generally show more aggressive clinical behavior than other forms of NET (*8,11*), with 5-y survival rates ranging between 25% and 75% (*2,24,25*). Therefore, the identification of specific prognostic factors assessed in a homogeneous population of NET patients with a pancreatic primary is mandatory.

In view of these clinical needs, the population under study included only patients with a pancreatic primary and a long follow-up (median,

Downloaded from jnm.snmjournals.org by on March 14, 2017. For personal use only.

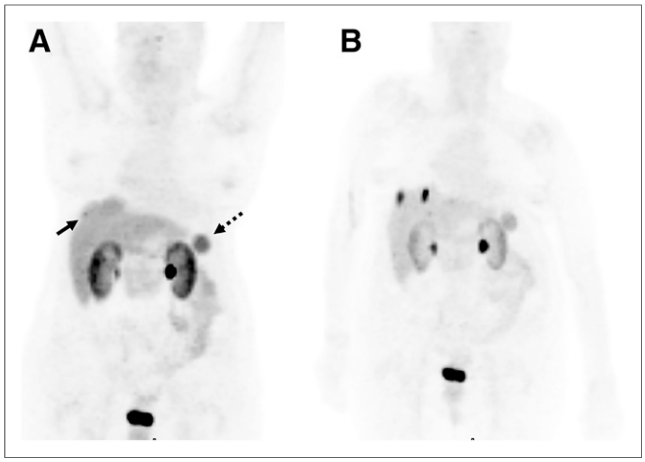


FIGURE 2. (A) ^{68}Ga-DOTANOC PET/CT maximum-intensity-projection images of patient who previously underwent surgery for pNET and presented with liver metastasis having SUV_{max} of 6.7 (solid arrow). (B) Patient showed disease progression at follow-up. Dashed arrow indicates accessory spleen.

20 mo); cases of multiple endocrine neoplasia (a condition known to present a different clinical behavior) were excluded.

Our study showed that SUV_{max} may be used to predict outcome in pNET patients. In particular, a higher SUV_{max} was associated with a better outcome. The best cutoff to discriminate between patients with stable disease or partial response and those with progressive disease ranged between 37.8 and 38.0. This range is higher than those reported in either previous study that included patients with different primary sites (19.3 and 14.5, respectively) (*9,10*). The explanation may in part be the documented higher SUV_{max} of the pancreatic primary tumors (*9*). A report by O'Toole et al. (*26*) noted a higher level of somatostatin receptor 2 and 5 messenger RNA in neuroendocrine tumor patients with a pancreatic primary than in those with a different primary.

To our knowledge, ours is the first report of the role of SUV_{max} in predicting PFS in pNETs. Several reports have analyzed the role of different prognostic factors in PFS. In particular, Panzuto et al. described the role of poorly differentiated tumors with a Ki-67 of more than 5% and no treatment after diagnosis as a risk factor for disease progression on multivariate analysis (*8*). In line with such results, our data support the use of a Ki-67 cutoff of 5% for differentiating patients who will present with more aggressive disease from those with more indolent disease (as opposed to the widely accepted cutoff of 2%, which is used for NETs with other primary sites) (*8*).

Recently, there has been much attention on the potential role of double-tracer imaging (^{68}Ga-DOTA-peptide/^{18}F-FDG) for a complete biologic characterization of the disease, since a poorer prognosis is generally driven by the presence of one or more ^{18}F-FDG–positive lesions. This approach may overcome the inherent limitations of Ki-67 tissue sampling (invasive assessment of only the biopsied site and the use of different manual and automated digital image analyses for its quantification). Although several papers have addressed this issue (*27,28*), larger prospective studies are needed to better clarify which patients may most benefit from double-tracer imaging and when it should be performed during the course of the disease. The latter is certainly a relevant issue, in terms of both health care costs and radioprotection, in view of the longer life expectancy of most of these patients. Interestingly, in a recent study by Sharma et al. (*10*) performed on a limited number of NETs with different primary sites and including cases of multiple endocrine neoplasia syndrome type 1, only SUV_{max} measured on ^{68}Ga-DOTANOC imaging was reported to correlate with prognosis (^{18}F-FDG SUV_{max} did not). Several reports indicated that when positive, ^{18}F-FDG is associated with a worse prognosis, although to our knowledge most studies investigated the impact on PFS of ^{18}F-FDG positivity and not the role of SUV_{max} specifically (*27,28*). Recently, in a population of 20 pNET patients undergoing pretreatment evaluation with ^{18}F-FDG PET/CT, Kim et al. (*29*) reported the potential utility of the metabolic tumor volume of the primary tumor, along with American Joint Committee on Cancer stage, as an independent prognostic factor for overall survival.

The current treatment approach to pNETs is not standardized, and several different options, not mutually exclusive, are available (*30*). Phase 3 clinical trials have been performed only for the long-acting somatostatin analogs everolimus and sunitinib. Although biased by the retrospective nature of data collection, our results showed a longer PFS in patients treated with PRRT (26 vs. 16 mo). This finding is in line with previous reports of pNET PFS in a recently published retrospective multicenter analysis (23 mo) (*18*) on radiolabeled somatostatin analog treatment. Acknowledging the inherent

TABLE 2
Risk Factors for Disease Progression During Follow-up at Univariate and Multivariate Analysis

Patient characteristic	Univariate			Multivariate		
	HR	95% confidence interval	*P*	HR	95% confidence interval	*P*
Sex (male vs. female)*	0.80	0.40–1.61	0.532	—	—	—
Syndrome (no vs. yes)*	1.86	0.71–4.89	0.205	—	—	—
Stage IV vs. IIIB*	1.87	0.71–4.94	0.209	3.31	1.16–9.47	0.026
NET G2 vs. NET G1	1.94	0.86–4.35	0.109			
Ki-67 (>5% vs. ≤5%)*	2.89	1.31–6.34	0.009	3.24	1.34–7.84	0.009
Ki-67 (continuous)	1.09	1.02–1.17	0.009			
SUV_{max} (≤37.8 vs. ≥38.0)*	3.09	1.46–6.57	0.003	2.37	1.03–5.47	0.043
Therapy (medical vs. PRRT)*	2.36	1.16–4.80	0.018	2.70	1.21–6.03	0.015

*Variables in multivariate analysis.

Downloaded from jnm.snmjournals.org by on March 14, 2017. For personal use only.

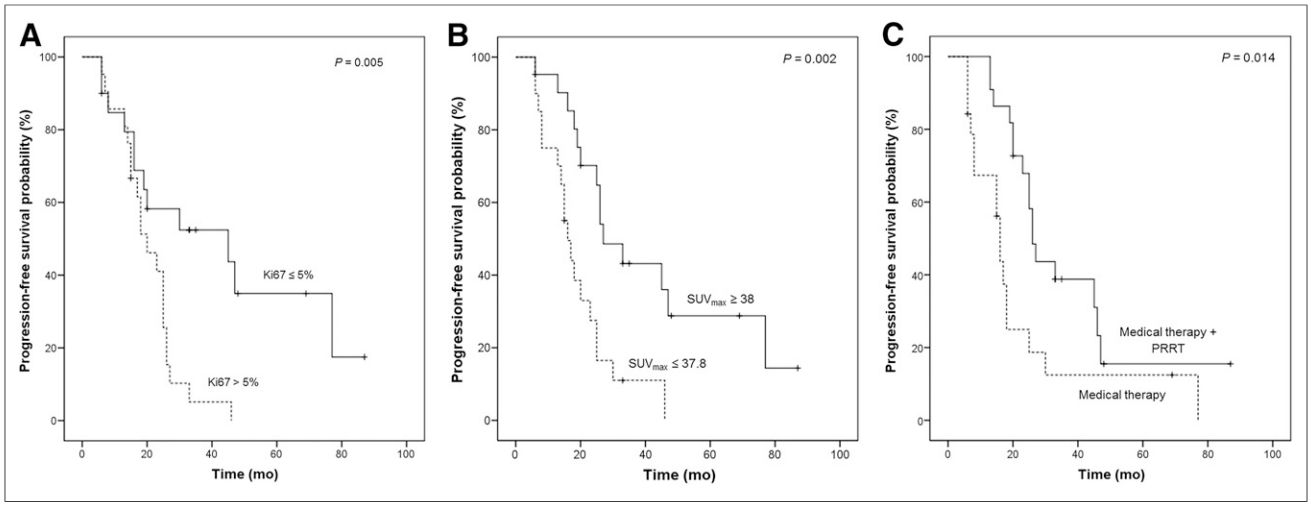


FIGURE 3. PFS in 43 patients with well-differentiated pNET (G1 and G2) according to Ki-67 (A) (dashed line = Ki-67 > 5%; solid line = Ki-67 < 5%; $P = 0.005$), SUV_{max} (B) (dashed line = $SUV_{max} < 37.8$; solid line = $SUV_{max} > 38$; $P = 0.002$), and treatment (C) (dashed line = medical therapy; solid line = medical therapy plus PRRT; $P = 0.014$).

problems of interstudy comparisons, the reported effect of PRRT on PFS (*18,31–33*) seems to be superior to that of chemotherapy (median PFS < 18 mo) (*34,35*) or targeted therapies such as sunitinib (11.4 mo) (*36*) and everolimus (11.0 mo) (*37*).

The results reported in this paper therefore support the role of PRRT in the therapeutic management of pNET patients and underline the need to standardize regimens over different centers and countries. In fact, for PRRT, only practical guidance signed by the International Atomic Energy Agency, European Association of Nuclear Medicine, and Society of Nuclear Medicine and Molecular Imaging is currently available (*30*).

CONCLUSION

^{68}Ga-DOTANOC SUV_{max} is a demonstrated prognostic parameter in patients with well-differentiated pNETs (G1 and G2) and should be used in clinical practice in association with other known prognostic factors to foresee patient outcome. Considering that different ^{68}Ga-DOTA-peptides are currently available for neuroendocrine tumor imaging and the fact that the corresponding SUV_{max} is not directly comparable, specific studies are needed to establish cutoffs for other β-emitting somatostatin analog tracers.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Halfdanarson TR, Rubin J, Farnell MB, Grant CS, Petersen GM. Pancreatic endocrine neoplasms: epidemiology and prognosis of pancreatic endocrine tumors. *Endocr Relat Cancer.* 2008;15:409–427.
2. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology.* 2008;135:1469–1492.
3. Bosman FT, Carneiro F, Hruban RH, Theise ND. *WHO Classification of Tumours of the Digestive System.* 4th ed. Lyon, France: IARC; 2010.
4. Rindi G, Klöppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch.* 2006;449:395–401.
5. Gabriel M, Decristoforo C, Kendler D, et al. [^{68}Ga]DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. *J Nucl Med.* 2007;48:508–518.
6. Kowalski J, Henze M, Schuhmacher J, Mäcke HR, Hofmann M, Haberkorn U. Evaluation of positron emission tomography imaging using [^{68}Ga]-DOTA-D Phe^{1}-Tyr^{3}-octreotide in comparison to [^{111}In]-DTPAOC SPECT: first results in patients with neuroendocrine tumors. *Mol Imaging Biol.* 2003;5:42–48.
7. Ambrosini V, Campana D, Bodei L, et al. ^{68}Ga-DOTA-NOC PET/CT clinical impact in patients with neuroendocrine tumors. *J Nucl Med.* 2010;51:669–673.
8. Panzuto F, Boninsegna L, Fazio N, et al. Metastatic and locally advanced pancreatic endocrine carcinomas: analysis of factors associated with disease progression. *J Clin Oncol.* 2011;29:2372–2377.
9. Campana D, Ambrosini V, Pezzilli R, et al. Standardized uptake values of ^{68}Ga-DOTANOC PET: a promising prognostic tool in neuroendocrine tumors. *J Nucl Med.* 2010;51:353–359.
10. Sharma P, Naswa N, Kc SS, et al. Comparison of the prognostic values of ^{68}Ga-DOTANOC PET/CT and ^{18}F-FDG PET/CT in patients with well-differentiated neuroendocrine tumor. *Eur J Nucl Med Mol Imaging.* 2014;41:2194–2202.
11. Panzuto F, Nasoni S, Falconi M, et al. Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. *Endocr Relat Cancer.* 2005;12:1083–1092.
12. Scarpa A, Mantovani W, Capelli P, et al. Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. *Mod Pathol.* 2010;23:824–833.
13. Pelosi G, Bresaola E, Bogina G, et al. Endocrine tumors of the pancreas: Ki-67 immunoreactivity on paraffin sections is an independent predictor for malignancy: a comparative study with proliferating-cell nuclear antigen and progesterone receptor protein immunostaining, mitotic index, and other clinicopathologic variables. *Hum Pathol.* 1996;27:1124–1134.
14. Virgolini I, Ambrosini V, Bomanji JB, et al. Procedure guidelines for PET/CT tumour imaging with ^{68}Ga-DOTA-conjugated peptides: ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TATE. *Eur J Nucl Med Mol Imaging.* 2010;37:2004–2010.
15. Zhernosekov KP, Filosofov DV, Baum RP, et al. Processing of generator-produced ^{68}Ga for medical application. *J Nucl Med.* 2007;48:1741–1748.
16. Weber WA, Ziegler SI, Thodtmann R, Hanauske AR, Schwaiger M. Reproducibility of metabolic measurements in malignant tumors using FDG PET. *J Nucl Med.* 1999;40:1771–1777.
17. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000;92:205–216.
18. Campana D, Capurso G, Partelli S, et al. Radiolabelled somatostatin analogue treatment in gastroenteropancreatic neuroendocrine tumours: factors associated

Downloaded from jnm.snmjournals.org by on March 14, 2017. For personal use only.

with response and suggestions for therapeutic sequence. *Eur J Nucl Med Mol Imaging.* 2013;40:1197–1205.
19. Kabasakal L, Demirci E, Ocak M, et al. Comparison of ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC PET/CT imaging in the same patient group with neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2012;39:1271–1277.
20. Poeppel TD, Binse I, Petersenn S, et al. ^{68}Ga-DOTATOC versus ^{68}Ga-DOTATATE PET/CT in functional imaging of neuroendocrine tumors. *J Nucl Med.* 2011;52:1864–1870.
21. Takeuchi S, Khiewvan B, Fox PS, et al. Impact of initial PET/CT staging in terms of clinical stage, management plan, and prognosis in 592 patients with non-small-cell lung cancer. *Eur J Nucl Med Mol Imaging.* 2014;41:906–914.
22. Garin E, Le Jeune F, Devillers A, et al. Predictive value of ^{18}F-FDG PET and somatostatin receptor scintigraphy in patients with metastatic endocrine tumors. *J Nucl Med.* 2009;50:858–864.
23. Kaemmerer D, Peter L, Lupp A, et al. Molecular imaging with ^{68}Ga-SSTR PET/CT and correlation to immunohistochemistry of somatostatin receptors in neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2011;38:1659–1668.
24. Ahmed A, Turner G, King B, et al. Midgut neuroendocrine tumours with liver metastases: results of the UKINETS study. *Endocr Relat Cancer.* 2009;16:885–894.
25. Durante C, Boukheris H, Dromain C, et al. Prognostic factors influencing survival from metastatic (stage IV) gastroenteropancreatic well-differentiated endocrine carcinoma. *Endocr Relat Cancer.* 2009;16:585–597.
26. O'Toole D, Saveanu A, Couvelard A, et al. The analysis of quantitative expression of somatostatin and dopamine receptors in gastro-entero-pancreatic tumours opens new therapeutic strategies. *Eur J Endocrinol.* 2006;155:849–857.
27. Bahri H, Laurence L, Edeline J, et al. High prognostic value of ^{18}F-FDG PET for metastatic gastroenteropancreatic neuroendocrine tumors: a long-term evaluation. *J Nucl Med.* 2014;55:1786–1790.
28. Partelli S, Rinzivillo M, Maurizi A, et al. The role of combined Ga-DOTANOC and ^{18}FDG PET/CT in the management of patients with pancreatic neuroendocrine tumors. *Neuroendocrinology.* 2014;100:293–299.
29. Kim HS, Choi JY, Choi DW, et al. Prognostic value of volume-based metabolic parameters measured by ^{18}F-FDG PET/CT of pancreatic neuroendocrine tumors. *Nucl Med Mol Imaging.* 2014;48:180–186.
30. Bodei L, Mueller-Brand J, Baum RP, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2013;40:800–816.
31. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate: toxicity, efficacy, and survival. *J Clin Oncol.* 2008;26:2124–2130.
32. Ezziddin S, Attassi M, Yong-Hing CJ, et al. Predictors of long-term outcome in patients with well-differentiated gastroenteropancreatic neuroendocrine tumors after peptide receptor radionuclide therapy with ^{177}Lu-octreotate. *J Nucl Med.* 2014;55:183–190.
33. Imhof A, Brunner P, Marincek N, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [^{90}Y-DOTA]-TOC in metastasized neuroendocrine cancers. *J Clin Oncol.* 2011;29:2416–2423.
34. Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG; Eastern Cooperative Oncology Group. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. *J Clin Oncol.* 2005;23:4897–4904.
35. Kouvaraki MA, Ajani JA, Hoff P, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol.* 2004;22:4762–4771.
36. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364:501–513.
37. Yao JC, Shah MH, Ito T, et al.; RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364:514–523.

Downloaded from jnm.snmjournals.org by on March 14, 2017. For personal use only.

JNM The Journal of NUCLEAR MEDICINE

Prognostic Value of ^{68}Ga-DOTANOC PET/CT SUV_{max} in Patients with Neuroendocrine Tumors of the Pancreas

Valentina Ambrosini, Davide Campana, Giulia Polverari, Chiara Peterle, Stefania Diodato, Claudio Ricci, Vincenzo Allegri, Riccardo Casadei, Paola Tomassetti and Stefano Fanti

J Nucl Med. 2015;56:1843-1848.
Published online: September 24, 2015.
Doi: 10.2967/jnumed.115.162719

This article and updated information are available at:
http://jnm.snmjournals.org/content/56/12/1843

Information about reproducing figures, tables, or other portions of this article can be found online at:
http://jnm.snmjournals.org/site/misc/permission.xhtml

Information about subscriptions to JNM can be found at:
http://jnm.snmjournals.org/site/subscriptions/online.xhtml

The Journal of Nuclear Medicine is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

© Copyright 2015 SNMMI; all rights reserved.

SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING