Prognostic value of 68Ga-DOTA-NOC PET/CT SUVmax in patients with neuroendocrine tumours of the pancreas

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ABSTRACT

Rationale: to investigate the role of 68Ga-DOTA-NOC SUVmax as a potential prognostic factor in patients with pancreatic neuroendocrine tumour (pNET).

Methods: Among the patients who underwent 68Ga-DOTANOC PET/CT, we retrospectively collected data of those with pNET G1 or G2 (2010 WHO classification), presenting disease at PET/CT and CT, with at least 6 months follow-up. MEN patients were excluded.

Results: Overall, 43 patients were included. No significant differences in the SUVmax values were observed with respect to gender, tumour syndrome, stage, WHO classification and Ki67. During follow-up (median 20 months), 11 patients (35.6%; median: 33 months; IQR: 20-48 months) had stable disease (SD) while 32 (74.4%) had progressive disease (PD, median: 19 months; IQR, 14-26 months).

SUVmax was significantly higher (p=0.022) in patients with SD at 24 months follow-up as compared to patients with PD. The best SUVmax cut-off ranged from 37.8 to 38.0.

The major risk factors for progression included a SUVmax ≤ 37.8 (HR=3.09, p=0.003), Ki67>5% (HR=2.89, p=0.009) and medical therapy alone (HR=2.36, p=0.018).

Advanced (IV) stage (p=0.026), SUVmax<37.8 (p=0.043), medical therapy alone (p=0.015) were also confirmed at multivariate analysis.

Overall, median progression-free survival (PFS) was 23 months. Significant differences in PFS were observed in relationship to Ki67 (median: 45 months for Ki67≤5%; 20 months for Ki67>5%; p=0.005; ), SUVmax (<37.8 vs > 38.0: 16.0 vs 27.0 months p=0.002) and type of therapy (medical vs PRRT: 16.0 vs 26.0 months; p=0.014).

Conclusions: 68Ga-DOTA-NOC SUVmax is a relevant prognostic factor in patients with pNET G1 and G2 and its routine employment will improve the characterization and management of these patients that may present with a heterogeneous clinical behaviour.
INTRODUCTION

Pancreatic neuroendocrine neoplasms (pNET, WHO 2010) are considered a rare pathology with a wide spectrum of clinical presentations. 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 pNET are characterized by an overall better prognosis as compared to other forms of solid tumours, the patient outcome can vary greatly depending on the tumour grading (3) and disease extent (4). However, the improved diagnostic and therapeutic management of these patients has led to an increase in the prevalence of the disease and, in turn, atypical presenting cases have increased, showing heterogeneous clinical behaviour, either at diagnosis or during the course of the disease. Therefore, the possibility to identify prognostic parameters that may help the clinicians to stratify patients in different risk groups is extremely relevant.

The diagnostic flow-chart of pNET currently includes several imaging modalities both morphological (US, CT, MRI) and functional (somatostatin receptors scintigraphy, PET/CT with 68Ga-DOTA-peptides) (5-7). In the past five years, PET/CT with 68Ga-DOTA-peptides has been increasingly employed for the high accuracy in lesions detection (at both the primary and metastatic sites), safety, contained costs (5-7) and for selecting patients to be addressed to Peptide Receptor Radionuclide Therapy (PRRT).

Once the tumour is detected, the possibility to identify accurate prognostic factors for disease progression is of crucial importance for the management of these patients. Previous studies investigated the role of grading, staging, functioning status and somatostatin receptors density as potential prognostic factors in pNET (8). Two previous studies indicated the SUVmax measured in the lesion with the 68Ga-DOTA-NOC highest uptake as a prognostic parameter in heterogeneous populations of neuroendocrine tumours with different primary site (including gastro-entero-pancreatic and lung tumours) (9,10).
However, since pNET may present a different clinical course as compared to NET with other primary sites \((8,11)\), aim of the present study is to investigate whether the SUVmax measured at 68Ga-DOTA-NOC PET/CT may be employed as a prognostic factor in patients with pancreatic primary.

MATERIALS AND METHODS

Among the patients who underwent 68Ga-DOTA-NOC PET/CT at our PET Center from September 2006 to October 2014, we retrospectively collected data of those with pathologically proven pNET G1 or G2 (2010 WHO classification) \((3)\). Additional inclusion criteria were: i) presence of disease at both 68Ga-DOTANOC PET/CT and CT (performed within a month of the PET/CT) and ii) clinical follow-up of at least 6 months.

Patients with MEN 1 syndrome, a condition well known to present with different clinical behaviour from other gastro-entero-pancreatic NET, were excluded from the analysis.

All patients underwent physical examination, and their clinical history was taken with the aim of investigating the putative clinical features of the functioning tumours. Laboratory and radiologic examinations were performed to evaluate the localization of the tumour and to stage the disease.

According to recent literature of pNET, patients were divided into two groups according to a Ki67 cut-off value of 5\% \((8,12,13)\).

Presence of clinical symptoms associated with an increase of serum peptide levels, was used to identify cases with functioning tumours.

Clinical follow-up was carried out at the Internal Medicine Out-Patient Service dedicated to pNET patients and included a CT scan every 3 months during the first year and every 6 months afterwards.

Treatment after PET/CT with Everolimus (Afinitor 10mg/day), cold somatostatin analogues alone every 28 days (Octreotide LAR, Novartis Oncology, 30 mg; or Lanreotide Autogel, Ipsen, 120 mg) or in association with PRRT was recorded.
All patients gave their written informed consent to participate in the study. The study protocol was approved by our local Ethical Committee of the S.Orsola-Malpighi Hospital and was performed according to the Helsinki Declaration for human studies.

PET/CT with 68Ga-DOTA-NOC was performed following current international guidelines (intravenous injection of 120-185MBq followed by an uptake time of 60 min (range 45-90), without specific exam preparation) (14). 68Ga-DOTANOC was synthesized by the Radiopharmacy of the Nuclear Medicine Unit of S.Orsola-Malpighi Hospital. 68Ga was eluted from a 68Ge/68Ga generator, and DOTANOC was labelled with 68Ga following the procedure described by Zhernosekov et al. (15).

68Ga-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 non-uniform 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 two 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, and urinary bladder) was considered to be indicative of somatostatin receptors expression.

The SUVmax was calculated by measuring the maximal concentration of the labelled tracer in the region of interest corrected for body weight and injected dose (SUVmax=maximum activity concentration/[injected dose/body weight]) (16). For each PET scan, the SUVmax was measured by choosing the region of interest in the lesion presenting the highest tracer uptake. For large tumours, the
region of interest was moved over several sites within the mass to ensure that the true SUVmax was obtained.

**STATISTIC ANALYSIS**

All data were collected and a computerized data sheet was created. Data on demographic, clinical and pathological features were retrospectively analysed. The tumours were classified according to the 2010 World Health Organization (WHO) classification (3) and the novel tumour node metastasis (TNM) classification/G grading system (4). The Ki67 proliferation index was expressed as a percentage based on the count of Ki67 positive cells in 2,000 tumour cells in areas of the highest immunostaining using the MIB1 antibody (DBA, Milan, Italy). The tumours were measured and scored according to the response evaluation criteria in solid tumors (RECIST) (17).

Median values and the respective interquartile range (IQR, 25th to 75th percentile) were used to describe the data. The comparison between groups was carried out using Pearson’s chi-square test (Fisher’s 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 the SUVmax at diagnosis in predicting the progression of the disease. The best prognostic cut-off value was estimated by a maximum likelihood ratio method.

Progression-free survival (PFS) was defined as the interval between 68Ga-DOTANOC PET/CT and the time of progression of disease (PD). PFS was measured using the Kaplan-Meier method, and the results were compared using the log-rank test. Analysis of the predictive risk factors for PD was carried out by univariate and multivariate analysis using the Cox proportional hazards method. Risk factors were expressed as hazard ratios (HR) [95 % confidence interval (CI)]. The multivariate model was constructed using the forward stepwise method after including all variables. All analyses carried out for risk factors are listed in the tables.
The p value was considered significant when less than 0.05. The statistical analysis was carried out using dedicated software (SPSS version 19.0, SPSS Inc.).

To evaluate the potential role of SUVmax on prognosis, we divided the patients on the basis of the disease status (PD vs stable disease, SD) at an arbitrary selected time-point follow-up. A 24 months time-point follow-up was chosen considering that about half of our patients underwent PRRT, that PFS in patients treated with PRRT was reported to be 23 months in the pancreatic subgroup of a recent multicenter trial (18) and that our follow-up schedule included a radiological evaluation at 24 months (CT scan every 3 months during the first year and every 6 months afterwards).

RESULTS

Patient Characteristics

Overall 43 patients (22 men and 21 women; median age 58 years; IQR 48-64 years) with pNET were included in the study. Eight patients (18.6%) had functioning tumours: 5 gastrinomas, one insulinoma, one VIPoma and one ACTH-oma. In the remaining 35 (81.4%) the tumour was non-functioning. According to the 2010 WHO classification, 14 patients (32.3%) had a NET G1, 29 (67.7%) had a NET G2.

The median Ki67 index was 6.1% (IQR, 2.0%-8.9%); 22 of 43 patients (51.2%) had a Ki67 of 5% or less, and 21 of 43 patients (48.8%) had a Ki67 greater than 5%.

According to the TNM classification, 7 patients (16.3%) had stage IIIB disease, 36 (83.7%) had stage IV.

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

68Ga-DOTANOC SUVmax
The median values and the respective interquartile range (IQR, 25th to 75th percentiles) of the SUVmax among the different groups of patients are reported in Table 1. Our data showed that there were no significant differences with respect to gender, the presence of tumour syndrome, stage, and 2010 WHO classification.

Follow-up
All patients were evaluated for a median period of 20 months (IQR, 15-33 months). Twenty of the 43 patients (46.5%) were treated with medical therapy: 13 with long-acting somatostatin analogs alone (Octreotide LAR [30 mg] every 28 days or Lanreotide Autogel [120 mg] every 28 days), 2 with long-acting somatostatin analogs plus Everolimus (Afinitor [10 mg] every day, Novartis Oncology) and 5 with Everolimus alone; 23 (53.5%) had a combined treatment with both long-acting somatostatin analogs and PRRT.

During the follow-up, 11 patients (35.6%; median: 33 months; IQR: 20-48 months) had stable disease (SD) while in 32 (74.4%) the disease progressed (median: 19 months; IQR, 14-26 months).

To evaluate the potential role of SUVmax on prognosis, we divided the patients on the basis of the disease status (PD vs SD) at 24 months follow-up. As reported in Table 1, our data showed that SUVmax was significantly higher (p=0.022) in patients with SD (Figure 1) at 24 months follow-up (18 cases; median: 49.8; IQR: 44.9-78.8) as compared to patients with PD (20 cases; median: 33.4; IQR, 26.1-52.4; Figure 2). Five patients were not included in the analyses since they presented stable disease and had a follow-up inferior to 24 months.

The receiver-operating-characteristic curve of the SUVmax in predicting patients who had PD after 24 month of follow-up was quite accurate (area under the curve±SE=0.715±0.084; p=0.023), and the best cut-off ranged from 37.8 to 38.0. The sensitivity and specificity obtained using the best cut-off values were 72.2% and 70.0% respectively.
Predictors for tumour progression

At univariate analysis, the variables considered as risk factors for tumour progression are summarized in Table 2. Risk factors for tumour progression at univariate analysis were: SUVmax ≤ 37.8 (HR 3.09, p=0.003), medical therapy alone (HR 2.36, p=0.0148) and Ki67>5% (HR 2.89, p=0.009). Ki67 >5% (HR 3.24), stage IV (HR 3.31), medical therapy alone (HR 2.70) and SUVmax ≤ 37.8 (HR 2.37) were risk factors for tumour progression at multivariate analysis.

Progression-free Survival

Overall, median PFS was 23 months (Figure 3). Significant differences in PFS were observed in relationship to Ki67 (median: 45 months for Ki67≤5%; 20 months for ki67>5%; p=0.005; Figure 3A), SUVmax (<37.8 vs > 38.0: 16.0 vs 27.0 months, p=0.002; Figure 3B) and type of therapy (medical vs PRRT: 16.0 vs 26.0 months; p=0.014; Figure 3C). No statistical difference was found according to 2010 WHO classification (NET G1 vs NET G2: 30.0 vs 23.0 months; p=0.097), stage of the disease (stage IIIB vs stage IV: 46.0 vs 20.0 months; p=0.195) and functioning status (functioning vs non-functioning: 26.0 vs 20.0 months; p=0.191).

DISCUSSION

In the past decade, both the optimization of the diagnostic algorithms (especially after the advent of 68Ga-DOTA-peptides PET/CT) and the employment of novel therapeutic strategies (mainly PRRT and novel biologic target drugs), determined an increase in NET prevalence. Correspondingly, clinicians witnessed an increment of atypical cases that do not fit in the classical paradigm of NET always being indolent tumours. Therefore, the identification of easily assessable prognostic parameters is crucial, for both an accurate evaluation at baseline and during the course of the disease, since an initially indolent
tumour may turn into a more aggressive behaviour. SUVmax is an optimal parameter since it can be easily assessed in a relatively non-invasive way. Moreover, being PET/CT a whole-body procedure, it provides a functional evaluation of the whole tumour burden, that is not feasible with the commonly used Ki67.

A wide literature on 68Ga-DOTA-peptides PET/CT imaging is focused on assessing the diagnostic accuracy (5,7) and the performance of one tracer over the other (19,20).

To our knowledge, on the contrary to 18F-FDG (21,22), the potential prognostic role of 68Ga-DOTA-peptides SUVmax has been scarcely investigated. Two recent papers reported how the 68Ga-DOTA-NOC SUVmax correlates with somatostatin receptors expression (9,23) and two previous studies investigated the potential prognostic role of SUVmax in patients with neuroendocrine tumours with different primary sites (9,10). However, pNET generally show a more aggressive clinical behaviour as compared to other forms of NET (8,11), with 5-years survival rates ranging between 25 and 75% (24-26). Therefore, the identification of specific prognostic factors assessed in an homogeneous population of NET patients with pancreatic primary is mandatory.

In view of these clinical needs, the population under study included only patients with pancreatic primary, with a long follow-up (median 20 months), while MEN cases (a condition known to present a different clinical behaviour) were excluded.

Our study showed that SUVmax may be used to predict outcome in pNET patients. In particular, a higher SUVmax was associated with a better outcome. The best cut-off to discriminate between patients with stable disease/partial response from those with progressive disease ranged between 37.8 - 38.0. This value is higher than the ones reported in both previous studies, including patients with different primary sites (19.3 and 14.5, respectively) (9,10). This may be partly explained by the documented higher SUVmax values of the pancreatic primary tumours (9). A previous report by
O'Toole et al. (27) observed higher level of SSTR2 and SSTR5 mRNA in patients with pancreatic NET as compared to neuroendocrine tumours with other primary.

To our knowledge this is the first report of the role of SUVmax in predicting progression-free survival in pNET. Several recent reports analysed the role of different prognostic factors in terms of progression free survival. In particular, Panzuto et al described the role of poorly differentiated tumours, Ki67>5% and no treatment after diagnosis, as risk factors for disease progression at multivariate analysis (8). In line with such results, our data support the employment of a Ki67 cut-off value of 5% for differentiating patients that will present a more aggressive behaviour from the ones with a more indolent disease (as opposed to the widely accepted cut-off of 2%, that is used for NET with other primary sites) (8).

Recently, much attention has being focused on the potential role of double tracer imaging (68Ga-DOTA-peptides/18F-FDG) for a complete biological characterization of the disease, since a worst prognosis is generally driven by the presence of one or more FDG-positive lesions. This approach may overcome the inherent limitations of Ki67 tissue sampling (invasive assessment of only the biopsied site and the employment of different manual and automated digital image analysis for its quantification). Although several papers have recently addressed this issue (28,29), larger prospective studies are needed to better clarify which patients may benefit the most from double tracer imaging and when it should be performed during the course of the disease. The latter is certainly a relevant issue, in both terms of healthcare costs and radioprotection, in view of the longer life expectancy of the majority these patients. Interestingly, in a recent report by Sharma et al (10) performed in an limited population of NET with different primary sites and including MEN1 cases, only the SUVmax measured at 68Ga-DOTA-NOC was reported to correlate with prognosis (while 18F-FDG SUVmax did not). Several reports indicated that when positive FDG is associated with a worse prognosis, although to our knowledge most studies investigated the impact on PFS of FDG-positivity and not the role of the
SUVmax specifically \((28,29)\). Recently in a population of 20 pNET undergoing a pre-treatment evaluation with 18F-FDG PET/CT, Kim et al \((30)\) reported the potential utility of MTV (metabolic tumour volume) of the primary tumour, along with the AJCC stage, as an independent prognostic factor for overall survival.

The current treatment approach to pNET is not standardised and several different treatment options, not mutually exclusive, are available \((31)\). Phase 3 clinical trials have been carried out only for long-acting somatostatin analogs, everolimus and sunitinib. Although biased by the retrospective nature of data collection, our results showed a longer progression-free survival in cases treated with PRRT (26 months vs 16 months). This is in line with previous reports of pNET progression-free survival in a recently published retrospective multicentre analysis (23 months) \((18)\) on radiolabelled somatostatin analogue treatment. Acknowledging the inherent problems of inter-study comparisons, the reported effect of PRRT in terms of progression free survival \((18,32-34)\) seems to be superior than chemotherapy (median PFS less than 18 months) \((35,36)\) or targeted therapies, such as sunitinib (11.4 months) \((37)\) and everolimus (11.0 months) \((38)\).

The results reported in this paper are therefore supporting the role of PRRT in the therapeutic management of pNET patients and underline the need to standardise regimens over different centers and countries. In fact, only practical guidance signed by the IAEA, EANM, and SNMMI is currently available for PRRT \((31)\).

CONCLUSIONS

68Ga-DOTA-NOC SUVmax is a demonstrated prognostic parameter in patients with well differentiated pNET (G1 and G2) and should be used in clinical practise in association with other known prognostic factors to foresee patients outcome. Considering that different 68Ga-DOTA-peptides are currently available for neuroendocrine tumour imaging and the fact that corresponding SUVmax
values are not directly comparable, specific studies are needed to establish cut-off values also for other beta-emitting somatostatin analog tracers.

All authors declare that they have no conflict of interest.
REFERENCES


TABLE 1. Median values and the respective interquartile range (IQR, 25th to 75th percentiles) of SUVmax among the different groups of patients.

<table>
<thead>
<tr>
<th>Patients (N. of cases)</th>
<th>SUVmax (Median [IQR])</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22</td>
<td>45.9 (36.3-58.2)</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>37.8 (35.7-69.3)</td>
</tr>
<tr>
<td><strong>Syndrome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>33.9 (19.8-95.6)</td>
</tr>
<tr>
<td>No</td>
<td>35</td>
<td>45.5 (38.6-57.4)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>7</td>
<td>34.3 (25.2-62.2)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>36</td>
<td>48.9 (39.9-62.1)</td>
</tr>
<tr>
<td><strong>2010 WHO classification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NET G1</td>
<td>14</td>
<td>57.7 (42.4-79.3)</td>
</tr>
<tr>
<td>NET G2</td>
<td>29</td>
<td>36.2 (33.2-55.7)</td>
</tr>
<tr>
<td><strong>Ki67</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5%</td>
<td>22</td>
<td>53.3 (42.5-68.6)</td>
</tr>
<tr>
<td>&gt;5%</td>
<td>21</td>
<td>36.0 (29.1-58.5)</td>
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<tr>
<td><strong>Follow-up at 24 months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable Disease/Partial Response</td>
<td>18</td>
<td>49.8 (44.9-78.8)</td>
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<tr>
<td>Progressive Disease</td>
<td>20</td>
<td>33.4 (26.1-52.4)</td>
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</table>
Table 2. Risk factors for disease progression during follow-up at univariate and multivariate analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
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</thead>
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<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
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<tr>
<td>Sex (Male vs. Female)*</td>
<td>0.80</td>
<td>0.40-1.61</td>
</tr>
<tr>
<td>Syndrome (no vs. yes)*</td>
<td>1.86</td>
<td>0.71-4.89</td>
</tr>
<tr>
<td>Stage IV vs IIIB*</td>
<td>1.87</td>
<td>0.71-4.94</td>
</tr>
<tr>
<td>NET G2 vs NET G1</td>
<td>1.94</td>
<td>0.86-4.35</td>
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<tr>
<td>Ki67 (&gt;5% vs. ≤5%)*</td>
<td>2.89</td>
<td>1.31-6.34</td>
</tr>
<tr>
<td>Ki67 (continuous)</td>
<td>1.09</td>
<td>1.02-1.17</td>
</tr>
<tr>
<td>SUVmax (≤37.8 vs. ≥38.0)*</td>
<td>3.09</td>
<td>1.46-6.57</td>
</tr>
<tr>
<td>Therapy (medical vs. PRRT)*</td>
<td>2.36</td>
<td>1.16-4.80</td>
</tr>
</tbody>
</table>

*Variables in multivariate analysis
FIGURE LEGENDS

Figure 1.

68Ga-DOTA-NOC PET/CT MIP (A) and transaxial images (B,C) of a patient with G2 pancreatic NET (A, B) and liver metastasis (A, C). The measured SUVmax was 56. The patient presented stable disease at follow-up.
Figure 2

68Ga-DOTA-NOC PET/CT MIP images of a patient previously operated for pancreatic NET and presenting a liver metastasis (A; SUVmax 6.7, black arrow). The patient showed disease progression at follow-up (B). Dotted arrow: accessory spleen.
Figure 3

Progression-free survival in 43 patients with well differentiated pNET (G1 and G2) according to ki67 (A; ki67>5%: dashed line; ki67<5%: continuous line; p=0.005), SUVmax (B; SUVmax<37.8: dashed line; SUVmax>38: continuous line; p=0.002) and treatment (C; medical therapy: dashed line; medical therapy+PRRT: continuous line; p=0.014).
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