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Comparison of the impact of ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT on clinical management in patients with neuroendocrine tumors

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ABSTRACT

This study aimed to assess the clinical impact of ^{68}Ga-DOTATATE and ^{18}F-fluorodeoxyglucose with respect to the management plan and to evaluate the prognostic value of both tracers.

Methods: A total of 104 patients (55 males, 49 females; median age 58 years, range 20–90) with histopathologically proven neuroendocrine tumors (NETs) underwent both ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT. Twenty-eight patients (26.9%) had poorly differentiated (PD) and 76 (73.1%), well-differentiated tumors. PET/CT results and SUVs were compared with prognostic factors such as pathologic grading (G1, G2, G3), chromogranin A, and proliferation index (Ki67).

Results: ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT findings were discordant in 65 (62.5%) and concordant in 39 (37.5%) pts. PET/CT results changed the therapeutic plan in 84 (80.8%) pts. In 22 (21.1%) pts decision making was based on ^{18}F-FDG findings, in 32 (30.8%) on findings with both radiotracers, and in 50 (48.1%) on ^{68}Ga-DOTATATE findings. The most frequent management decision based on ^{18}F-FDG was initiation of chemotherapy (10 pts, 47.6%). The most common treatment decision due to ^{68}Ga-DOTATATE was initiation of peptide receptor radionuclide therapy (14 pts, 27.4%). In 11/28 (39.2%) pts with PD NETs the management decision was based only on ^{18}F-FDG results. For ^{68}Ga-DOTATATE, SUV_{max} was higher for G1 and lower for G3 tumors (p=0.012). However, no significant differences in 18F-FDG-derived SUVs were observed between different tumor grades (p=0.38). Mann-Whitney test showed significant differences in ^{68}Ga-DOTATATE SUV_{max} between tumors with Ki<5% and tumors with Ki>5% (p=0.004), without significance differences in 18F-FDG SUV_{max}. Log-rank analysis showed statistically significant differences in survival for patients with bone vs soft tissue or no metastasis for both 18F-FDG (p=0.037) and ^{68}Ga-DOTATATE (p=0.047). Overall survival was found to decline rapidly with increasing histological grade (p=0.001), with estimated survival of 91 months for G1, 59 months for G2, and 48 months for G3.

Conclusion: ^{18}F-FDG PET/CT had no clinical impact in G1 NETs and moderate impact in G2 NETs. However in PD NETs, ^{18}F-FDG PET/CT plays a significant clinical role in combination with ^{68}Ga-DOTATATE. ^{68}Ga DOTATATE SUV_{max} values relate to tumor grade and Ki67 index and can be used prognostically.

IINTRODUCTION

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies ranging from well-differentiated, slowly growing tumors to poorly differentiated neoplasms, which are less frequent and aggressive [1]. Neuroendocrine cells have the ability to express several peptide receptors in high volumes, especially somatostatin receptors, which are heptahelical G-protein-coupled glycoprotein transmembrane receptors [2]. In the past, evaluation of NETs was based mainly on somatostatin receptor scintigraphy and other conventional imaging methods such as ultrasound, CT, endoscopy, and MRI [3,4]; however, following the advent of Postitron Emission Tomography/Computed Tomography (PET/CT) systems, novel PET tracers have been developed and investigated, including biogenic amine precursors (e.g., fluorine-18 dihydroxyphenylalanine [^{18}F-DOPA]), somatostatin analogs (gallium-68 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra-acetic acid [DOTA]), and metabolic markers (^{18}F-FDG) [3].

Three main DOTA-peptides (DOTATOC, DOTANOC, and DOTATATE) that specifically bind to somatostatin receptors overexpressed on the surface of NET cells, allowing visualization of NETs, have been used in the clinical setting for either NET diagnosis or peptide receptor radionuclide therapy (PRRT) [5,6]. PET/CT with ^{68}Ga-DOTA-peptides has been reported to present a higher sensitivity for the detection of well-differentiated, less aggressive NETs than CT and scintigraphy [7,8]. On the other hand, ^{18}F-FDG PET/CT is preferred for more aggressive, less-differentiated NETs as there is emerging evidence that the presence of increased glucose in NETs highlights an increased propensity for invasion and metastasis, and overall poorer prognosis [9]. In fact, a strong association has recently been shown between high ^{18}F-FDG uptake and worse outcome even in patients with well-differentiated or low-grade tumors, with provision of prognostic information independently of the mitotic rate [9]. Accordingly, ^{18}F-FDG may retain an important role in managing patients with NETs owing to its high prognostic value and its higher sensitivity in delineating disease extent, especially in aggressive and high-grade tumors (*4)*.

Although the value of PET findings with both ^{68}Ga-DOTA-peptides and ^{18}F-FDG is therefore well established, the detection of additional sites of disease is not necessarily associated with alteration of therapeutic approach. The aims of this study were to evaluate and compare the clinical impact of ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT on the management plan in patients

with NETs and to assess the prognostic value of maximum standardized uptake value (SUV_{max}) values for both tracers.

MATERIALS AND METHODS

Patient population

We retrospectively reviewed findings in the first 104 patients (55 male, 49 female, age range 20–90 years, median 58 years) with histopathologically proven NETs who underwent contemporaneous ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT at our institution between September 2006 and February 2014. All patients gave informed consent and institutional board ethics approval was received. The interval between the two studies ranged from 0 to 3 weeks (median 1 week), which was considered sufficiently short given that NETs show relatively slow progression.

All NETs were classified as high, intermediate, or low grade according to the histology reports, based on recent consensus statements of the European Neuroendocrine Tumor Society, using mitotic index and Ki67 index in staging of NETs along with immunohistochemistry [10] The study was approved by the institutional review board (study no. 15N10051) and all subjects signed a written informed consent.

Image acquisition

Images were acquired 1 h post injection of 370 MBq ^{18}F-FDG or 45–60 mins after the injection of 120–200 MBq ^{68}Ga-DOTATATE. No adverse effects were observed after the injection of ^{68}Ga-DOTATATE. Imaging was performed using a dedicated combined GE Discovery ST PET/16 detector CT unit (GE Healthcare, Detroit, Mich.); whole-body examinations (brain to mid-thigh) were performed with the patient in the supine position. The CT exposure factors for all examinations were 120 kVp and 80 mA in 0.8 s. Maintaining patient position, a whole-body PET emission scan was performed, covering an area identical to that covered by CT. PET acquisition was carried out in 3dimension with 4 min per bed position and nine-slice overlap. PET images were reconstructed using CT for attenuation correction. Transaxial PET data were reconstructed using ordered subsets expectation maximization with 2

iterations and 21 subsets. Transaxial PET slice thickness was 3.27 mm with an in-slice pixel size of 4.68 mm. The CT data were reconstructed to axial slices of 3.75 mm and 2.5 mm thickness with a soft tissue reconstruction algorithm and 2.5 mm thickness

Image reporting

^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT images were reported in consensus by an experienced dedicated nuclear medicine physician and a dual-accredited radiologist/nuclear medicine physician. For the evaluation of ^{68}Ga-DOTATATE PET/CT studies, any area with an intensity greater than background that could not be identified as physiologic activity (pituitary gland, spleen, liver, adrenal glands, head of the pancreas, thyroid, and urinary tract) was considered to indicate tumor tissue [6]. 68Ga-DOTATATE scans have been performed after discontinuation of 72h of short acting SSA and 28days of long acting. The imaging findings of the two modalities were compared with each other and with histology. Furthermore, SUVmax was calculated by measuring the maximum concentration of the labelled tracer (kBq/ml) in the lesion divided by the decay corrected injected activity (kBq) and normalised for body weight.

Clinical impact

To evaluate the clinical impact of PET/CT findings, referring physicians were subsequently asked to provide information on how patients were managed and how PET/CT results had influenced clinical decisions after retrieving all clinical data. Overall impact was evaluated patient by patient and was correlated with histopathological findings. In order to perform a survival analysis, last date of survival and follow-up were recorded and patients were censored regarding whether the cause of death was related to their disease.

Statistical analysis

Metric data such as age were expressed as means ± standard deviations. One-way ANOVA was used to assess differences in SUV_{max} across the different histological grades for both ^{68}Ga-DOTATATE and ^{18}F-FDG. Mann-Whitney test was used to assess differences in

SUV_{max} between Ki67 (<5%) and Ki67 (>5%) as well as threshold of Ki67 of 12% for both ^{68}Ga-DOTATATE and ^{18}F-FDG. A p value <0.05 was considered significant. Statistical analysis was performed with SPSS software (SPSS Inc., IBM, 22.0, USA).

Correlation of ^{68}Ga-DOTATATE and FDG SUV_{max} values with Ki67 index was assessed using Spearman's correlation coefficient. Kaplan-Meier survival analysis was performed to assess the prognostic value of ^{68}Ga-DOTATATE and ^{18}F-FDG findings regarding overall survival. To assess whether different scan findings related to overall survival, the Kaplan-Meier product limit estimators were calculated and compared by log rank tests. Specifically it was tested whether soft tissue and bone metastasis results in statistically significant differences in survival. Finally, the prognostic value of histological grading and Ki67 index regarding survival was also evaluated.

RESULTS

One hundred and four patients (55 men, 49 women; mean age 58 years, age range 20–90 years) who underwent ^{18}F-FDG and ^{68}Ga-DOTATATE PET/CT were enrolled in the study. Their clinical and epidemiologic characteristics are shown in Table 1.

Discordant findings

^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT findings were discordant in 65 (62.5%) patients and concordant in 39 (37.5%). Discordant findings were observed in 25 patients (38.4%) with G1 NETs, in 24 (36.9%) with G2 NETs, and 16 (24.7%) with G3 NETs ($p>0.05$). Only in one (2.7%) of 36 patients with G1 tumors (Ki67 index ≤2) ($p<0.05$) and five (12.5%) of 40 with G2 tumors (Ki67 index ≤12%) ($p<0.05$) were ^{18}F-FDG findings more prominent than ^{68}Ga-DOTATATE findings. However, in all six of these patients the ^{18}F-FDG-avid findings were not correlated with NET disease as shown either by biopsy or follow up imaging. The two patients with increased metabolic bowel activity had subsequent colonoscopy that showed in one case large bowel adenocarcinoma and the second inflammatory changes. The remaining four patients

had lung FDG avid abnormalities, all of which benign as confirmed in the follow-up lung CECT. Especially in two patients there was a need for follow-up for 12 months to confirm the inflammatory pathology.

Of the 25 patients with discordant results, 22 (88%) with G1 NETs had ^{68}Ga-DOTATATE-positive findings ($p<0.05$) and nine (56%) of 16 with G3 NETs had ^{18}F-FDG-positive findings ($p<0.05$), confirming that ^{68}Ga-DOTATATE results are predominant with a lower Ki67 index while ^{18}F-FDG results are positive with a higher Ki67 index.

Clinical impact

Considering all cases, the combination of ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT modified therapy in 84 (80.8%) patients. The treatments before the PET/CT scans are listed in Table 2. In 22 (21.1%) patients the modification was based on ^{18}F-FDG findings, in 32 (30.8%) on findings with both radiotracers, and in 50 (48.1%) on ^{68}Ga-DOTATATE findings (Table 3). The most frequent management impact of only ^{18}F-FDG findings was initiation or continuation of chemotherapy in ten (47.6%) patients while the second most frequent was surgery in five (23.8%) patients, followed by active surveillance. The most common treatment modification due to ^{68}Ga-DOTATATE findings was initiation of PRRT in 14 (27.4%) patients, followed by commencement of somatostatin analogs in 12 (23.5%). In general there has been change of medical treatment in 40 pts (38.5%, confirmation of current treatment in 36pts (34.6%), change in surgical planning 15 (14.4%) and cancellation of surgery in 13pts (12.5%).

Table 4 illustrates the histological NET grading in correlation with the PET/CT tracer with the most clinical impact. In 11 of 28 (39.2%) patients with PD NETs the management decision was based only on ^{18}F-FDG results. Only in 1 (2.7%) of 36 patients with G1 tumors (Ki67 index ≤2%) ($p=0.001$) and 10 (12.5%) of 40 with G2 tumors with a Ki index ≤12% ($p=0.003$) was the management changed owing to the ^{18}F-FDG results. There was no statistically significant correlation between presence of chromogranin A in the histological specimen and results with either radiotracer ($p=0.69$ for ^{68}Ga-DOTATATE, $p=0.37$ for ^{18}F-FDG). Overall, ^{68}Ga-DOTATATE was more likely to affect the final decision for tumors with low Ki67 expression, while ^{18}F-FDG was better in tumors with high Ki67 expression, as demonstrated by Figure 1.

Regarding the G2 NET group, we found that in patients with tumors with a Ki67 index ≤12%, ^{68}Ga-DOTATATE made a greater contribution to clinical management than ^{18}F-FDG.

Using Kaplan-Meier plots and log-rank comparisons, survival was found to decline rapidly with increasing histological grade (p=0.001), with estimated survival of 91 months for G1, 59 months for G2, and 48 months for G3.

Using one-way ANOVA, ^{68}Ga-DOTATATE SUV_{max} was significantly higher for G1 than for G3 tumors (p=0.012). However, no significant differences in ^{18}F-FDG-derived SUV_{max} results between tumor grades were detected (p=0.38). As expected, there was a statistically significant negative correlation between Ki67 and ^{68}Ga-DOTATATE SUV_{max} (Spearman rho=-0.374, p=0.001). On the other hand, a significant positive correlation was noted between Ki67 and ^{18}F-FDG SUV_{max} (rho=-0.345, p=0.002). Further analysis showed significant differences in ^{68}Ga-DOTATATE SUV_{max} between tumors with a Ki67 <5% and tumors with a Ki67>5% (p=0.004), while no significance difference in ^{18}F-FDG SUV_{max} values was detected using this cut-off value. Interestingly, Mann-Whitney test showed more significant differences in ^{68}Ga-DOTATATE SUV_{max} for tumours with a Ki67≤12% and with Ki67>12% (p=0.002) and not for ^{18}F-FDG SUV_{max}, indicating that tumours with a Ki67>12% show more aggressive disease behaviour.

Grading patients as zero for no metastasis, 1 for soft tissue metastasis and 2 for bone metastasis, log-rank analysis showed statistically significant differences in survival for patients with bone vs soft tissue or no metastasis (Figs. 2 and 3). This was true for both ^{18}F-FDG (p=0.037) and ^{68}Ga-DOTATATE scans (p=0.047), with estimated survival time significantly reduced in patients with bone metastasis (48 and 49 months for ^{68}Ga-DOTATATE and ^{18}F-FDG respectively) vs. soft tissue (74 and 62 months) or no metastasis (80 and 81 months).

DISCUSSION

Imaging plays a crucial role in the diagnosis and management of NETs, as after histological confirmation of disease, the initial diagnostic work-up and tumor staging form the basis for the decision to perform surgical resection or initiate medical therapy. The small size of NETs makes it difficult for conventional anatomic imaging to visualize the primary tumor or its metastases, given that these modalities are unable to depict specific endocrine features; consequently the diagnostic accuracy of functional imaging is significantly higher than that of conventional imaging [7,11–14].

^{18}F-FDG PET/CT imaging has also been compared with ^{68}Ga-DOTA peptide imaging in several studies that have shown it to have variable sensitivity in detecting NETs [15–22]. However, the presence of increased glucose in NETs highlights an increased propensity for invasion and metastasis, and ^{18}F-FDG PET/CT accordingly has higher sensitivity in delineating disease extent, especially in aggressive and high-grade tumors [23]. Detection of a higher number of lesions is nevertheless not always followed by a change in disease staging and most importantly does not always affect the therapeutic approach. While a number of studies have demonstrated the clinical impact of ^{68}Ga-DOTA peptides, few have compared the clinical impact of both PET tracers in NET patients [24–27].

To the best of our knowledge, our study is the first to determine the clinical impact of combined ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT in such a large histologically proven NET population in correlation with the histological grade. The vast majority of previous studies have compared the diagnostic accuracy of both radiotracers, with a relative lack of information regarding the influence on treatment approach.

Our study demonstrates that routine use of both ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT is not recommended for G1 NETs. In this NET subgroup the clinical impact was influenced predominately by the ^{68}Ga-DOTATATE study, which we suggest should be performed solely. In the G3 NET group the combination of both exams is suggested, with emphasis on the ^{18}F-FDG results in patients with higher Ki67 index values, reflecting a high level of glycolytic metabolism in high-risk patients with aggressive disease and poorer prognosis in whom chemotherapy is favourable [9]. However, ^{68}Ga-DOTATATE should also be considered in this subgroup, especially

in the event of relapse on chemotherapy regimen, as the somatostatin receptor positivity makes PRRT a potential therapeutic option. Jamali et al. have reported that ^{18}F-FDG-positive high-grade gastroenteropancreatic NET patients have benefited from PRRT [28]. Nevertheless, this should be proven by a pre- and post-PRRT ^{68}Ga-DOTA-peptide study to delineate better the tumor burden and further assess treatment response.

The current study demonstrates also that ^{18}F-FDG PET/CT has moderate clinical impact in G2 NETs. We propose that in NET patients with a Ki67 index of ≤12% the use of ^{18}F-FDG PET/CT should be limited and tailored to the individual patient, especially when suspicion of a second synchronous primary tumor is raised by atypical disease distribution or in cases with previous neoplastic process. It should be noted that NETs with a Ki67 index lower than 10% may tend to fall in the low-grade category, which may be why they have been reported to have a better prognosis [29].

Strosberg et al. have proposed chemotherapy as an earlier treatment option for tumors with a Ki67 higher than 10% following PRRT or somatostatin therapy; such tumors show higher ^{18}F-FDG activity, reflecting their high proliferative capacity and aggressive behaviour [30]. Although Ki67 index has been well proven to be correlated with prognostic information in NETs, certain aspects of histological staining, such as intratumoral heterogeneity, may rarely cause false determination of tumor grade, especially in the G2 category, where the nearly flip-flop phenomenon of the dual tracers is more evident [31]. Furthermore, the availability of new treatment regimens has emphasized the need for new prognostic and predictive biomarkers, leading to better assessment of therapeutic response for individual patients [32]. Tumor heterogeneity cannot be fully assessed by tumor biopsy, and this is an area where combined dual-tracer PET/CT offers distinct advantages, even though referring clinicians rely mainly in the histological grading. In our population there have been few patients with discrepant lesions, predominantly in the liver, with discordant findings between 68Ga-DOTATATE and 18F-FDG PET/CT studies. Biopsy from the liver lesions in the same patients showed mildly different Ki67 index (>10% <20%) of patients in the G2 category. In such cases we considered as valid the higher Ki67 value, taking into consideration the tumour aggressiveness that the metabolic avid tumour provides.

The clinical impact of ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE has been well described previously. It has been demonstrated that ^{68}Ga-DOTA-peptide imaging influences the

management of more than half of patients, with a particular impact on initiation or continuation of PRRT or SSA medical therapy on the basis of the demonstration of somatostatin receptor expression [24,33,34]. Our results similarly show that ^{68}Ga-DOTATATE impacted on the management plan in 48% of NET patients. Regarding ^{18}F-FDG, Kayani et al. in a limited cohort, concluded that the use of ^{18}F-FDG led to a change from PRRT to chemotherapy in 25% of patients with intermediate- or high-grade NETs [15]. Our study demonstrated similar results, with ^{18}F-FDG findings impacting on 21% of patients, half of whom had G3 tumors [30].

Recent papers investigated the value of ^{68}Ga-DOTANOC SUV_{max} as a potential prognostic factor [35–37]. We used a cut-off of 5% when relating Ki67 to SUV_{max} based on the study of Panzuto et al. reporting that patients with a Ki67>5% show more aggressive disease behaviour [37]. Our data validated their findings, with significant differences in ^{68}Ga-DOTATATE SUV_{max} according to whether the Ki67 index was above or below 5%. However we found that there is stronger association between aggressive tumour behaviour and functional activity when cutoffs of Ki67>12 is implemented.

The study also showed that SUV_{max} for ^{68}Ga-DOTATATE is related to NET grade, another important prognostic marker. Interestingly there was no relation between FDG SUV_{max} values and tumor grade. The only report with similar findings was by Sharma et al. in a limited population of NET patients with different primary sites [36]. In their study, SUV_{max} for ^{68}Ga-DOTANOC correlated with prognosis, while ^{18}F-FDG SUV_{max} did not. Several reports have indicated that ^{18}F-FDG positivity is associated with a worse prognosis, although to our knowledge most of these studies did not specifically investigate the role of SUV_{max} [22,38]. In our study we found that metastases demonstrated by either tracer correlated with shorter survival time, with bone metastases correlating with the worst prognosis.

In regards to the study limitation, the fact that only patients with histologically proven NETs were enrolled restricted the possibility of specificity measurement. A second limitation of the study includes the histological confirmation from two or more sites of the tumour in patients with discrepant findings in both PET/CT tracers. However it would be unethical and not feasible to have histological confirmation of all the tumour avid lesions.

CONCLUSION

^{18}F-FDG PET/CT has no clinical impact in G1 NETs and moderate impact in G2 NETs. In NETs with a Ki67 index ≤12%, use of ^{18}F-FDG PET/CT should be limited and tailored to the individual patient. However in PD NETs ^{18}F-FDG PET/CT plays a significant clinical role in combination with ^{68}Ga-DOTATATE. ^{68}Ga-DOTATATE SUV_{max} values are related to tumor grade and Ki67 index and can be used prognostically.

REFERENCES

1. Sundin A, Garske U, Orlefors H. Nuclear imaging of neuroendocrine tumours. *Best Pract Res Clin Endocrinol Metab*. 2007;21(1):69-85. doi:10.1016/j.beem.2006.12.003.

2. Patel RC, Kumar U, Lamb DC, et al. Ligand binding to somatostatin receptors induces receptor-specific oligomer formation in live cells. *Proc Natl Acad Sci U S A*. 2002;99(5):3294-3299. doi:10.1073/pnas.042705099.

3. Panagiotidis E, Bomanji J. Role of 18F-fluorodeoxyglucose PET in the study of neuroendocrine tumors. *PET Clin*. 2014;9(1):43-55. doi:10.1016/j.cpet.2013.08.008.

4. Ramage JK, Ahmed A, Ardill J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut*. 2012;61(1):6-32. doi:10.1136/gutjnl-2011-300831.

5. Pettinato C, Sarnelli A, Di Donna M, et al. 68Ga-DOTANOC: biodistribution and dosimetry in patients affected by neuroendocrine tumors. *Eur J Nucl Med Mol Imaging*. 2008;35(1):72-79. doi:10.1007/s00259-007-0587-y.

6. Shastry M, Kayani I, Wild D, et al. Distribution pattern of 68Ga-DOTATATE in disease-free patients. *Nucl Med Commun*. 2010;31(12):1025-1032. doi:10.1097/MNM.0b013e32833f635e.

7. Gabriel M, Decristoforo C, Kendler D, et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. *J Nucl Med Off Publ Soc Nucl Med*. 2007;48(4):508-518.

8. Kowalski J, Henze M, Schuhmacher J, Mäcke HR, Hofmann M, Haberkorn U. Evaluation of Positron Emission Tomography Imaging Using [68Ga]-DOTA-D Phe1-Tyr3-Octreotide in Comparison to [111In]-DTPAOC SPECT. First Results in Patients with Neuroendocrine Tumors. *Mol Imaging Biol*. 2003;5(1):42-48. doi:10.1016/S1536-1632(03)00038-6.

9. Binderup T, Knigge U, Loft A, Federspiel B, Kjaer A. 18F-Fluorodeoxyglucose Positron Emission Tomography Predicts Survival of Patients with Neuroendocrine Tumors. *Clin Cancer Res*. 2010;16(3):978-985. doi:10.1158/1078-0432.CCR-09-1759.

10. Rindi G, Klöppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch Int J Pathol*. 2006;449(4):395-401. doi:10.1007/s00428-006-0250-1.

11. Ambrosini V, Nanni C, Zompatori M, et al. 68Ga-DOTA-NOC PET/CT in comparison with CT for the detection of bone metastasis in patients with neuroendocrine tumours. *Eur J Nucl Med Mol Imaging*. 2010;37(4):722-727. doi:10.1007/s00259-009-1349-9.

12. Albanus DR, Apitzsch J, Erdem Z, et al. Clinical value of 68Ga-DOTATATE-PET/CT compared to stand-alone contrast enhanced CT for the detection of extra-hepatic metastases

in patients with neuroendocrine tumours (NET). *Eur J Radiol*. June 2015. doi:10.1016/j.ejrad.2015.06.024.

13. Schraml C, Schwenzer NF, Sperling O, et al. Staging of neuroendocrine tumours: comparison of [68Ga]DOTATOC multiphase PET/CT and whole-body MRI. *Cancer Imaging*. 2013;13(1):63-72. doi:10.1102/1470-7330.2013.0007.

14. Treglia G, Castaldi P, Rindi G, Giordano A, Rufini V. Diagnostic performance of Gallium-68 somatostatin receptor PET and PET/CT in patients with thoracic and gastroenteropancreatic neuroendocrine tumours: a meta-analysis. *Endocrine*. 2012;42(1):80-87. doi:10.1007/s12020-012-9631-1.

15. Kayani I, Bomanji JB, Groves A, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using68Ga-DOTATATE (DOTA-DPhe1,Tyr3-octreotate) and18F-FDG. *Cancer*. 2008;112(11):2447-2455. doi:10.1002/cncr.23469.

16. Kayani I, Conry BG, Groves AM, et al. A Comparison of 68Ga-DOTATATE and 18F-FDG PET/CT in Pulmonary Neuroendocrine Tumors. *J Nucl Med*. 2009;50(12):1927-1932. doi:10.2967/jnumed.109.066639.

17. Has Simsek D, Kuyumcu S, Turkmen C, et al. Can complementary 68Ga-DOTATATE and 18F-FDG PET/CT establish the missing link between histopathology and therapeutic approach in gastroenteropancreatic neuroendocrine tumors? *J Nucl Med Off Publ Soc Nucl Med*. 2014;55(11):1811-1817. doi:10.2967/jnumed.114.142224.

18. Krausz Y, Freedman N, Rubinstein R, et al. 68Ga-DOTA-NOC PET/CT Imaging of Neuroendocrine Tumors: Comparison with 111In-DTPA-Octreotide (OctreoScan®). *Mol Imaging Biol*. 2011;13(3):583-593. doi:10.1007/s11307-010-0374-1.

19. Naswa N, Sharma P, Gupta SK, et al. Dual Tracer Functional Imaging of Gastroenteropancreatic Neuroendocrine Tumors Using 68Ga-DOTA-NOC PET-CT and 18F-FDG PET-CT: Competitive or Complimentary? *Clin Nucl Med*. 2014;39(1):e27-e34. doi:10.1097/RLU.0b013e31827a216b.

20. Jindal T, Kumar A, Venkitaraman B, et al. Evaluation of the role of [18F]FDG-PET/CT and [68Ga]DOTATOC-PET/CT in differentiating typical and atypical pulmonary carcinoids. *Cancer Imaging*. 2011;11(1):70-75. doi:10.1102/1470-7330.2011.0010.

21. Lococo F, Perotti G, Cardillo G, et al. Multicenter comparison of 18F-FDG and 68Ga-DOTA-peptide PET/CT for pulmonary carcinoid. *Clin Nucl Med*. 2015;40(3):e183-189. doi:10.1097/RLU.0000000000000641.

22. 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(4):293-299. doi:10.1159/000368609.

23. Howe JR. The Supporting Role of 18FDG-PET in Patients with Neuroendocrine Tumors. *Ann Surg Oncol*. 2015;22(7):2107-2109. doi:10.1245/s10434-015-4484-5.

24. Ambrosini V, Campana D, Bodei L, et al. 68Ga-DOTANOC PET/CT Clinical Impact in Patients with Neuroendocrine Tumors. *J Nucl Med*. 2010;51(5):669-673. doi:10.2967/jnumed.109.071712.

25. Frilling A, Sotiropoulos GC, Radtke A, et al. The Impact of 68Ga-DOTATOC Positron Emission Tomography/Computed Tomography on the Multimodal Management of Patients With Neuroendocrine Tumors: *Ann Surg*. 2010;252(5):850-856. doi:10.1097/SLA.0b013e3181fd37e8.

26. Haug AR, Cindea-Drimus R, Auernhammer CJ, et al. The Role of 68Ga-DOTATATE PET/CT in Suspected Neuroendocrine Tumors. *J Nucl Med*. 2012;53(11):1686-1692. doi:10.2967/jnumed.111.101675.

27. Deppen SA, Liu E, Blume JD, et al. Safety and Efficacy of 68Ga-DOTATATE PET/CT for Diagnosis, Staging, and Treatment Management of Neuroendocrine Tumors. *J Nucl Med Off Publ Soc Nucl Med*. 2016;57(5):708-714. doi:10.2967/jnumed.115.163865.

28. Jamali M, Chetty R. Predicting prognosis in gastroentero-pancreatic neuroendocrine tumors: an overview and the value of Ki-67 immunostaining. *Endocr Pathol*. 2008;19(4):282-288. doi:10.1007/s12022-008-9044-0.

29. Pavel M, Baudin E, Couvelard A, et al. ENETS Consensus Guidelines for the Management of Patients with Liver and Other Distant Metastases from Neuroendocrine Neoplasms of Foregut, Midgut, Hindgut, and Unknown Primary. *Neuroendocrinology*. 2012;95(2):157-176. doi:10.1159/000335597.

30. Strosberg JR. Systemic treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETS): current approaches and future options. *Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol*. 2014;20(2):167-175. doi:10.4158/EP13262.RA.

31. Yang Z, Tang LH, Klimstra DS. Effect of tumor heterogeneity on the assessment of Ki67 labeling index in well-differentiated neuroendocrine tumors metastatic to the liver: implications for prognostic stratification. *Am J Surg Pathol*. 2011;35(6):853-860. doi:10.1097/PAS.0b013e31821a0696.

32. Hofman MS, Hicks RJ. Changing paradigms with molecular imaging of neuroendocrine tumors. *Discov Med*. 2012;14(74):71–81.

33. Herrmann K, Czernin J, Wolin EM, et al. Impact of 68Ga-DOTATATE PET/CT on the management of neuroendocrine tumors: the referring physician's perspective. *J Nucl Med Off Publ Soc Nucl Med*. 2015;56(1):70-75. doi:10.2967/jnumed.114.148247.

34. Deppen SA, Blume J, Bobbey AJ, et al. 68Ga-DOTATATE Compared with 111In-DTPA-Octreotide and Conventional Imaging for Pulmonary and Gastroenteropancreatic Neuroendocrine Tumors: A Systematic Review and Meta-Analysis. *J Nucl Med Off Publ Soc Nucl Med*. 2016;57(6):872-878. doi:10.2967/jnumed.115.165803.

35. 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 Off Publ Soc Nucl Med*. 2010;51(3):353-359. doi:10.2967/jnumed.109.066662.

36. Sharma P, Naswa N, Kc SS, et al. Comparison of the prognostic values of 68Ga-DOTANOC PET/CT and 18F-FDG PET/CT in patients with well-differentiated neuroendocrine tumor. *Eur J Nucl Med Mol Imaging*. 2014;41(12):2194-2202. doi:10.1007/s00259-014-2850-3.

37. 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(4):1083-1092. doi:10.1677/erc.1.01017.

38. Bahri H, Laurence L, Edeline J, et al. High prognostic value of 18F-FDG PET for metastatic gastroenteropancreatic neuroendocrine tumors: a long-term evaluation. *J Nucl Med Off Publ Soc Nucl Med*. 2014;55(11):1786-1790. doi:10.2967/jnumed.114.144386.

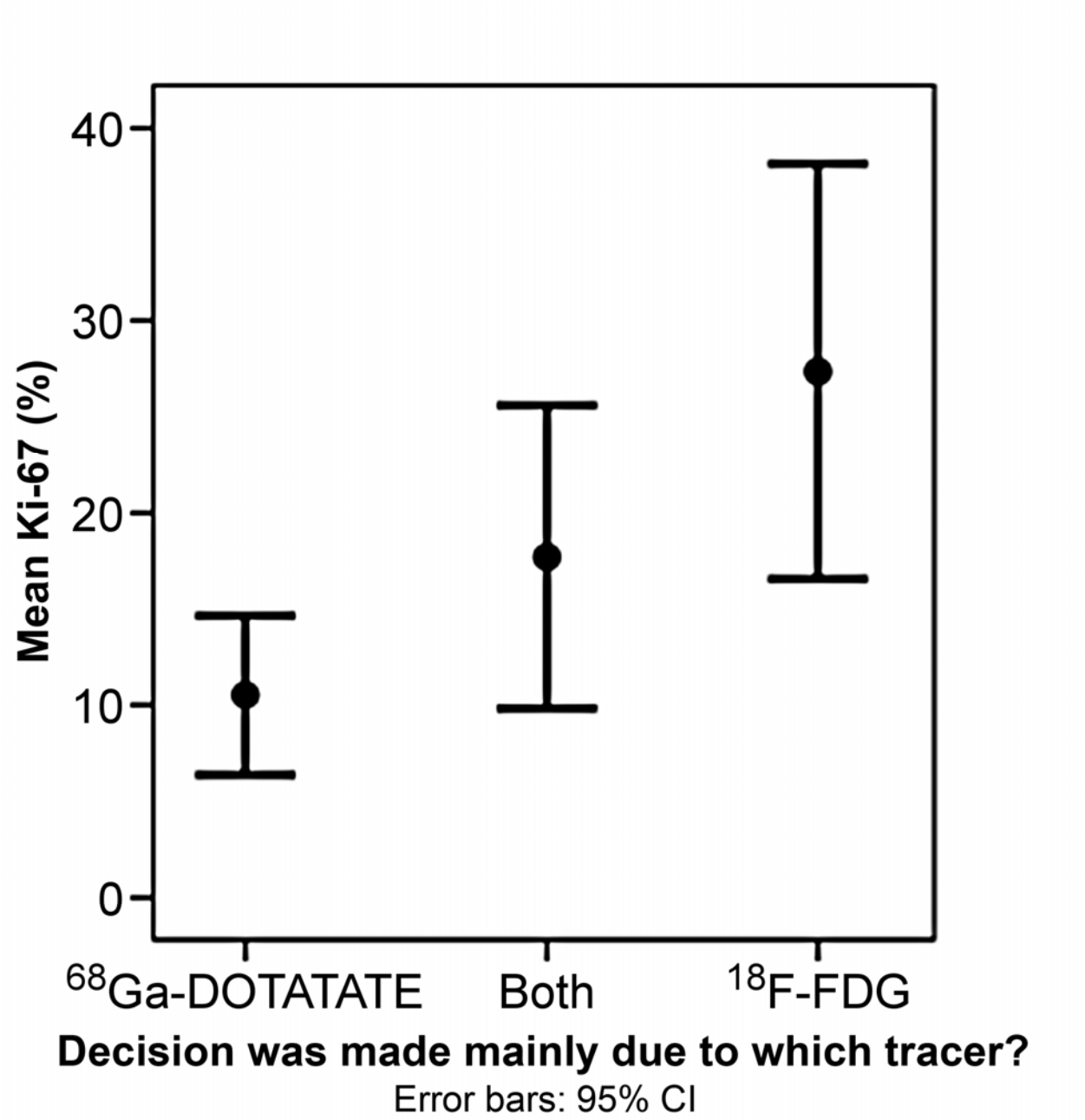

FIGURE 1. Correlation between mean Ki67 (%) of NETs and PET/CT tracer results on which the clinical management decision was based

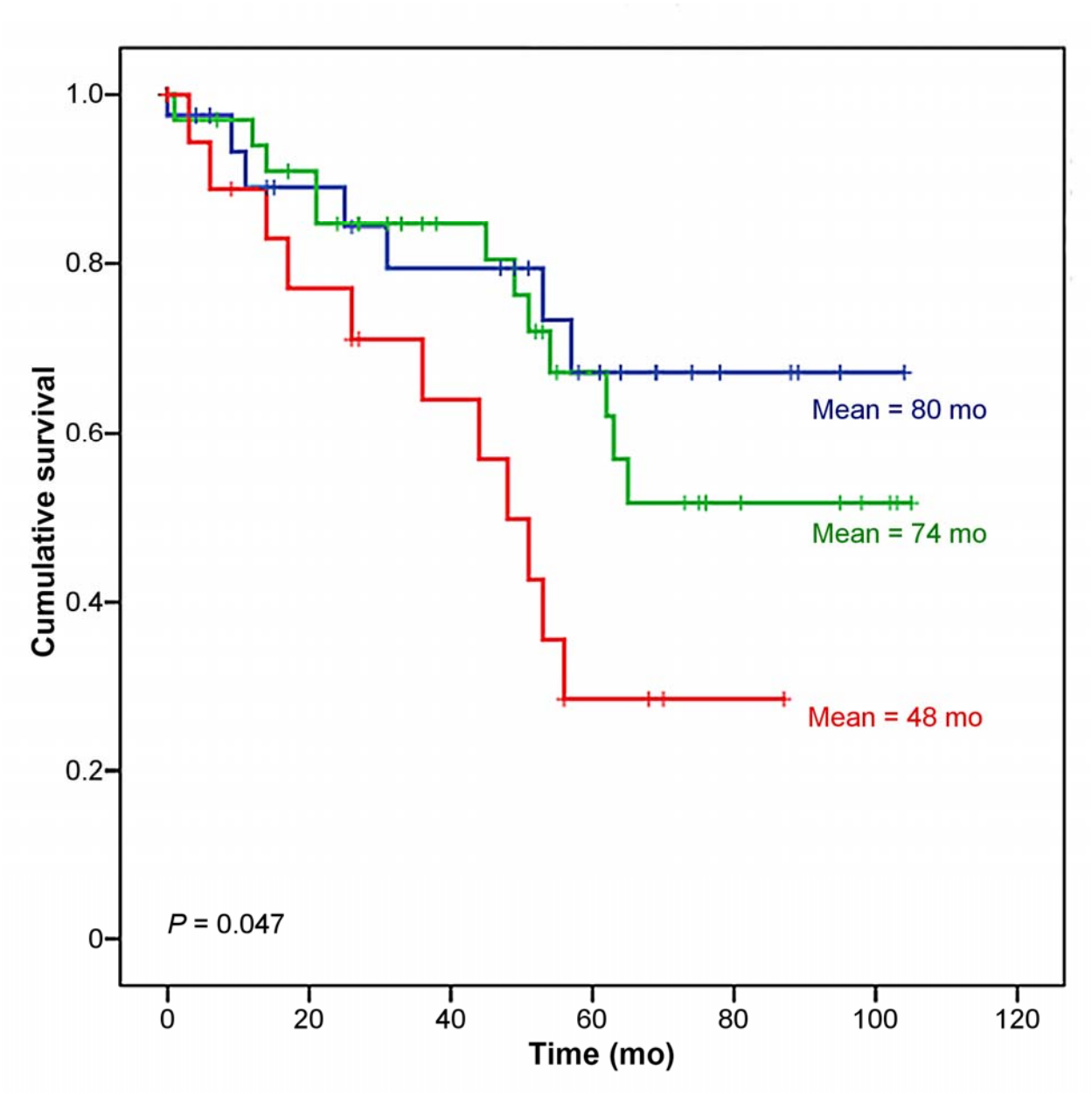

FIGURE 2: Survival curves for patients with bone (*red*) vs soft tissue (*green*) or no metastasis (*blue*) detected using ^{68}Ga-DOTATATE

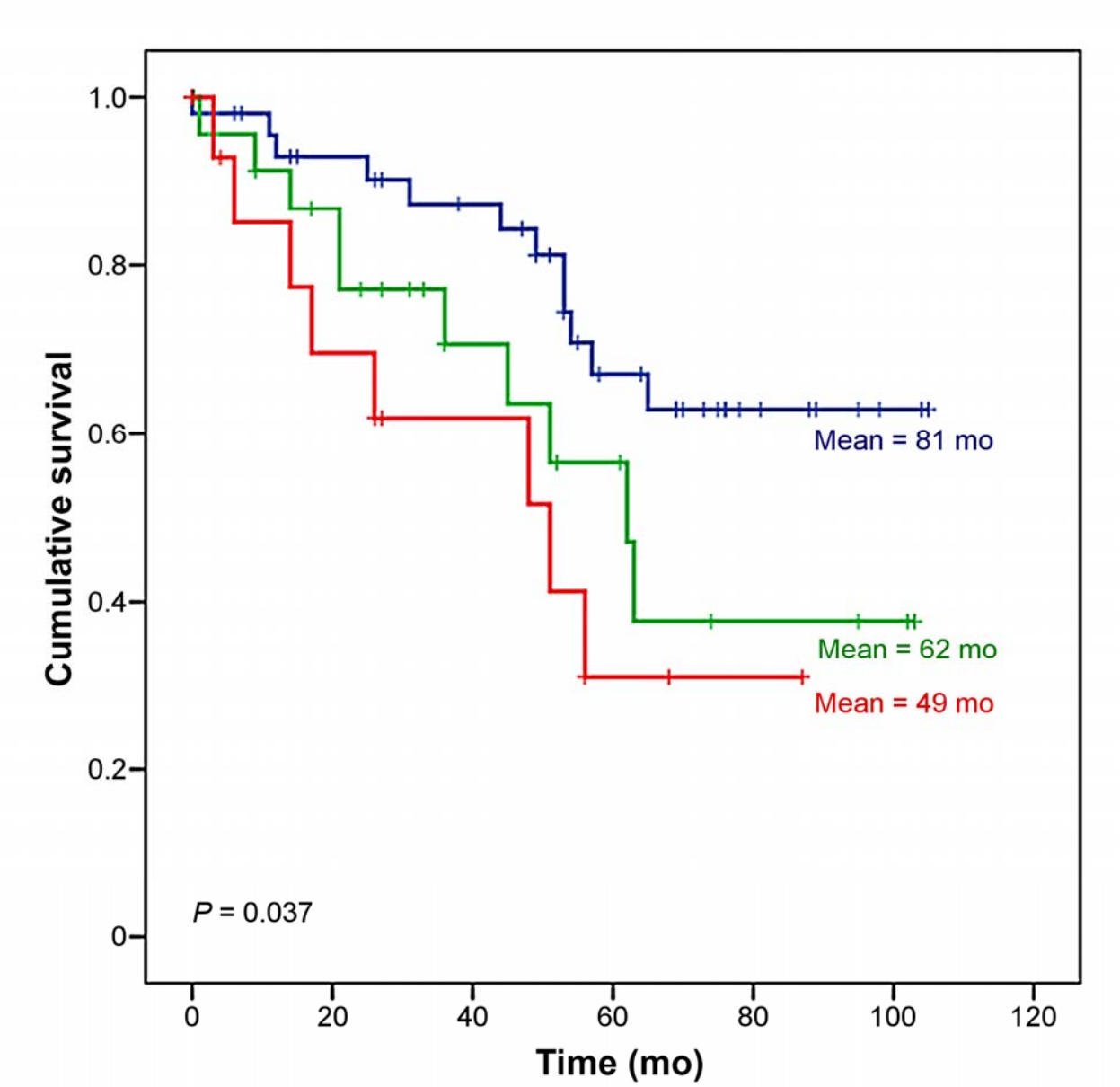

FIGURE 3: Survival curves for patients with bone (*red*) vs soft tissue (*green*) or no metastasis (*blue*) detected using ^{18}F-FDG

TABLE 1. Patient clinical and epidemiologic characteristics						
	n	%			n	%
Female	49	47.1		**Primary tumor site**	33	31.7
Male	55	52.9		CUP	31	29.8
Age (years)				Midgut	16	15.4
Median	58			Lung	11	10.6
Range	20–90	14.2		Pancreas	5	4.8
				Stomach	4	3.8
Indication for PET/CT				Ovary	3	2.9
Recurrence	57	54.8		Oesophagus	33	31.7
Follow-up	13	12.5				
Equivocal conventional imaging	13	12.5		**Histopathologic grade of NETs**		
Staging	11	10.6		G1 well differentiated	36	34.6
Consideration of starting PRRT	10	9.6		G2 moderately differentiated	40	38.5
Recurrence	57	54.8		G3 poorly differentiated	28	26.9
Ki67 (%)				**Chromogranin A on histology**		
Median	6.5			Positive	88	84.6
Range	1–80	20.2		Negative	13	12.5
				Positive (weak)	3	2.9

Values are n with percentage or median with IQR

SD, Standard Deviation; PRRT, Peptide Receptor Radionuclide Therapy; CI, Conventional Imaging; CUP, Cancer of Unknown Primary

TABLE 2. Treatment before ^{18}F-FDG and ^{68}Ga-DOTATATE PET/CT

	No.	%
Surgery	21	20.2
Active surveillance	20	19.2
Long Acting SSA	13	12.5
Short Acting SSA		
Nil	12	11.5
CMT	11	10.6
Surgery, CMT	10	9.6
Further diagnostic procedure	5	4.8
Surgery, Interferon	4	3.8
Surgery, Y-90, SSA	4	3.8
PRRT	1	1.0
Surgery, CMT, SSA, TACE, LDT	1	1.0
Surgery, RFA	1	1.0
LDT	1	1.0

SSA, Somatostatin Analogs; CMT, Chemotherapy; Y-90, ^{90}Y-DOTATATE therapy; PRRT, Peptide receptor Radionuclide Therapy; TACE, Transcatheter Arterial Chemoembolization; LDT, Liver Directed Therapy; RFA, Radiofrequency Ablation

TABLE 3. Management after ^{18}F-FDG and ^{68}Ga-DOTATATE PET/CT based on PET/CT findings

Management post ^{18}F-FDG and ^{68}Ga-DOTATATE scans	PET/CT tracer findings on which clinical management was based			Total
	^{68}Ga-DOTATATE	Both	^{18}F-FDG	
Active surveillance	5	22	4	31 (29.8%)
Chemotherapy	8	2	10	20 (19.2%)
Chemotherapy, TACE	0	1	0	1 (1%)
Everolimus	1	0	0	1 (1%)
Interferon	0	2	0	2 (1.9%)
PRRT	14	1	0	15 (14.4%)
RFA	0	0	1	1 (1%)
SSA	11	2	2	15 (14.4%)
Surgery	9	2	5	16 (15.4%)
LDT	2	0	0	2 (1.9%)
Total	50	32	22	104

Abbreviations as in Table 2

TABLE 4. Correlation of histological NET grade with ^{18}F-FDG and ^{68}Ga-DOTATATE PET/CT findings

NET histological grade	PET/CT tracer findings on which clinical management was based			
	^{68}Ga-DOTATATE	Both	^{18}F-FDG	Total
G1	25	10	1	36 (34.6%)
G2	16	14	10	40 (38.4%)
G3	9	8	11	28 (27%)
Total	50	32	22	104