Comparison of the Impact of ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT on Clinical Management in Patients with Neuroendocrine Tumors

Emmanouil Panagiotidis[1], Alshaima Alshammari[1], Sofia Michopoulou[1], Evangelia Skoura[1], Keval Naik[2], Emmanouil Maragkoudakis[2], Mullan Mohmaduvesh[2], Mohammed Al-Harbi[1], Maria Belda[1], Martyn E. Caplin[2], Christos Toumpanakis[2], and Jamshed Bomanji[1]

[1]Institute of Nuclear Medicine, University College London Hospital, London, United Kingdom; and [2]Neuroendocrine Tumour Unit, ENETS Centre of Excellence, Royal Free Hospital, London, United Kingdom

This study aimed to assess the clinical impact of ^{68}Ga-DOTATATE and ^{18}F-FDG with respect to the management plan and to evaluate the prognostic value of both tracers. **Methods:** A total of 104 patients (55 male and 49 female; median age, 58 y; range, 20–90 y) with histologically proven neuroendocrine tumors (NETs) underwent both ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT. Twenty-eight patients (26.9%) had poorly differentiated tumors, and 76 (73.1%) had well-differentiated tumors. PET/CT results and SUVs were compared with prognostic factors such as histologic grade (G1, G2, or G3, for low-grade [well differentiated], intermediate-grade [moderately differentiated], and high-grade [poorly differentiated], respectively), chromogranin A, and proliferation index (Ki-67). **Results:** The ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT findings were discordant in 65 patients (62.5%) and concordant in 39 patients (37.5%). The results changed the therapeutic plan in 84 patients (80.8%). In 22 patients (21.1%), decision making was based on the ^{18}F-FDG findings; in 32 (30.8%), on the findings with both radiotracers; and in 50 (48.1%), on the ^{68}Ga-DOTATATE findings. The most frequent management decision based on ^{18}F-FDG was initiation of chemotherapy (10 patients, 47.6%). The most common treatment decision due to ^{68}Ga-DOTATATE was initiation of peptide receptor radionuclide therapy (14 patients, 27.4%). In 11 (39.2%) of 28 patients with poorly differentiated NETs, the management decision was based on only the ^{18}F-FDG results. For ^{68}Ga-DOTATATE, SUV_{max} was higher for G1 tumors and lower for G3 tumors ($P = 0.012$). However, no significant differences in ^{18}F-FDG-derived SUVs were observed between different grades ($P = 0.38$). The Mann–Whitney test showed significant differences in ^{68}Ga-DOTATATE SUV_{max} between tumors with a Ki-67 of less than 5% and tumors with a Ki-67 of more than 5% ($P = 0.004$), without significance differences in ^{18}F-FDG SUV_{max}. Log-rank analysis showed statistically significant differences in survival for patients with bone metastasis versus soft-tissue or no metastasis for both ^{18}F-FDG ($P = 0.037$) and ^{68}Ga-DOTATATE ($P = 0.047$). Overall survival declined rapidly with increasing grade ($P = 0.001$), at an estimated 91 mo for G1, 59 mo for G2, and 48 mo for G3. **Conclusion:** ^{18}F-FDG PET/CT had no clinical impact on G1 NETs and a moderate impact on G2 NETs. However, in poorly differentiated NETs, ^{18}F-FDG PET/CT plays a significant clinical role in combination with ^{68}Ga-DOTATATE. ^{68}Ga DOTATATE SUV_{max} relates to grade and Ki-67 and can be used prognostically.

Key Words: ^{68}Ga-DOTATATE; ^{18}F-FDG PET/CT; neuroendocrine tumors; clinical impact; prognosis

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Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies ranging from well-differentiated, slowly growing tumors to poorly differentiated neoplasms, which are aggressive and less frequent (*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, after the advent of PET/CT systems, novel PET tracers have been developed and investigated, including biogenic amine precursors (e.g., ^{18}F-dihydroxyphenylalanine), somatostatin analogs (^{68}Ga-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 or 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 an overall poorer prognosis (*9*). In fact, a strong association has recently been shown between higher ^{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 because of 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

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For correspondence or reprints contact: Emmanouil Panagiotidis, Institute of Nuclear Medicine, University College London Hospital, 235 Euston Rd., London NW1 2BU, United Kingdom.
E-mail: m_panagiotidis@yahoo.com
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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 SUV_{max} for both tracers.

MATERIALS AND METHODS

Patient Population

We retrospectively reviewed the findings for the first 104 patients (55 male and, 49 female; age range, 20–90 y; median, 58 y) with histologically proven NETs who underwent contemporaneous ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT at our institution between September 2006 and February 2014. The interval between the two studies ranged from 0 to 3 wk (median, 1 wk), which was considered sufficiently short given that NETs show relatively slow progression.

Each case of NET was 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 Ki-67 index in staging of NETs along with immunohistochemistry (*10*) The study was approved by the institutional review board (study 15N10051), and all subjects gave written informed consent.

Image Acquisition

Images were acquired 1 h after injection of 370 MBq of ^{18}F-FDG or 45–60 min after injection of 120–200 MBq of ^{68}Ga-DOTATATE. No adverse effects were observed after the injection of ^{68}Ga-DOTATATE or ^{18}F-FDG. Imaging was performed using a dedicated Discovery ST PET/CT unit, with a 16-detector CT component (GE Healthcare); whole-body examinations (brain to midthigh) were performed with the patient supine. The CT exposure factors were 120 kVp and 80 mA in 0.8 s. Maintaining patient position, a whole-body PET emission scan was performed over an area identical to that covered by the CT scan. The PET acquisition was performed in 3 dimensions at 4 min per bed position, using a 9-slice overlap. The 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. The 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 3.75 and 2.5 mm thick using a soft-tissue algorithm.

Image Interpretation

The ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT images were interpreted in consensus by an experienced dedicated nuclear medicine physician and a dual-accredited radiologist/nuclear medicine physician. For the ^{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*). The ^{68}Ga-DOTATATE scanning was performed after discontinuation of short-acting somatostatin analogs for 72 h and long-acting somatostatin analogs for 28 d. The findings of the two modalities were compared with each other and with the histologic findings. Furthermore, SUV_{max} was calculated by measuring the maximum concentration of the labeled tracer (kBq/mL) in the lesion divided by the decay-corrected injected activity (kBq) and normalized for body weight.

Clinical Impact

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

Statistical Analysis

Metric data such as age were expressed as mean ± SD. One-way ANOVA was used to assess differences in SUV_{max} across grades for both ^{68}Ga-DOTATATE and ^{18}F-FDG. The Mann–Whitney test was used to assess for differences in SUV_{max} between a Ki-67 of less than 5% and a Ki-67 of more than 5%, as well as a Ki-67 threshold of 12%, for both ^{68}Ga-DOTATATE and ^{18}F-FDG. A P value of less than 0.05 was considered significant. Statistical analysis was performed with SPSS software (version 22.0; IBM).

The Spearman correlation coefficient was used to assess for a correlation between the SUV_{max} for either tracer and Ki-67. Kaplan–Meier survival analysis was performed to assess the prognostic value of the ^{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 metastases will result in statistically significant differences in survival. Finally, the prognostic value of histologic grade and Ki-67 regarding survival was also evaluated.

RESULTS

The clinical and epidemiologic characteristics of the 104 patients are shown in Table 1.

Discordant Findings

The ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT findings were discordant in 65 patients (62.5%) and concordant in 39 (37.5%). Discordant findings were observed in 25 patients (38.4%) with G1 NETs (low-grade: well differentiated), in 24 (36.9%) with G2 NETs (intermediate-grade: moderately differentiated), and in 16 (24.7%) with G3 NETs (high-grade: poorly differentiated) ($P > 0.05$). In only 1 (2.7%) of 36 patients with G1 tumors (Ki-67 ≤ 2) ($P < 0.05$) and 5 (12.5%) of 40 with G2 tumors (Ki-67 ≤ 12%) ($P < 0.05$) were the ^{18}F-FDG findings more prominent than the ^{68}Ga-DOTATATE findings. However, in all 6 of these patients the ^{18}F-FDG–avid findings did not correlate with NET disease as shown either by biopsy or by follow-up imaging. The two patients with increased metabolic bowel activity underwent a subsequent colonoscopy that showed, in one case, large-bowel adenocarcinoma and, in the second, inflammatory changes. The remaining 4 patients had lung ^{18}F-FDG–avid abnormalities, all of which were benign as confirmed on follow-up lung contrast-enhanced CT. In 2 patients in particular, there was a need for follow-up for 12 mo 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 9 (56%) of 16 with G3 NETs had ^{18}F-FDG–positive findings ($P < 0.05$), confirming that ^{68}Ga-DOTATATE is positive predominantly with a lower Ki-67 whereas ^{18}F-FDG is positive with a higher Ki-67.

Clinical Impact

Considering all cases, the combination of ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT modified therapy in 84 patients (80.8%). The treatments before the PET/CT scans are listed in Table 2. In 22 patients (21.1%), the modification was based on ^{18}F-FDG findings; in 32 (30.8%), on the findings with both radiotracers; and in 50 (48.1%), on the ^{68}Ga-DOTATATE findings (Table 3). The most frequent management impact of only ^{18}F-FDG findings was initiation or continuation of chemotherapy in 10 patients (47.6%), whereas the second most frequent was surgery in 5 patients (23.8%), followed by active surveillance. The most common treatment modification due to ^{68}Ga-DOTATATE findings was initiation of PRRT in 14

TABLE 1
Clinical and Epidemiologic Characteristics of the Patients

Characteristic	*n*	Characteristic	*n*
Sex (*n*)		Primary site (*n*)	
Female	49 (47.1%)	CUP	33 (31.7%)
Male	55 (52.9%)	Midgut	31 (29.8%)
Age (y)		Lung	16 (15.4%)
Median	58	Pancreas	11 (10.6%)
Interquartile range	20–90	Stomach	5 (4.8%)
PET/CT indication		Ovary	4 (3.8%)
Recurrence	57 (54.8%)	Esophagus	3 (2.9%)
Follow-up	13 (12.5%)	Grade (*n*)	
Equivocal CI	13 (12.5%)	G1	36 (34.6%)
Staging	11 (10.6%)	G2	40 (38.5%)
Before PRRT	10 (9.6%)	G3	28 (26.9%)
Recurrence	57 (54.8%)	Chromogranin A (*n*)	
Ki-67 (%)		Strongly positive	88 (84.6%)
Median	6.5	Negative	13 (12.5%)
Interquartile range	1–80	Weakly positive	3 (2.9%)

CUP = cancer of unknown primary; CI = conventional imaging.

patients (27.4%), followed by commencement of somatostatin analogs in 12 (23.5%). In general, there was a change of medical treatment in 40 patients (38.5%: confirmation of current treatment in 36 patients (34.6%), change in surgical planning in 15 (14.4%), and cancellation of surgery in 13 (12.5%).

Table 4 correlates grade with the PET/CT tracer that had the greatest clinical impact. In 11 of 28 patients (39.2%) with poorly differentiated NETs, the management decision was based on only the ^{18}F-FDG results. In only 1 (2.7%) of 36 patients with G1 tumors (Ki-67 $\leq$ 2%) ($P = 0.001$) and 10 (12.5%) of 40 with G2 tumors (Ki-67 $\leq$ 12%) ($P = 0.003$) was the management changed because of the ^{18}F-FDG results. There was no statistically significant correlation between the presence of chromogranin A in the histologic specimen and the 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 a low Ki-67 expression, whereas ^{18}F-FDG was better in tumors with a high Ki-67 expression, as demonstrated by Figure 1. Regarding the G2 group, we found that in patients with tumors with a Ki-67 of no more than 12%, ^{68}Ga-DOTATATE made a greater contribution to clinical management than did ^{18}F-FDG.

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

Using 1-way ANOVA, ^{68}Ga-DOTATATE SUV_{max} was significantly higher for G1 tumors than for G3 ($P = 0.012$). However, no significant differences in ^{18}F-FDG–derived SUV_{max} results between grades were detected ($P = 0.38$). As expected, there was a statistically significant negative correlation between Ki-67 and ^{68}Ga-DOTATATE SUV_{max} (Spearman $\rho = -0.374$, $P = 0.001$). On the other hand, a significant positive correlation was noted between Ki-67 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 Ki-67 of less than 5% and tumors with a Ki-67 of more than 5% ($P = 0.004$), whereas no significance difference in ^{18}F-FDG SUV_{max} was detected using this cutoff. Interestingly, the Mann–Whitney test showed more statistically significant differences in SUV_{max} for tumors with a Ki-67 of 12% or less than for those with a Ki-67 of more than 12%

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

Treatment	*n*
Surgery	21 (20.2%)
Active surveillance	20 (19.2%)
Long-acting SSA	13 (12.5%)
None	12 (11.5%)
CMT	11 (10.6%)
Surgery, CMT	10 (9.6%)
Further diagnostic procedure	5 (4.8%)
Surgery, interferon	4 (3.8%)
Surgery, ^{90}Y, SSA	4 (3.8%)
PRRT	1 (1.0%)
Surgery, CMT, SSA, TACE, LDT	1 (1.0%)
Surgery, radiofrequency ablation	1 (1.0%)
LDT	1 (1.0%)

SSA = somatostatin analogs; CMT = chemotherapy; ^{90}Y = ^{90}Y-DOTATATE therapy; TACE = transcatheter arterial chemoembolization; LDT = liver-directed therapy.

TABLE 3
Management Based on ^{18}F-FDG and ^{68}Ga-DOTATATE PET/CT Findings

Management	Findings on which management was based			Total
	^{68}Ga-DOTATATE	^{18}F-FDG	Both	
Active surveillance	5	4	22	31 (29.8%)
Chemotherapy	8	10	2	20 (19.2%)
Chemotherapy, TACE	0	0	1	1 (1%)
Everolimus	1	0	0	1 (1%)
Interferon	0	0	2	2 (1.9%)
PRRT	14	0	1	15 (14.4%)
Radiofrequency ablation	0	1	0	1 (1%)
Somatostatin analogs	11	2	2	15 (14.4%)
Surgery	9	5	2	16 (15.4%)
Liver-directed therapy	2	0	0	2 (1.9%)
Total	50	22	32	104

TACE = transcatheter arterial chemoembolization.

($P = 0.002$) for ^{68}Ga-DOTATATE but not for ^{18}F-FDG, indicating that tumors with a Ki-67 of more than 12% are more aggressive.

Using a grade of 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 metastasis versus soft-tissue or no metastasis (Figs. 2 and 3). This was true both for ^{18}F-FDG scans ($P = 0.037$) and for ^{68}Ga-DOTATATE scans ($P = 0.047$), with estimated survival significantly reduced in patients with bone metastasis (48 and 49 mo for ^{68}Ga-DOTATATE and ^{18}F-FDG, respectively) versus those with soft-tissue metastasis (74 and 62 mo) or no metastasis (80 and 81 mo).

DISCUSSION

Imaging plays a crucial role in the diagnosis and management of NETs, because the initial diagnostic work-up and staging after histologic confirmation form the basis for the decision on whether to perform surgical resection or to 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*).

TABLE 4
Correlation of Grade with ^{18}F-FDG and ^{68}Ga-DOTATATE PET/CT Findings

Grade	Findings on which management was based			Total
	^{68}Ga-DOTATATE	^{18}F-FDG	Both	
G1	25	1	10	36 (34.6%)
G2	16	10	14	40 (38.4%)
G3	9	11	8	28 (27%)
Total	50	22	32	104

^{18}F-FDG PET/CT imaging has also been compared with ^{68}Ga-DOTA peptide imaging in several studies, which 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 stage and, most importantly, does not always affect the therapeutic approach. Although several 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 grade. Most 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 examinations is suggested, with emphasis on the ^{18}F-FDG results in patients with higher Ki-67 values, reflecting a high level of glycolytic metabolism in high-risk patients with aggressive disease and poorer prognosis in whom chemotherapy is favorable (*9*). However, ^{68}Ga-DOTATATE should also be considered in this subgroup, especially in the event of a

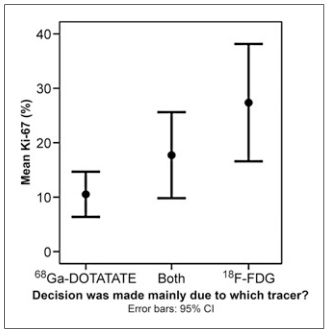

FIGURE 1. Correlation between mean Ki-67 of NETs and PET/CT tracer results on which clinical management decision was based.

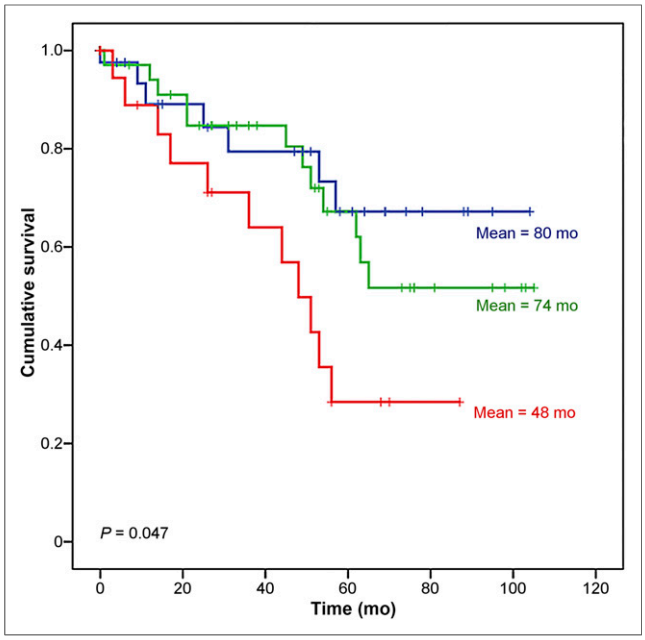

FIGURE 2. Survival curves for patients with bone metastasis (red) vs. soft-tissue metastasis (green) or no metastasis (blue) detected using ^{68}Ga-DOTATATE.

relapse during a 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 better delineate the tumor burden and further assess treatment response.

The current study demonstrates also that ^{18}F-FDG PET/CT has a moderate clinical impact in G2 NETs. We propose that in NET patients with a Ki-67 of 12% or less, 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 an atypical disease distribution or when the patient had a previous neoplastic process. NETs with a Ki-67 of lower than 10% may tend to fall into the low-grade category, which may be why the patients in such cases have been reported to have a better prognosis (*29*).

Strosberg et al. have proposed chemotherapy as an earlier treatment option for tumors with a Ki-67 of higher than 10% after PRRT or somatostatin therapy; such tumors show higher ^{18}F-FDG activity, reflecting their high proliferative capacity and aggressive behavior (*30*). Although the correlation between Ki-67 and prognostic information in NETs has been well proven, certain aspects of histologic staining, such as intratumoral heterogeneity, may rarely cause a false determination of grade, especially in the G2 category, in which 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 that can lead to better assessment of therapeutic response for individual patients (*32*). Tumor heterogeneity cannot be fully assessed by tumor biopsy, and this is an area in which combined dual-tracer PET/CT offers distinct advantages even though referring clinicians rely mainly on the histologic grading. In our population, there have been few patients with discordant findings between ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT studies, predominantly in the liver. Biopsy of the liver lesions in the same patients showed a mildly different Ki-67 value (>10% and <20%) for patients in the G2 category. In such cases, we considered as valid the higher Ki-67 value, taking into consideration the aggressiveness of metabolically active tumor.

The clinical impact of ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE has been well described previously. ^{68}Ga-DOTA-peptide imaging has been shown to influence the management of more than half of patients, with a particular impact on initiation or continuation of PRRT or somatostatin analog medical therapy based on the demonstration of somatostatin receptor expression (*24,33,34*). Our results similarly show that ^{68}Ga-DOTATATE affected the management plan in 48% of NET patients. Regarding ^{18}F-FDG, Kayani et al., in a limited cohort, concluded that its use 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 affecting 21% of patients, half of whom had G3 tumors (*30*).

Recent papers have investigated the value of ^{68}Ga-DOTANOC SUV_{max} as a potential prognostic factor (*35–37*). We used a cutoff of 5% when relating Ki-67 to SUV_{max} based on the study of Panzuto et al. reporting that patients with a Ki-67 of more than 5% show more aggressive disease (*37*). Our data validated their findings, with significant differences in ^{68}Ga-DOTATATE SUV_{max} according to whether the Ki-67 was above or below 5%. However, we found that there is a stronger association between aggressive tumor behavior and functional activity when a Ki-67 cutoff of 12 is implemented.

The study also showed that the SUV_{max} for ^{68}Ga-DOTATATE is related to NET grade, another important prognostic marker. Interestingly, there was no relation between FDG SUV_{max} and 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, whereas that for ^{18}F-FDG 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 a shorter survival, with bone metastases correlating with the worst prognosis.

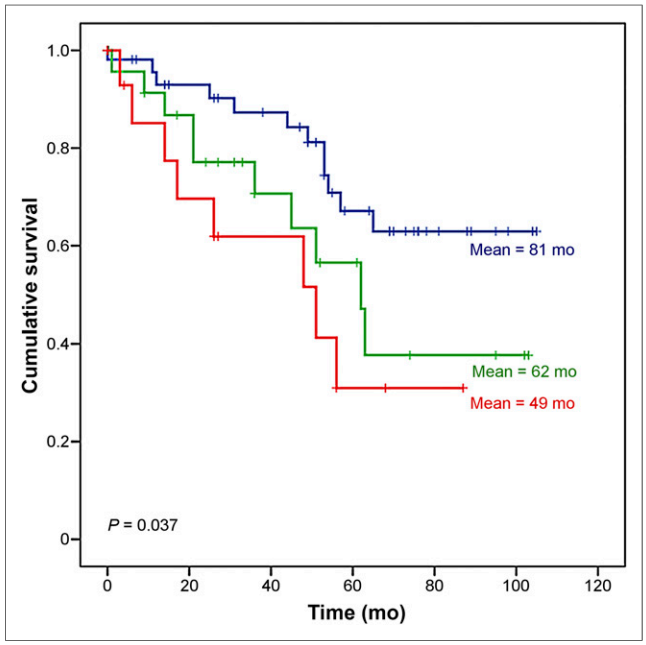

FIGURE 3. Survival curves for patients with bone metastasis (red) vs. soft-tissue metastasis (green) or no metastasis (blue) detected using ^{18}F-FDG.

With regard to study limitations, the fact that only patients with histologically proven NETs were enrolled restricted the possibility of specificity measurement. A second limitation of the study is that it lacked histologic confirmation from two or more tumor sites in patients with discrepant findings between the two PET/CT tracers. However, it would be unethical and not feasible to have histologic confirmation of all the tumor-avid lesions.

CONCLUSION

^{18}F-FDG PET/CT has no clinical impact on G1 NETs and a moderate impact on G2 NETs. In NETs with a Ki-67 index of 12% or less, use of ^{18}F-FDG PET/CT should be limited and tailored to the individual patient. However, in poorly differentiated NETs, ^{18}F-FDG PET/CT plays a significant clinical role in combination with ^{68}Ga-DOTATATE. ^{68}Ga-DOTATATE SUV_{max} is related to tumor grade, and Ki-67 and can be used prognostically.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Sundin A, Garske U, Orlefors H. Nuclear imaging of neuroendocrine tumours. *Best Pract Res Clin Endocrinol Metab.* 2007;21:69–85.
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 USA.* 2002;99:3294–3299.
3. Panagiotidis E, Bomanji J. Role of ^{18}F-fluorodeoxyglucose PET in the study of neuroendocrine tumors. *PET Clin.* 2014;9:43–55.
4. Ramage JK, Ahmed A, Ardill J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut.* 2012;61:6–32.
5. Pettinato C, Sarnelli A, Di Donna M, et al. ^{68}Ga-DOTANOC: biodistribution and dosimetry in patients affected by neuroendocrine tumors. *Eur J Nucl Med Mol Imaging.* 2008;35:72–79.
6. Shastry M, Kayani I, Wild D, et al. Distribution pattern of ^{68}Ga-DOTATATE in disease-free patients. *Nucl Med Commun.* 2010;31:1025–1032.
7. 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.
8. Kowalski J, Henze M, Schuhmacher J, Mäcke HR, Hofmann M, Haberkorn U. Evaluation of positron emission tomography imaging using [^{68}Ga]-DOTA-D Phe1-Tyr3-octreotide in comparison to [^{111}In]-DTPAOC SPECT: first results in patients with neuroendocrine tumors. *Mol Imaging Biol.* 2003;5:42–48.
9. Binderup T, Knigge U, Loft A, Federspiel B, Kjaer A. ^{18}F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. *Clin Cancer Res.* 2010;16:978–985.
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.* 2006;449:395–401.
11. Ambrosini V, Nanni C, Zompatori M, et al. ^{68}Ga-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;37:722–727.
12. Albanus DR, Apitzsch J, Erdem Z, et al. Clinical value of ^{68}Ga-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.* 2015;84:1866–1872.
13. Schraml C, Schwenzer NF, Sperling O, et al. Staging of neuroendocrine tumours: comparison of [^{68}Ga]DOTATOC multiphase PET/CT and whole-body MRI. *Cancer Imaging.* 2013;13:63–72.
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;42:80–87.
15. Kayani I, Bomanji JB, Groves A, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using ^{68}Ga-DOTATATE (DOTA-DPhe1,Tyr3-octreotate) and ^{18}F-FDG. *Cancer.* 2008;112:2447–2455.
16. Kayani I, Conry BG, Groves AM, et al. A comparison of ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT in pulmonary neuroendocrine tumors. *J Nucl Med.* 2009;50:1927–1932.
17. Has Simsek D, Kuyumcu S, Turkmen C, et al. Can complementary ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT establish the missing link between histopathology and therapeutic approach in gastroenteropancreatic neuroendocrine tumors? *J Nucl Med.* 2014;55:1811–1817.
18. Krausz Y, Freedman N, Rubinstein R, et al. ^{68}Ga-DOTA-NOC PET/CT imaging of neuroendocrine tumors: comparison with ^{111}In-DTPA-octreotide (OctreoScan®). *Mol Imaging Biol.* 2011;13:583–593.
19. Naswa N, Sharma P, Gupta SK, et al. Dual tracer functional imaging of gastroenteropancreatic neuroendocrine tumors using ^{68}Ga-DOTA-NOC PET-CT and ^{18}F-FDG PET-CT: competitive or complimentary? *Clin Nucl Med.* 2014;39:e27–e34.
20. Jindal T, Kumar A, Venkitaraman B, et al. Evaluation of the role of [^{18}F]FDG-PET/CT and [^{68}Ga]DOTATOC-PET/CT in differentiating typical and atypical pulmonary carcinoids. *Cancer Imaging.* 2011;11:70–75.
21. Lococo F, Perotti G, Cardillo G, et al. Multicenter comparison of ^{18}F-FDG and ^{68}Ga-DOTA-peptide PET/CT for pulmonary carcinoid. *Clin Nucl Med.* 2015;40:e183–e189.
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;100:293–299.
23. Howe JR. The supporting role of ^{18}FDG-PET in patients with neuroendocrine tumors. *Ann Surg Oncol.* 2015;22:2107–2109.
24. Ambrosini V, Campana D, Bodei L, et al. ^{68}Ga-DOTANOC PET/CT clinical impact in patients with neuroendocrine tumors. *J Nucl Med.* 2010;51:669–673.
25. Frilling A, Sotiropoulos GC, Radtke A, et al. The impact of ^{68}Ga-DOTATOC positron emission tomography/computed tomography on the multimodal management of patients with neuroendocrine tumors. *Ann Surg.* 2010;252:850–856.
26. Haug AR, Cindea-Drimus R, Auernhammer CJ, et al. The role of ^{68}Ga-DOTATATE PET/CT in suspected neuroendocrine tumors. *J Nucl Med.* 2012;53:1686–1692.
27. Deppen SA, Liu E, Blume JD, et al. Safety and efficacy of ^{68}Ga-DOTATATE PET/CT for diagnosis, staging, and treatment management of neuroendocrine tumors. *J Nucl Med.* 2016;57:708–714.
28. Jamali M, Chetty R. Predicting prognosis in gastroentero-pancreatic neuroendocrine tumors: an overview and the value of Ki-67 immunostaining. *Endocr Pathol.* 2008;19:282–288.
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;95:157–176.
30. Strosberg JR. Systemic treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETS): current approaches and future options. *Endocr Pract.* 2014;20:167–175.
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;35:853–860.
32. Hofman MS, Hicks RJ. Changing paradigms with molecular imaging of neuroendocrine tumors. *Discov Med.* 2012;14:71–81.
33. Herrmann K, Czernin J, Wolin EM, et al. Impact of ^{68}Ga-DOTATATE PET/CT on the management of neuroendocrine tumors: the referring physician's perspective. *J Nucl Med.* 2015;56:70–75.
34. Deppen SA, Blume J, Bobbey AJ, et al. ^{68}Ga-DOTATATE compared with ^{111}In-DTPA-octreotide and conventional imaging for pulmonary and gastroenteropancreatic neuroendocrine tumors: a systematic review and meta-analysis. *J Nucl Med.* 2016;57:872–878.
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.* 2010;51:353–359.
36. 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.
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;12:1083–1092.
38. 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.