Comparison of F-18-DOPA Versus Ga-68-DOTATOC as Preferred PET Imaging Tracer in Well-Differentiated Neuroendocrine Neoplasms

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Comparison of ^{18}F-DOPA Versus ^{68}Ga-DOTATOC as Preferred PET Imaging Tracer in Well-Differentiated Neuroendocrine Neoplasms

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Purpose: The aim of this study was to retrospectively compare ^{18}F-FDOPA versus ^{68}Ga-DOTATOC PET in lesion detection rates and laboratory tumor markers in patients with neuroendocrine neoplasms (NENs).

Patients and Methods: All patients with histologically proven NEN between May 2015 and February 2019 were included who underwent both ^{18}F-DOPA and ^{68}Ga-DOTATOC PET scans within 6 months from each other (mean, 75; median, 38; range, 2–168 days). All patients, except those with pancreatic NEN, received carbidopa before ^{18}F-DOPA PET. Based on the number of lesions on both modalities, patients were divided into 3 categories: more lesions on ^{18}F-DOPA (DOPA > DOTA), more lesions on ^{68}Ga-DOTATOC (DOTA > DOPA), and equal number of lesions (DOPA = DOTA). Tumor markers chromogranin A, serotonin, and 5-hydroxyindoleacetic acid (5-HIAA) within a maximum of 3 months around either scan were retrieved from the patients' charts.

Results: ^{18}F-DOPA revealed significantly more lesions compared with ^{68}Ga-DOTATOC (611 vs 385, $P < 0.05$). Twenty-four patients were included in the DOPA > DOTA group with 16 small intestinal (SI) NENs, 3 large intestinal, 4 pancreatic, and 1 tumor of unknown origin (TUO). For the 9 patients in the DOTA > DOPA group, 4 were SI, 2 pancreatic, 1 lung, and 2 TUOs. Twelve patients in the DOPA = DOTA group had 6 pancreatic tumors, 3 SI, 1 ovarian, and 2 TUOs. Only serotonin and 5-HIAA showed significant higher values for DOPA > DOTA compared with DOTA > DOPA (mean 24 vs 4, $P < 0.05$, and 320 vs 81, $P < 0.05$, respectively). Cutoff values of 20 nmol/10^9 for serotonin, 185 μg/L for chromogranin A, and 200 nmol/L for 5-HIAA were found to include almost exclusively DOPA > DOTA patients.

Conclusions: There is an advantage of carbidopa pretreated ^{18}F-DOPA over ^{68}Ga-DOTATOC PET, especially for large intestinal NENs with high levels of biomarkers. There seems to be a relationship between increased biomarker value and improved lesion detection rates with the ^{18}F-DOPA PET scan, which requires further prospective analysis.

Key Words: neuroendocrine tumor, PET tracer, ^{18}F-DOPA, ^{68}Ga-DOTATOC, tumor markers

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Neuroendocrine neoplasms (NENs) are a group of heterogeneous and rare tumors with both neural and endocrine histologic features. Most NENs are derived from the enterochromaffin-like cells in the gastrointestinal tract; however, they can be located throughout the whole body. Because of the often indolent growth of the tumor, 50% of the patients present with metastasis during diagnosis.[1] Establishing the extent and progression of NENs is challenging, as imaging with computed tomography (CT) alone is often inadequate to identify the primary tumor and metastatic lesions.[2]

Neuroendocrine neoplasms differ in their origin and biology, which enables them to secrete different neuropeptides and hormones, frequently expressing a high density of somatostatin receptors (SSTRs). Another property of neuroendocrine cells is their ability to metabolize the dopamine precursor dihydroxyphenylalanine (DOPA). However, no correlation exists between SSTR expression and metabolic activity of the tumor.[3] The discovery of these tumor characteristics led to the use of PET tracers.[2,4]

Two PET tracers that are commonly studied for their diagnostic capabilities in gastroenteropancreatic (GEP) NENs are ^{18}F-DOPA and ^{68}Ga-DOTATOC. ^{18}F-DOPA is a substrate for aromatic amino acid decarboxylase within NEN cells. The retention of ^{68}Ga-DOTATOC depends on the expression of SSTR, mainly of subtype 2, which gives ^{68}Ga-DOTATOC the ability to provide information regarding tumor cell receptor status.[3] Historically, the use of ^{18}F-DOPA was limited due to complicated synthesis, whereas ^{68}Ga could be eluted from commercially available generators with easier radiolabelling process. These differences led to ^{68}Ga-DOTATOC being the preferred tracer in current clinical practice, although recent developments made ^{18}F-DOPA commercially more accessible due to optimized methods of synthesis. Although most NENs express SSTR2, the expression is sometimes too limited for adequate visualization using ^{68}Ga-DOTATOC PET.[5,6] In cases of low SSTR expression, ^{18}F-DOPA PET is often used, with increased image quality compared with ^{68}Ga-DOTATOC, especially in locating small intestinal (SI) tumors.[7] Although both ^{18}F-DOPA and ^{68}Ga-DOTATOC PET have demonstrated superiority to conventional somatostatin scintigraphy[2,4] in GEP-NENs, comparative studies with both tracers are rare and limited by small patient cohorts and absent use of carbidopa in ^{18}F-DOPA PET scans.

In standard of care, patients with NEN undergo ^{68}Ga-DOTATOC PET for PRRT eligibility and for diagnosing foregut and pancreatic tumors. ^{18}F-DOPA PET is often used after excision of the primary tumor to detect potential metastasis, and both tracers are used in cases of midgut tumors. Also, tracer selection is often influenced by stock availability, sometimes resulting in patients receiving both tracers. Discrepancies between ^{18}F-DOPA and ^{68}Ga-DOTATOC exist, as

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Conflicts of interest and sources of funding: none declared.

Ethics approval: According to the Dutch Medical Research Involving Human Subject Act, the local medical ethical committee exempted approval without additional procedures in view of the retrospective nature of the study, and all the procedures being performed were part of the routine care. No additional informed consent was required.

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both tracers use different metabolic pathways.[7] A potential link has been found between elevated biomarker levels of the serotonin and catecholamine pathways and increased uptake of ^{18}F-DOPA.[8] This discovery hints at potential better ways of patient tracer selection for certain NEN tumors. Which is why the aim of our study was to compare lesion detection rates between ^{68}Ga-DOTATOC and ^{18}F-DOPA PET scans in patients with well-differentiated gastrointestinal NEN. We argue that tumor marker results together with clinical status and primary tumor location could potentially be used as input for tracer decision making. Location of primary tumor and metastases will be compared within the same patients by both tracers. In addition, we want to explore any relationship between tumor markers and tumor characteristics.

PATIENTS AND METHODS

Patients and Study Design

This retrospective study included all adult patients with histologically proven gastrointestinal neuroendocrine tumors, who underwent both ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT scans for staging and restaging purposes at the University Medical Center of Groningen, between May 2015 and February 2019. Both imaging procedures had to be performed within 6 months of each other. Patients were excluded if excision of tumor tissue or PRRT was performed between both scans. Duplicate cases and patients with missing laboratory marker results would be excluded. The following baseline characteristics were retrospectively retrieved from patients' medical record: tumor grade during time of diagnosis according to the 2010 World Health Organization classification and KI-67 index. The laboratory markers noted were chromogranin A (CgA; reference, 20–100 μg/L), serotonin in platelets (2.8–5.4 nmol/10^9), and 5-hydroxyindoleacetic acid (5-HIAA; 0.8–3.8 mmol/mol) in 24-hour urine collection. Laboratory measurements closest to both scans were taken from the patient charts, with a maximum of 3 months before and after each scan. In case only one set of measurements was available around either scan date, the same laboratory results were used for both scans. According to the Dutch Medical Research Involving Human Subject Act, the local medical ethical committee exempted approval without additional procedures. No additional informed consent was required. Patient information was anonymized before data analysis.

^{68}Ga-DOTATOC and ^{18}F-DOPA PET

^{68}Ga-DOTATOC was produced using a Scintomics module and an Eckert & Ziegler ^{68}Ge/^{68}Ga generator.[9] ^{18}F-DOPA synthesis was performed using the Raytest synthesis module as previously published by our institution.[10] Imaging for both tracers was realized by using the Siemens Biograph mCT 40 or 64 slices, 4 detector rings (Siemens Healthcare, Germany). Attenuation and scatter correction of the PET emission data were achieved by a low-dose CT scan with 120 kV and 35 mAs. Reconstruction of the PET data was done with Siemens Ultra HD (TrueX and time of flight), using 3 iterations and 21 subsets with a 400 matrix size and a 5-mm Gaussian (isotropic) filter.[11] CT scans were performed on the Biograph mCT PET/CT, 40 slices or 64 slices. CT scans of the chest and abdomen were obtained by using iodine-containing IV iomeprol (Iomeron) 350 mg/mL and oral contrast agents.

All patients were hydrated with 1 L of water before acquisition in both scans. When undergoing the ^{18}F-DOPA PET scan, patients were fasted for 6 hours and 1 hour for the ^{68}Ga-DOTATOC PET scan. Sixty minutes before the injection of ^{18}F-DOPA, patients were pretreated with carbidopa (2 mg/kg body weight, maximum 150 mg), with exception of patients who were scanned for pancreatic NEN. Patients received an intravenously injected dose of 200 MBq (5.41 mCi) ^{18}F-DOPA or 120 MBq (3.24 mCi) ^{68}Ga-DOTATOC. Images were acquired after 60 ± 5 minutes, scanning from head to midthigh. ^{18}F-DOPA PET was acquired in 1.5 minutes per bed position in patients ranging from 0 to 60 kg bodyweight, 2 minutes per bed position in patients weighing 60 to 90 kg bodyweight, and 3 minutes per bed position in patients over 90 kg bodyweight. ^{68}Ga-DOTATOC PET was also acquired from head to proximal femur, however, with 3 minutes per bed position, irrespective of body weight.

Image Data Analysis

Scans were analyzed with Syngo.via (version VB20; Siemens Healthcare, Germany). In the case of doubt, verification of potential malignant activity was done by evaluating CT images and radiologist or histopathologic reports. A lesion was positive if the lesion could not be attributed to a physiologic uptake pattern and was clearly demarcated, with tracer accumulation higher than the liver and/or physiologic activity. Areas of physiologic ^{18}F-DOPA uptake include the striatum and pancreas, with subsequent elimination through the biliary, digestive, and urinary tracts, whereas ^{68}Ga-DOTATOC physiologic uptake areas include the pituitary gland, spleen, liver, adrenal glands, head of the pancreas, thyroid, and urinary tract. Around all PET-positive tumor lesions, a volume of interest was manually drawn. If a large amount of liver lesions were present, single lesions could not be identified separately and were counted as a single full liver metastasis. Long and short axis diameters of only the 5 largest lesions were determined in the transverse plane, along with their corresponding SUV_{max}.

Statistical Analysis

Based on the number of identified lesions, 3 categories were created: DOPA > DOTA in which ^{18}F-DOPA PET showed more lesions than ^{68}Ga-DOTATOC PET, DOTA > DOPA for all the patients in which ^{68}Ga-DOTATOC PET revealed more lesions, and lastly DOPA = DOTA in which both scans showed an equal amount of lesions. Laboratory markers were compared per patient between the results during ^{18}F-DOPA and ^{68}Ga-DOTATOC PET. Comparisons between laboratory markers and lesion sizes per patient were performed using a related samples Student *t* test; between groups, a one-way analysis of variance was used with a Games-Howell post hoc test. A nonparametric test (Mann-Whitney *U*) was used to determine the differences between the mean total lesions and SUV lesion per patient for both tracers. Statistical analysis was done using SPSS 23.0.

RESULTS

Patients

During the selected period of retrospective study, 906 NEN patients were identified that received both tracers (Fig. 1). A total of 835 patients were excluded due to being duplicate entries, having more than 6 months between both PET scans, and if both scans did not detect any tumor lesions. Of the 45 patients included in our study, 35 received ^{18}F-FDOPA before ^{68}Ga-DOTATOC. No routine scanning of either one before the other tracer was performed. All patients received both scans incidentally, whether this was due to stock availability or to detect suspected metastases with a second tracer. In addition, 7 patients underwent an additional ^{68}Ga-DOTATOC PET scan in preparation for PRRT, whereas diagnosis and follow-up were performed by ^{18}F-FDOPA. After gathering tumor marker data, an additional 24 patients were excluded due to erroneous tumor marker values of which 2 patients used proton-pump inhibitors, which can influence CgA readings.[12] In total, 45 patients (mean age, 63 years;

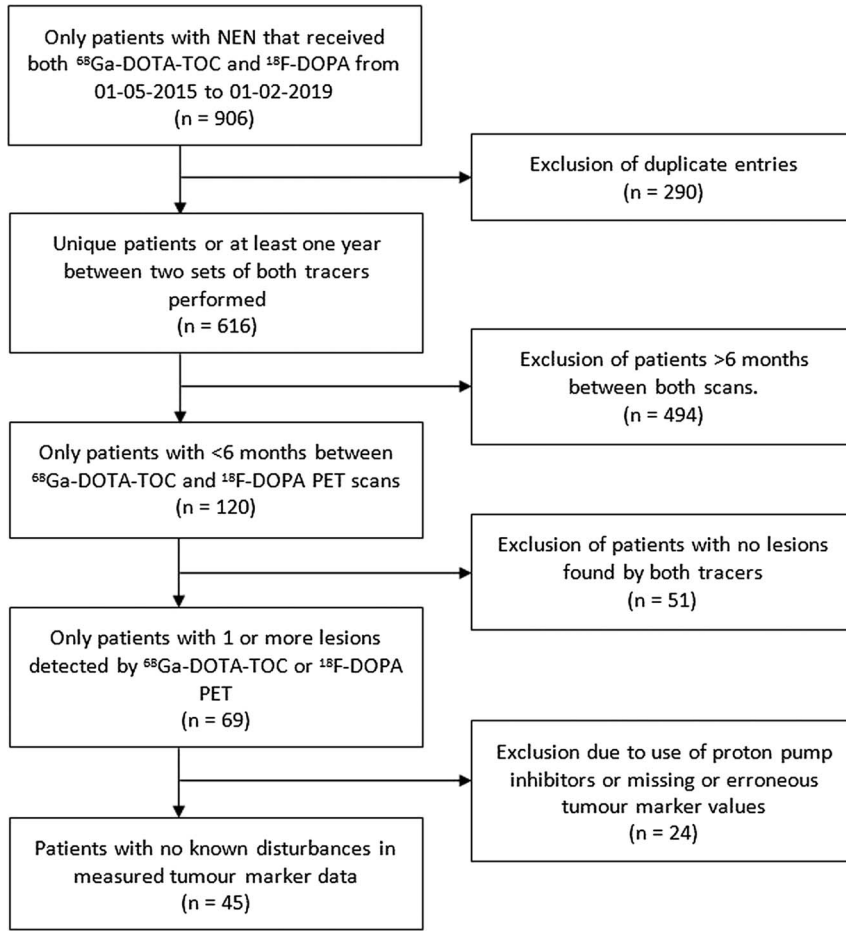

FIGURE 1. Flowchart of inclusion of ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT scans.

range, 29–80 years; 26 males; Table 1) with neuroendocrine tumors were included with a mean of 75 days between both scans (range, 2–168; median, 38). For most patients, the primary tumor was located in the small intestine (48%), followed by pancreas (26%) and large intestine (11%) (Fig. 2). Of the 12 pancreatic NENs, 3 were functional insulinomas. In all cases, the tumor was well-differentiated with 30 grade 1 (67%) and 12 grade 2 (26%) tumors. In 3 cases, no definitive histopathologic grade could be found but were still included

TABLE 1. Baseline Patients Characteristics (n = 45)

Age, mean ± SD, y	63 ± 11			
Sex, n (%)				
Male	26 (55%)			
Female	19 (45%)			
Histopathologic grade				
1	30 (67%)			
2	12 (26%)			
No data available	3 (7%)			
Primary tumor location	Total	DOPA > DOTA	DOTA > DOPA	DOPA = DOTA
Small intestine	22 (48%)	16	4	3
Pancreas	12 (26%)	4	2	6
Large intestine	5 (11%)	3	—	—
Lung	1 (2%)	—	1	—
Ovarium	1 (2%)	—	—	1
Unknown origin	5 (11%)	1	2	2
Total	45	24	9	12

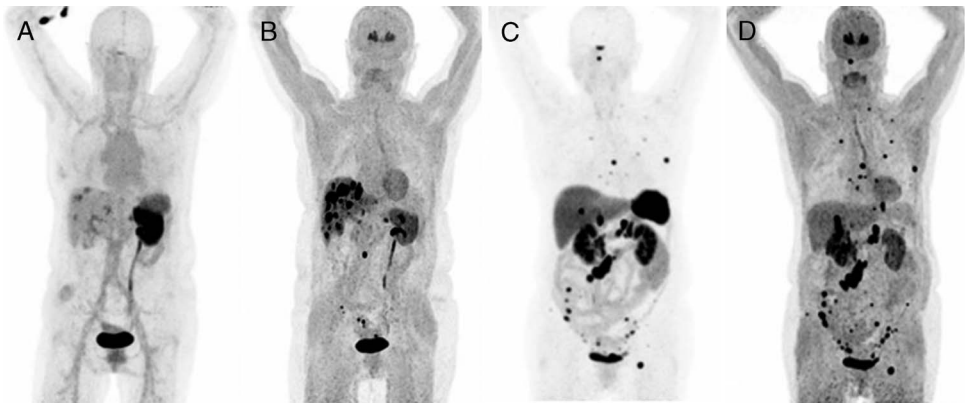

FIGURE 2. **A** and **B**, Imaging in a 63-year-old woman with metastatic NEN, after a previously resected colon NEN. **A**, ^{68}Ga-DOTATOC. MIP image showed intense focal ^{68}Ga-DOTATOC uptake in several lesions of the liver. **B**, Carbidopa-enhanced ^{18}F-FDOPA. MIP showing, in comparison with ^{68}Ga-DOTATOC, additional intense focal para-aortal, sigmoid, and mesenterial ^{18}F-FDOPA uptake. A large number of liver lesions were found as well. **C** and **D**, Imaging in a 73-year-old woman with a metastasized primary pancreas NEN. **C**, ^{68}Ga-DOTATOC. MIP image showed focal uptake of ^{68}Ga-DOTATOC at multiple bone lesions, several retroperitoneal and mesenterial lymph nodes, and the liver. In addition, visualization of the primary tumor at the pancreatic tail and histologically confirmed metastasis in the left breast. **D**, ^{18}F-FDOPA. MIP image showing a comparable image to ^{68}Ga-DOTATOC, but note the improved visibility of the large number of bone metastasis.

after reviewing secondary rapports, which stated that the tumor was well differentiated.

Primary Tumor and Lesion Category

Sixteen patients of 24 in the DOPA > DOTA group had SI NEN, 3 large intestinal, 4 pancreatic, and 1 tumor of unknown origin (TUO) (Table 1). The DOTA > DOPA group consisted mostly of SI NEN with 4 cases of 9, 2 pancreatic, 1 lung, and 2 unknown primary tumors. In 12 cases where an equal number of tumors were found, 6 primary tumors were derived from pancreas, 3 small intestine, 1 ovarian, and 2 TUOs. For DOPA > DOTA, 15 patients (63%) had a grade 1 tumor, and 7 patients (29%) grade 2. In

TABLE 2. Per-Patient DOPA and DOTA Scan Characteristics

	DOPA		DOTA		*P*
Total no. lesions (range)	611	0–54	385	0–26	0.006
Metastasis present	39	83%	35	75%	NA
Lesion surface, median (range)	3.16	0–26	3.50	0–46	0.112
SUV_{max}, median (range)	11.70	0–50	16.00	0–72	0.234
Laboratory markers, mean (range)					
Chromogranin A	183	23–735	188	24–604	0.454
Serotonin	16	0–45	17	0–44	0.215
5-HIAA	234	0–785	260	26–1077	0.114
Laboratory markers per tumor group, mean	DOPA > DOTA	DOTA > DOPA	DOPA = DOTA		
Chromogranin A	234	137	109		
Serotonin	24	4	10		
5-HIAA	318	81	154		
Location of metastasis					
Liver	28		21		
Lymph node	20		18		
Pancreas	16		15		
Bone	14		16		
Mesentery	12		13		
Small intestine	12		11		
Peritoneum	8		7		
Full liver*	8		6		
Lung	7		7		
Heart	6		4		
Large intestine	5		4		
Breast	2		2		

*In the case, a large amount of separate liver tumors were undistinguishable.

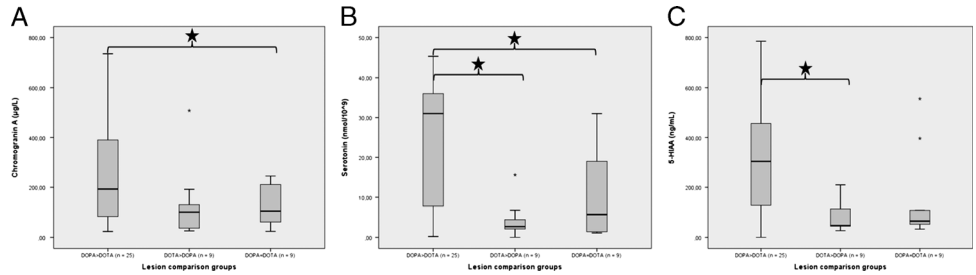

FIGURE 3. A–C, Lesion comparison groups and tumor markers.

DOTA > DOPA, 6 patients (67%) were classified with grade 1, 2 with grade 2.

Per-Tracer Lesion Analysis

^{18}F-DOPA PET revealed 611 lesions, significantly more compared with the 385 lesions that were found by ^{68}Ga-DOTATOC PET (Table 2, $P = 0.006$). Slightly more metastatic disease was found with ^{18}F-DOPA (n = 39) compared with ^{68}Ga-DOTATOC (n = 35). Based on the number of lesions found with each tracer, 24 patients were included in the DOPA > DOTA group, 9 for DOTA > DOPA, and 12 for DOPA = DOTA. In the 24 cases where ^{18}F-DOPA detected more lesions than ^{68}Ga-DOTATOC, a median of 5 more lesions (range, 1–47) was found. In the 9 cases that ^{68}Ga-DOTATOC detected more lesions, the difference was smaller with a mean of 2 more lesions (range, 1–13). In 2 patients, ^{68}Ga-DOTATOC found no lesions, whereas ^{18}F-DOPA revealed liver metastasis. The first patient had a primary colon tumor, which metastasized to the liver with 25 lesions. The latter showed a large number of hepatic metastases from a primary pancreatic tumor of which only 2 lesions were distinguishable from a larger consolidated liver tumor mass. Alternatively, in 1 patient, ^{68}Ga-DOTATOC revealed a large single lesion (4 × 3.4 cm), which was located in the small intestine, with no ^{18}F-DOPA uptake. All 4 patients with primary large intestinal tumors were found in the DOPA > DOTA group with at least 20 lesions more compared with DOTA and showing high tumor marker readings (CgA > 400 µg/L, 5-HIAA > 300 ng/mL).

Tumor Marker Analysis

High tumor markers were found in most patients, with elevated CgA in 30 patients, serotonin in 24 patients, and 5-HIAA in 26 patients. Only serotonin ($P < 0.001$) and 5-HIAA ($P < 0.001$) showed significant higher values for DOPA > DOTA compared with DOTA > DOPA (Figs. 3A–C). No significant differences were found between the 2 samples per patient. Serotonin levels greater than 20 nmol/10^9 thrombocytes showed 14 DOPA > DOTA patients, no DOTA > DOPA patients, and 2 in the DOPA = DOTA group. For CgA levels greater than 185 µg/L, 13 patients were in the DOPA > DOTA group, 2 DOTA > DOPA, and 3 DOPA = DOTA. Elevated 5-HIAA levels greater than 200 nmol/L revealed 14 DOPA > DOTA patients, 1 DOTA > DOPA, and 2 DOPA = DOTA (Figs. 4A–C). Serotonin and 5-HIAA values were not available in 3 patients.

DISCUSSION

Overall, our study found more lesions with ^{18}F-DOPA compared with ^{68}Ga-DOTATOC PET. Analysis of primary tumor locations revealed that all large intestinal NENs showed more lesions in the ^{18}F-DOPA PET scan, SI NENs were equally distributed over both tracer groups, and pancreatic NENs mostly revealed an even amount of lesions between the 2 tracers. Elevated tumor markers were significantly related to patients who showed more lesions in the ^{18}F-DOPA PET scan. Grade 2 tumors were seen more frequently in DOPA > DOTA, with grade 1 tumors having a comparable frequency between the groups. This study is the first to identify potential tumor marker threshold values, for which above, ^{18}F-DOPA PET predominantly shows more lesions than ^{68}Ga-DOTATOC PET.

A relationship between elevated plasma serotonin and pathologic ^{18}F-DOPA uptake has been noted in a smaller study.[3] Not only is this comparable with our results, but our study also gives evidence regarding potential laboratory marker cutoff values. We found that measurements greater than 185 µg/L for CgA, 20 nmol/10^9 thrombocytes for serotonin, and 200 nmol/L for 5-HIAA resulted in selecting patients who almost exclusively had more lesions with ^{18}F-DOPA. Although the field of biomarkers is under constant development, with novel ways such as disease-specific mRNA and gene transcription being studied,[13,14] traditional serum tumor biomarkers are still mainstay in NENs. The clinical validation of these cutoff values and tracer relationship with primary tumor location need to be established in future studies.

The DOPA > DOTA group was characterized mostly by midgut tumors (19/25), which commonly have a higher production of 5-HTP and its metabolites, whereas elevated CgA is often found in foregut and hindgut tumors (5/9 in DOTA > DOPA).[15] It can therefore be theorized that our results are a representation of the predominantly midgut GEP-NEN patients that were included and that

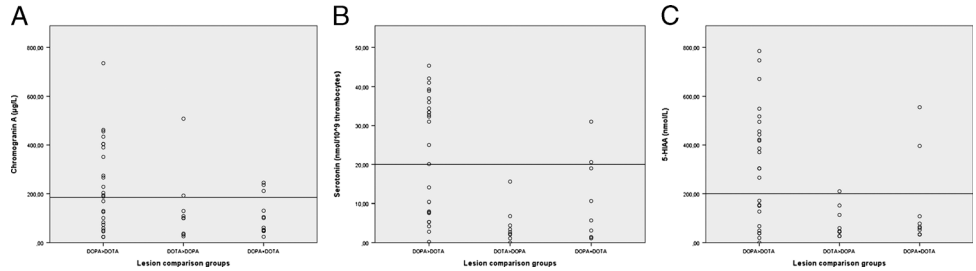

FIGURE 4. A–C, Tumor marker distribution according to lesion comparison groups with proposed cutoff values.

TABLE 3. Studies That Compare ^{18}F-DOPA and ^{68}Ga-DOTATOC/NOC/TATE[3,16–18]

Study	Patients, n	Tumor Types	PET Interval	Outcomes	Notes
Putzer et al[3]	15	GEP-NEN, ganglioma, pheochromocytoma, and others	6 wk (mean)	^{68}Ga-DOTATOC (total lesions: 208) showed more lesions in 6 patients, ^{18}F-DOPA (86) in 4	Results indicate that the ^{18}F-DOPA tracer can identify a different subset of metabolic active NENs, no carbidopa
Ambrosini et al[16]	13	GEP-NEN, pulmonary NEN	<30 d	^{68}Ga-DOTANOC (total lesions: 71) positive in all cases, with ^{18}F-DOPA positive (45) in 9 of 13	No carbidopa
Kroiss et al[18]	20	Extra-adrenal paraganglioma	3.1 mo (max)	^{68}Ga-DOTATOC total lesions, 45; ^{18}F-DOPA total lesions, 32	No carbidopa
Haug et al[17]	25	GEP-NEN, pulmonary NEN, and others	42 d (median)	^{68}Ga-DOTATATE total lesions, 54; ^{18}F-DOPA total lesions, 2	No carbidopa

midgut GEP-NENs are preferably measured and followed with serotonin-based tumor markers.

To date, only one study directly compared ^{68}Ga-DOTATOC and ^{18}F-DOPA in GEP-NENs,[3] and 2 other studies using the DOTANOC and DOTATATE tracer variants[16,17] (Table 3). One case study detailing tracer comparison in paraganglioma was omitted from the review.[15] As these studies presented case series with heterogeneous population, our study had only 2 patients with primary non–GEP-NEN (lung and ovarian). Generally, these studies conclude that ^{68}Ga-DOTA may be superior to ^{18}F-DOPA in NENs, due to more lesions found. Differences in results to the performed study could be related to the limited group sizes, especially considering GEP-NENs (1 patient Kroiss et al,[18] 11 Ambrosini et al[16]). Also, no patients in the reviewed studies were pretreated with carbidopa, which is proven to aid in the process of increasing ^{18}F-DOPA retention.[19,20] Our patients received carbidopa before ^{18}F-DOPA PET, and our results show potential evidence for a clinically relevant effect of carbidopa in GEP-NENs.

Our study was limited by its retrospective nature, but is currently the largest cohort of GEP-NEN patients studied for direct tracer comparison. The 6-month interval between both scans was deemed appropriate due to the indolent behavior of well-differentiated NENs. Some patient's tumor markers were sampled only once during both PET scans, but often times, this was due to both scans being performed closely after each other. Although our results suggest that for some patients more lesions could be found with ^{18}F-DOPA, SSTR2 expression still plays an important role in treatment and follow-up. In the case a patient is a potential candidate for PRRT, ^{68}Ga-DOTATOC is still the most effective tracer available detecting SSTR2 receptor presence.

In conclusion, our study found a potential advantage for ^{18}F-DOPA combined with carbidopa over ^{68}Ga-DOTATOC in low-differentiated GEP-NENs, especially for large intestinal NENs producing high levels of biomarkers. More specifically, there seems to be a relationship between increased biomarker value and improved lesion detection rates with the ^{18}F-DOPA PET scan, but this requires validation in a prospective setting.

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