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Title:

^{18}F-Fluorodihydroxyphenylalanine PET/CT at the Forefront for Initial and/or Pre-surgical Evaluation of Small Intestine Neuroendocrine Tumors

Running Title:

PET/CT for SiNET staging

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ABSTRACT

To compare the respective value of ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT for initial staging or pre-surgical work-up of patients with small intestine neuroendocrine tumors (SiNET).

Methods. This is a retrospective, multicenter, non-interventional investigation involving 53 non-operated SiNET patients who underwent both ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT within a 6-months interval without therapeutic intervention or change between the two PET/CT studies. Detection rate (DR %) was calculated according to *per-region* and *per-lesion* analyses. Sensitivity for primary tumor detection was assessed in 37 operated patients taking surgical results (76 SiNET) as diagnostic gold standard.

Results. Each of ^{68}Ga-DOTATOC PET/CT and ^{18}F-DOPA PET/CT individually identified at least one primary SiNET in 92% (34/37) of the patients. Tumor intestinal multifocality was confirmed by histology in 8 patients. ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT were concordant positive for tumor multifocality in 5, discordant positive in 2, and concordant negative in 1 case. DR % for subdiaphragmatic nodal metastases on *per-region*-based analysis was 91 % and 98 % for ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT, respectively (p=0.18). ^{18}F-DOPA PET/CT detected a higher number of abnormal subdiaphragmatic nodes (p=0.009). Regarding mesenteric nodes only, ^{18}F-DOPA PET/CT detected more positive regions (p=0.005) and nodal lesions (p=0.003) than ^{68}Ga-DOTATOC PET/CT, including nodes located at the origin of mesenteric vessels. For detection of distant metastases, ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT performed equally on a *per-region*-based analysis. As compared to ^{68}Ga-DOTATOC, ^{18}F-DOPA PET/CT detected more hepatic ($p<0.001$), peritoneal ($p<0.001$), and lung metastases ($p<0.001$).

Conclusions. ^{18}F-DOPA PET/CT detects more lesions than ^{68}Ga-DOTATOC PET/CT in studied patients. Their respective role should be discussed in terms of disease staging and treatment selection.

Keywords: ^{68}Ga-DOTATOC, ^{18}F-DOPA, PET, neuroendocrine, small intestine, carcinoid, staging

INTRODUCTION

Neuroendocrine tumors (NET) originating from the gastroenteropancreatic system (GEP-NET) account for approximately 60 % of all NET. Small intestine, mainly ileum, is the most common site of primary tumor origin. Despite their slow pace of progression, small intestinal NET (SiNET) can extensively spread to mesenteric nodal stations, liver and bone and can cause pronounced fibrosis locally in the mesentery and at distant sites, as in the heart, leading to extremely serious complications. Surgery is the only potentially curative treatment for non-metastatic SiNET (*1*,*2*). Identification of distant metastases usually do not prevent (if indicated) surgical resection of primary SiNET, mesenteric lymph nodes, and mesenteric fibrosis to avoid potential complications (*2*,*3*). If curative surgery is possible, the extent of lymph nodes metastases must be carefully evaluated because a complete lymphadenectomy decreases the risk of recurrence (*4*–*6*). In addition, a 19 % rate of missed metastases was reported in the retro-pancreatic area, a region not systematically explored during surgery (*7*).

Imaging plays a central role in initial diagnosis for staging (screening for primary multifocality, lymph nodes and systemic metastases, fibrosis) and determining operability, the latter being related to the location of nodal lesion and/or mesenteric fibrosis to the mesenteric arteries (*8*). Functional imaging can be performed in addition to whole-body CT and liver MRI (*9*). ^{68}Ga-labeled somatostatin analogs (^{68}Ga-SSA) used for somatostatin receptor (SSTR) PET/CT has achieved consensus or near consensus among expert panels as a forefront radiopharmaceutical for SiNET. ^{68}Ga-SSA PET/CT have indeed been shown to provide comparable results to ^{18}F-DOPA PET/CT at the patient-based level, adding information on SSTR expression status for theranostic application, which is tightly linked to tumor differentiation and patient prognosis. However, a systematic review (*10*) has shown that despite similar high patient- and region-based pooled sensitivities (83 % and 89 % for ^{18}F-DOPA PET; 88 % and 92 % for SSTR PET), ^{18}F-DOPA was superior in terms of lesion detection (lesion-based pooled sensitivity: 95 % vs. 82 %). These data are in agreement with 2017 EANM guidelines positioning ^{18}F-DOPA and ^{68}Ga-SSA as first-choice radiotracer for SiNET, except when evaluation of SSRT expression is mandatory before treatment (*11*). Moreover, the most accurate modality should be required when the assessment of tumor extension needs to be as precise as possible. To this end, in the present study we have compared

^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT in initial staging or in the pre-surgical work-up of patients with SiNET.

MATERIAL AND METHODS

Patient Population

This was a retrospective, multicenter, non-interventional investigation conducted in the department of nuclear medicine of five academic NET centers in France (Beaujon, Lyon, Marseille, Nancy, and Strasbourg), involving patients with SiNET evaluated by PET/CT between 2017 and 2021. Patients were retrospectively included according to the following criteria: (1) well-differentiated SiNET, (2) PET investigations performed for initial staging and/or presurgical work-up, (3) ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT performed within a 6-months period, and (4) absence of any therapeutic intervention or change between the two PET studies. Patients with history of oncologic intestinal surgery for SiNET were not considered for the study. Demographics, presence of carcinoid syndrome, imaging results, and pathological results after surgical resection were collected. Values of serum chromogranin-A (CgA) and 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) were collected when available. Tumors were graded according to the 2019 World Health Organization classification (*12*). In accordance with local guidelines, all patients gave informed consent for the use of anonymous data extracted from their medical records for scientific or epidemiological purposes. The institutional review board approved this retrospective study, and all subjects signed a written informed consent (CE 2021-93).

^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT: Acquisition/Reconstruction Parameters

All examinations were performed on combined PET/CT devices equipped with 3D-time of flight technology, and without iodinated contrast-media administration. Patients in a given center were scanned on the same instrument regarding the two tracers. Patients were injected with 2-3 MBq/kg of ^{68}Ga-DOTATOC and 3-4 MBq/kg of ^{18}F-DOPA. ^{68}Ga-DOTATOC (SOMAKIT TOC®, Advanced Accelerator Applications, Saint Genis-Pouilly, France) and ^{18}F-DOPA (DOPACIS, CISBIO International, Nancy, France) were used in the setting of marketing

authorization. In case of concurrent octreotide therapy, ^{68}Ga-DOTATOC PET/CT was performed just before the next octreotide injection. Carbidopa premedication (200 mg orally) was done in 24 cases (45 %) 60–90 min before ^{18}F-DOPA iv injection. The PET/CT protocol included an acquisition from the upper thigh to the top of the skull (3-5 min/step or continuous bed motion when available), starting approximately 60/30 minutes following injection of ^{68}Ga-DOTATOC or ^{18}F-DOPA, respectively. PET image datasets were reconstructed iteratively (OSEM algorithm) using non-contrast-enhanced data for attenuation correction. CT, PET (attenuation-corrected), and PET/CT were independently interpreted by one experienced nuclear medicine physician who was aware of patients' clinical data and results of biological, pathological, and anatomical imaging investigations but was blinded to the results of the other PET study. ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT from the same patients were analyzed more than 7 days apart.

Interpretation Criteria of PET Studies

PET was interpreted as either positive or negative. A positive PET was defined by the detection of at least one focal area of pathologically increased radiotracer uptake relative to surrounding tissue and physiological biodistribution. For *per region* analysis, the following 9 anatomical regions were analyzed: small intestine (i.e., primary tumors), peritoneum, liver, abdominal lymph nodes, left-sided supraclavicular lymph nodes, supra-diaphragmatic lymph nodes (excluding the left supraclavicular region), lungs/pleura, bones, and others. Moreover, mesenteric lymph nodes were analyzed independently, according to the Pasquer *et al.*(*7*) classification: group-1: in contact with the small bowel, group-2 in the middle of the mesentery, and group-3 at the origin of the mesenteric vessels under the pancreatic uncus. A region was considered positive when it contained at least one focal uptake abnormality, regardless of the number of positive foci. Finally, for *per lesion* analysis, the number of lesions was recorded in each region. If the number of lesions exceeded 20, the count was fixed at 20.

Statistical Analysis

Results for continuous variables were expressed as mean and standard deviation or range values as appropriate, whereas categorical variables were expressed as frequencies and

percentages. For ethical reasons, histological proof of all potentially metastatic lesions was not possible, and a pathological ^{68}Ga-DOTATOC or ^{18}F-DOPA uptake was considered as a true positive result. The sum of positive regions and lesions on either ^{68}Ga-DOTATOC or ^{18}F-DOPA PET/CT was considered as the total number of involved regions and lesions. The detection rate (DR%) of ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT was calculated according to *per-region* and *per-lesion* analyses. ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT sensitivity for primary tumor detection was assessed in operated patients using surgical findings as diagnostic gold standard. Region-to-region, and lesion-to-lesion comparisons between ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT were performed using the McNemar test. Correlations were assessed using Spearman's rho correlation test. Two-sided p value < 0.05 was considered as significant. Statistical analyses were performed using a free available statistical software (Jamovi, version 1.8, www.jamovi.org).

RESULTS

Patient Population

On 59 screened patients, 2 were excluded because they have been operated before PET/CT, 2 because of a delay >6 months between the two PET/CT, 1 because ^{18}F-DOPA PET/CT data were not available, and 1 patient with more than 100 SiNETs. Hence, fifty-three patients were included in the analysis. Patients' characteristics are summarized in Table 1. The studied population was composed of 31 (58%) women and 22 (42%) men with a mean age of 65±13 years (range: 33-89 years). Fifteen patients (28%) were referred for clinical and radiological suspicion of SiNET (afterwards histologically confirmed), and 38 (72%) cases presented with biopsy proven metastatic SiNET.

Tumors were classified as G-1 in 23 cases (43%), G-2 in 25 (47%) cases, and well-differentiated G-3 in 3 (6%) cases (mean Ki67: 5.8%±8.7%; median Ki67: 3.7%; range: 1%-44%). The Ki67 index was not available for 2 (4 %) patients with well-differentiated tumors. Nineteen (36%) patients had a carcinoid syndrome. Serum CgA and urinary 5-HIAA were elevated in 28 (53%) and 14 (26%) cases, respectively. At the time of PET/CT, 13 (25%) patients were treated by long-acting somatostatin analogs. Mean time interval between the two modalities was 29±76 days

(range: 1-161 days), and 68 % of patients had the two exams within 28 days. After PET/CT, 37/53 (70%) patients underwent oncologic surgery, and histology revealed a total of 76 primary SiNET.

^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT Showed Similar Primary SiNET Detection Rates

^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT sensitivity for primary SiNET detection was assessed from the analysis of 37 operated patients and 76 histologically detected SiNET. The ability of both imaging modalities to detect a multifocal intestinal disease was also evaluated.

In 32 (86%) cases ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT were concordant and identified at least one primary SiNET. PET/CT were discordant in additional 4 (11%) cases: 2 patients showed positive uptake on ^{68}Ga-DOTATOC PET/CT only, and two other patients showed positive uptake on ^{18}F-DOPA PET/CT only. The Ki67 of tumors detected by ^{18}F-DOPA PET (44% and 10 %) was higher than that of tumors revealed by ^{68}Ga-DOTATOC PET (1% and 2%). However, no statistical considerations are possible.

In the remaining case (3%) no primary SiNET was revealed by either PET/CT modality despite two siNENs detected by pathology. Accordingly, *per-region* sensitivity was 94 % for both techniques (Supplementary Table 1).

According to a lesion-based analysis, 45 out of 76 (59%) histologically confirmed SiNET were detected by both modalities, 13 (17%) by ^{68}Ga-DOTATOC only, and 8 (11%) exclusively by ^{18}F-DOPA. Ten (13%) tumors were not detected by both modalities. Sensitivity of ^{68}Ga-DOTATOC and ^{18}F-DOPA was respectively 76% and 70% (p=0.275) (Table 2). CgA and 5-HIAA values were not different according to metabolic tumor imaging profile (p=0.73 for CgA, p=0.80 for 5-HIAA). Tumor intestinal multifocality was confirmed by histology in 8 (16%) patients. Among them, ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT were concordant positive for tumor multifocality in 5 (63%) patients. In 2 cases (25%) PET/CT studies were discordant positive (1 case with only ^{68}Ga-DOTATOC PET/CT positivity, and one case with only ^{18}F-DOPA PET/CT positivity). In the last patient both ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT failed to detect multifocal disease.

^{18}F-DOPA Performed Better than ^{68}Ga-DOTATOC PET/CT for the Evaluation of LN Metastases

Mesenteric Lymph Nodes. Three lymph node groups have been considered (*7*): group-1: in contact with the small bowel, group-2 in the middle of the mesentery, and group-3 at the origin of the mesenteric vessels under the pancreatic uncus. Pathological data about nodal PET/CT positivity according to the above mentioned 3-scale classification was available for 32 selected patients (Figure 1) from Strasbourg and Beaujon University Hospitals.

On a *per-region* analysis, 33 of the 96 (34%) analyzed regions were considered positive by both modalities and 5 (5%) were only ^{18}F-DOPA positive. No regions showed exclusive ^{68}Ga-DOTATOC abnormality. ^{18}F-DOPA detected significatively more positive regions than ^{68}Ga-DOTATOC (100% *vs* 87%; p=0.025). Regarding subgroup analysis, two group-1 regions (17%) (p=0.157), two group-2 regions (10%) (p=0.157), and one group-3 regions (17%) (p=0.317) were positive only on ^{18}F-DOPA PET/CT (Supplementary Table 1).

Per-lesion-based analysis revealed a total of 67 nodal mesenteric pathologic focal uptake of either ^{68}Ga-DOTATOC or ^{18}F-DOPA, of which 58 (87%) were common to both modalities: 14/16 (88%) for group-1, 33/36 (92%) for group-2, and 11/14 (79%) for group-3. No lymph node was positive only on ^{68}Ga-DOTATOC PET/CT, and 9 (14%) were positive only on ^{18}F-DOPA studies. Global DR% of ^{18}F-DOPA PET/CT was significantly higher than that of ^{68}Ga-DOTATOC PET/CT (100% vs. 88%, p=0.003). Moreover, a statistically significant difference was observed for group-3 when considered independently (100% *vs.* 79%, p=0.046) or pooled with group-2 (100% *vs.* 86%, p=0.008). Finally, DR% was equivalent for both group-1 (100% *vs* 88%, p=0.16) and group-2 lymph nodes (100% *vs* 92%, p=0.32) when analyzed independently. Results are summarized in Table 2.

Subdiaphragmatic Lymph Nodes. On a *per-region* analysis, 40 (75%) patients had at least one subdiaphragmatic lymph node detected by ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT, one (2%) patient had at least one subdiaphragmatic lymph node detected by ^{68}Ga-DOTATOC only, and four (8%) patients had at least one subdiaphragmatic lymph node detected by ^{18}F-DOPA only. In eight (15%) patients, no pathological subdiaphragmatic lymph nodes were detected by both modalities. DR% of ^{68}Ga-DOTATOC and ^{18}F-DOPA were not significatively different (91% vs. 98%, p=0.18 (Supplementary Table 1).

On a *per-lesion* analysis, a total of 184 subdiaphragmatic foci of lymph-node pathologic uptake of either ^{68}Ga-DOTATOC or ^{18}F-DOPA were revealed, and 159 (86%) were common to both modalities. Six (3%) and 19 (10%) additional nodal abnormalities were detected by ^{68}Ga-DOTATOC and by ^{18}F-DOPA PET/CT, respectively (DR%: 90% vs. 97%, p=0.009). Results are summarized in Table 2.

^{18}F-DOPA PET/CT Detected More Distant Metastases than ^{68}Ga-DOTATOC PET/CT

On a *per-region*-based analysis, 28 (53%) patients showed liver uptake abnormalities. Among them, 26 (93%) showed both positive ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT. In the remaining two (7%) patients, only ^{18}F-DOPA PET revealed liver metastases (p=0.346) (Figure 2). No patient had hepatic lesions detectable only on ^{68}Ga-DOTATOC PET/CT. No significant difference was shown between ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT for the remaining anatomical regions (i.e.: peritoneum, abdominal lymph nodes, left-sided supraclavicular lymph nodes, supra-diaphragmatic lymph nodes (excluding the left supraclavicular region), lung/pleura, bones, and other metastatic sites). Results are summarized in Supplementary Table 1.

On a *per-lesion*-based analysis, a total of 671 foci of pathologic uptake on either ^{68}Ga-DOTATOC or ^{18}F-DOPA indicating extra-nodal metastases were detected (Table 2). Among them, 491 (73%) were common to both modalities, 38 (6%) were detected on ^{68}Ga-DOTATOC only, and 142 (21%) exclusively on ^{18}F-DOPA. ^{18}F-DOPA had a better global DR% for detection of distant metastases than ^{68}Ga-DOTATOC (94% vs. 79%, p<0.001). ^{18}F-DOPA PET/CT performed better than ^{68}Ga-DOTATOC PET/CT for the detection of liver metastases (98.9% *vs* 87.4%, p<0.001), peritoneal carcinomatosis (95.5% *vs* 47.3%, p<0.001), and lung metastases (100% *vs* 50.0%, p<0.001). ^{68}Ga-DOTATOC PET/CT detected significantly more left supra-clavicular lymph nodes than ^{18}F-DOPA (100 % *vs* 82.6%, p=0.046). Finally, no statistically significant difference was observed for bone metastases and supra-diaphragmatic lymph nodes.

Imaging Protocol, Ki67, Tumor Grade, Biological Markers

Thirty-one and 22 patients underwent ^{68}Ga-DOTATOC before ^{18}F-DOPA PET/CT and vice versa, respectively. In both cases, ^{18}F-DOPA PET revealed more lesions than ^{68}Ga-DOTATOC

PET (p=0.002, ^{18}F-DOPA first; p<0.001, ^{68}Ga-DOTATOC first). The number of discordant lesions was not correlated to the time elapsed between the two PET studies (ρ=0.286; p=0.081), suggesting a minor influence of the imaging sequence on final PET/CT results.

No correlation was showed between Ki67 index and the number of discordant lesions in the entire population (ρ=0.06; p=0.67) and only in patients with discordant PET results (ρ=0.23; p=0.17).

Lesion-based detection rate of ^{18}F-DOPA PET was better than that of ^{68}Ga-DOTATOC PET regardless the tumor grade (G1: p<0.001, G2: p<0.001, G3: p<0.004) and patient treatment (long-acting somatostatin analogs: p<0.001, no treatment: p<0.001).

Quantitative values of serum CgA and urinary 5-HIAA were available for 35 (66%) and 26 (49%) patients, respectively. CgA and 5-HIAA levels were increased in 28 and 14 patients, respectively. A moderate statistically significant correlation was shown between the total number of lesions detected by either ^{68}Ga-DOTATOC or ^{18}F-DOPA, and the level of CgA ($r_{DOTATOC}$=0.32, p=0.003; r_{DOPA}=0.36, p=0.016) and 5-HIAA ($r_{DOTATOC}$=0.34, p=0.043; r_{DOPA}=0.44, p=0.013).

DISCUSSION

Only a few studies have compared ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT in patients with SiNET. Before further considerations, it is necessary to distinguish diagnostic from theragnostic applications. ^{68}Ga-SSA PET/CT remains mandatory for selecting candidates for PRRT. By contrast, the choice of the most appropriate diagnostic imaging modality should rely on diagnostic performances. Thus, there is no reason to disqualify ^{18}F-DOPA PET/CT in a purely diagnostic setting (*13*).

In our series, ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT identified at least one primary SiNET in 86 % of cases achieving a similar *per lesion* sensitivity of 76 % and 70 %, respectively. Several reasons may decrease detectability of small primaries on PET/CT such as partial volume effect and bowel peristalsis. The sensitivity of conventional pre-surgical diagnostic investigations remains suboptimal and intraoperative palpation of the entire small intestine should be routinely performed to improve the detection of multifocal primary SiNET (*14*).

Resection of at least 8 lymph nodes is advocated (when possible) alongside with the resection of the primary SiNET (*6*,*15*). A systematic extensive nodal resection including the retro

pancreatic area around the origin of the superior mesenteric vessels has been proposed to prevent unresectable local recurrence (*3*,*16*). Moreover, up to 67 % of patients could present with skip metastases of which 19 % are retropancreatic (group-3) without nodal invasion around the mesenteric vessels (*7*). In our study, the DR % of subdiaphragmatic metastatic lymph nodes during initial staging was significantly higher for ^{18}F-DOPA compared to ^{68}Ga-SSTR PET/CT. Moreover, when focusing exclusively on mesenteric lymph-node metastases, ^{18}F-DOPA PET/CT detected more positive regions (group-1 to -3) and metastatic lymph nodes than ^{68}Ga-DOTATOC PET/CT (p=0.005 and p=0.003, respectively). Noteworthy, a statistically significant difference (p=0.046) was also shown for the detection of group-3 pathologic lymph nodes. This result appears to be novel and given its potential therapeutic impact in patients with siNENs, it will need to be confirmed by prospective clinical trials.

^{18}F-DOPA performed better than ^{68}Ga-DOTATOC PET/CT for the detection of liver (p<0.001), peritoneal (p<0.001), and lung lesions (p<0.001). Similar results have been recently reported by our group from the retrospective comparison of ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT in a series of 41 patients with well-differentiated SiNET during the post-surgical follow-up (*17*). ^{18}F-DOPA PET/CT was found to have a significantly higher metastatic DR % than ^{68}Ga-DOTATOC PET/CT (p<0.001). 122/605 (20 %) lesions were revealed exclusively by ^{18}F-DOPA PET/CT. The liver was the region with the highest number of discordant results. Moreover, a trend toward significance (p=0.07) was shown for the detection of bone metastases, in favor of ^{18}F-DOPA PET/CT. In the recent study of Deleval et al. (*18*) ^{18}F-DOPA PET/CT detected bone metastases in 46 of 155 (29.7 %) SiNET patients with negative prognostic impact.

Ansquer et al. (*19*) retrospectively compared ^{18}F-DOPA and ^{68}Ga-DOTANOC PET/CT in 30 patients with SiNET. PET/CT were performed for primary staging in 9 patients, including 4 patients before surgery and 5 after surgical removal of the primary SiNET. The remaining 21 patients were investigated during regular follow-up. A total of 221 lesions were detected. Even in this case, ^{18}F-DOPA PET/CT identified significantly more lesions than ^{68}Ga-DOTANOC PET/CT with a sensitivity of 95.5 % and 88.2 %, respectively (p<0.0001). ^{18}F-DOPA PET/CT detected more lesions than ^{68}Ga-DOTANOC PET/CT in nine patients (30 %) and revealed 22 additional lesions from variable locations. Concerning the detection of primary SiNET, both imaging methods showed excellent sensitivity with detection in all the 14 patients without previous surgery. When considering only liver metastases visualized by both radiotracers, the ratio tumor SUVmax/liver

SUVmean was higher for ^{18}F DOPA than ^{68}Ga-DOTANOC for 30 out of 46 lesions (62.5 %). These findings could explain the better sensitivity of ^{18}F-DOPA for liver metastases detection. Perhaps, the upcoming clinical availability of SSTR antagonists will allow better detection of lesions (*20*) warranting further head-to-head comparative studies. In these two comparative reports, different ^{68}Ga-SSTR analogues were used for PET/CT imaging (i.e., DOTATOC and DOTANOC) but the results always remained in favor of ^{18}F-DOPA. The choice of the SSTRs subtype remains probably marginal without explaining the diagnostic difference between ^{18}F-DOPA and ^{68}Ga-SSTR PET/CT (*21*).

Veenstra et al. (*22*) retrospectively compared the detection rates of ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT for the localization of primary tumor and metastases in 45 patients with NET, including 23 (51%) SiNET. ^{18}F-DOPA revealed significantly more lesions compared with ^{68}Ga-DOTATOC in 16 SiNET patients (70%) with high circulating biomarkers levels. The relationship between tumor markers, clinical features and primary tumor location has been previously highlighted to optimize radiotracer selection in patients with NET (*23*,*24*).

We acknowledge that the present study is not tailored, as previous ones (*17*,*19*,*22*), for assessing the potential therapeutic impact of the detection of additional sites on ^{18}F-DOPA PET/CT compared to SSTR PET/CT. An additional limitation of our study consists in the lack of objective gold standard for imaging comparator for all radiotracer uptake pathological findings. However, histologic proof of all metastatic lesions was neither reasonable nor feasible.

CONCLUSION

^{18}F-DOPA PET/CT detects more lesions than ^{68}Ga-DOTATOC PET/CT in studied patients. Our results provide a great impetus towards the use of ^{18}F-DOPA PET/CT in the evaluation of SiNET at initial diagnosis and/or prior surgery. We believe that the respective role of ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT should be discussed according to the expected results in terms of disease staging and treatment selection.

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KEY POINTS

Question

Which is the most sensitive nuclear imaging modality for tumor metastatic assessment at initial staging or pre-surgical work-up in patients with SiNET?

Pertinent findings

^{18}F-DOPA PET/CT detects more lesions than ^{68}Ga-DOTATOC PET/CT in studied patients. When clinically available, ^{18}F-DOPA should be considered as the first-choice PET tracer for exhaustive metastatic assessment.

Implications for patient care

Our results encourage the use of ^{18}F-DOPA PET/CT in the evaluation of SiNET at initial diagnosis and/or prior surgery. The respective role of ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT should be discussed according to the expected results in terms of disease staging and treatment selection.

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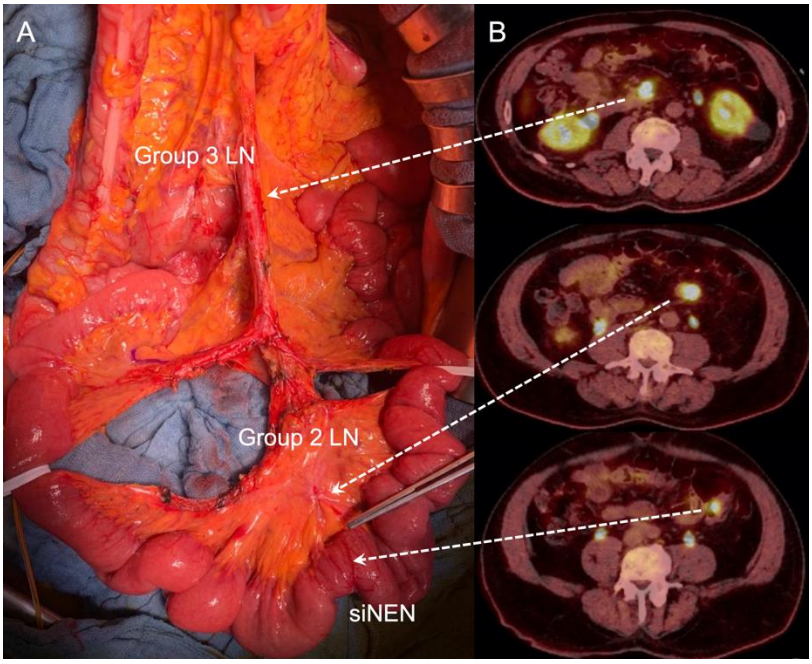


FIGURE 1. Correlation of surgical exploration and ^{18}F-DOPA PET/CT findings in a patient with G1-SiNET and metastatic mesenteric lymph nodes of group-2 and 3 according to Pasquer et al. (24).

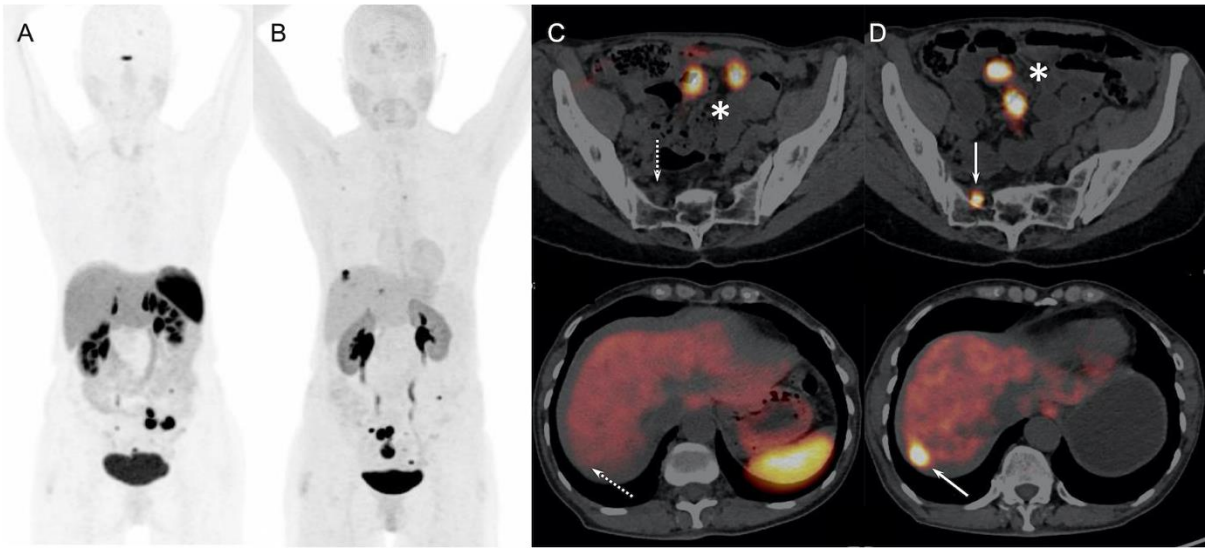


FIGURE 2. Head-to-head comparison between ^{68}Ga-DOTATOC (A, C) and ^{18}F-DOPA PET/CT (B, D) in an oligometastatic patient with bifocal SiNET (*). ^{68}Ga-DOTATOC PET/CT failed to detect hepatic and peritoneal metastases (dotted arrows) visible only on ^{18}F-DOPA PET/CT imaging (arrows).

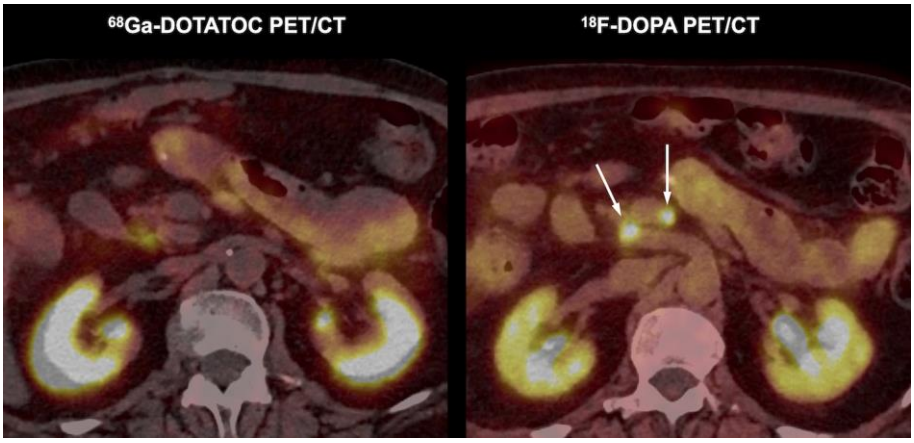
TABLE 1. Patient population and tumor characteristics. CgA, Chromogranin A; 5-HIAA; 24-hour urine 5-Hydroxyindoleacetic acid; n (%), mean (SD).

Patients	53
Women (%)	31(58)
Age (years), mean (SD)	65(13)
PET/CT indication	
Suspicion of SiNET (%)	15(28)
Staging of a histologically proven metastatic SiNET (%)	38(72)
Grade (WHO 2019)	
G1 (%)	23(43)
G2 (%)	25(47)
G3 (%)	3(6)
Ki-67, mean (SD)/median	5.8(8.7)/3.7
Biochemical tumor markers	
Elevated serum CgA (%)	28(53)
Elevated urinary 5-HIAA (%)	14(26)
Long-acting somatostatin analogs (%)	13(25)

TABLE 2. Comparison between ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT for primary SiNET and metastases (DR %): *per-lesion* analysis. LN: lymph nodes; *: 76 primary SiNET detected at histology (sensitivity) in 37 operated patients.

	^{68}Ga-DOTATOC	^{18}F-DOPA	Lesions	Discordant patients	*p*
All primary SiNET	106(91%)	103(88%)	117	14	0.549
Operated primary SiNET	58(76%)	53(70%)	76*	12	0.275
Primary multifocality	6(75%)	6(75%)	8(100%)	5	1.000
All metastases	694(81%)	811(95%)	855	38	<0.001
Subdiaphragmatic LN	165(90%)	178(97%)	184	14	0.009
Mesenteric LN	58(88%)	67(100%)	67	7	0.003
Mesenteric LN, group-1	14(88%)	16(100%)	16	2	0.157
Mesenteric LN, group-2	33(92%)	36(100%)	36	3	0.317
Mesenteric LN, group-3	11(79%)	15(100%)	15	3	0.046
Liver	312(87%)	353(99%)	357	12	<0.001
Peritoneal	53(47%)	107(96%)	112	12	<0.001
Lung	13(50%)	26(100%)	26	4	<0.001
Bone	98(84%)	100(86%)	116	7	0.732
Supradiaphragmatic LN	30(81%)	28(76%)	37	10	0.617
Left supraclavicular LN	23(100%)	19(83%)	23	3	0.046

509 **Graphical Abstract**



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SUPPLEMENTAL MATERIAL

Supplemental TABLE 1. Comparison between ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT for primary SiNET and metastases (DR%): *per-region* analysis. Abbreviations: LN, lymph nodes; n (%). *: 37 (70%) patients underwent surgery after PET/CT.

	^{68}Ga-DOTATOC	^{18}F-DOPA	Total	*p*
All primaries	46(96%)	45(94%)	48	0.655
Operated primaries	34(94%)	34(94%)	37*	1.000
All metastatic regions	117(93%)	118(95%)	126	0.808
Subdiaphragmatic LN	41(91%)	44(98%)	45	0.180
Mesenteric LN, all groups	33(87%)	38(100%)	38	0.025
Mesenteric LN, group-1	10(83%)	12(100%)	12	0.157
Mesenteric LN, group-2	18(90%)	20(100%)	20	0.157
Mesenteric LN, group-3	5(83%)	6(100%)	6	0.317
Hepatic	26(93%)	28(100%)	28	0.346
Peritoneal	12(86%)	12(86%)	14	1.000
Lung	5(100%)	5(100%)	5	1.000
Bone	15(100%)	14(93%)	15	0.317
Supradiaphragmatic LN	9(75%)	12(100%)	12	0.083
Left supraclavicular LN	7(100%)	5(71%)	7	0.157