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par

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La TEP/TDM aux analogues de la somatostatine marqués au gallium-68 dans l'exploration des paragangliomes et phéochromocytomes. Intérêt de l'association avec d'autres traceurs TEP : retour d'expérience du CHU de Nantes.

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Abstract

Introduction

PET/CT with gallium-68-labelled somatostatin analogues (^{68}Ga-SMSa PET/CT) is recommended in patients with paraganglioma (PGL) and pheochromocytoma (PHEO). Our retrospective study analyzed the sensitivity of ^{68}Ga-SMSa PET/CT in PGL/PHEO patients explored in the University Hospital of Nantes between 2014 and 2020, in comparison with the other PET/CT procedures.

Methods

Consecutive patients with PGL/PHEO who underwent a ^{68}Ga-SMSa-PET/CT in addition to morphological imaging (at least thoraco-abdomino-pelvic CT, head and neck MR-angiography) for pre-symptomatic screening, initial staging or follow-up were included.When performed, data from ^{18}F-DOPA-PET/CT and ^{18}FDG-PET/CT were also analyzed and compared to ^{68}Ga-SMSa-PET/CT. For each tracer, uptake higher than physiological background was considered as pathological and was confronted to the gold standard (histopathology, positivity of at least another imaging modality or follow-up).

Results

A total of 48 patients (25 women, 23 men; median age 53,5 years) were explored by ^{68}Ga-SMSa PET/CT: 9 for presymptomatic screening, 17 for initial staging and 22 for follow-up. Eight patients were free of disease and at least one lesion had been confirmed in 40 patients: 20 localized PGL/PHEO, 13 metastatic or multifocal PGL and 7 metastatic or multifocal PHEO. A total of 197 lesions were confirmed by the gold standard corresponding to 59 primary tumors or local recurrences and 138 metastases. Germline mutations were identified in 19 out of these 40 patients (1 SDHA, 12 SDHB, 2 SDHC, 4 SDHD), not identified in 18 patients and remained indeterminate in 3 patients. Among the 8 disease-free patients, ^{68}Ga-SMSa-PET/CT was true negative in seven and false positive in one case.

In the whole population, per-patient sensitivities were 95% (38/40) with ^{68}Ga-SMSa PET/CT, 86% (12/14) with ^{18}F-DOPA PET/CT and 96% (27/28) with ^{18}FDG PET/CT and per-lesion sensitivities were 92% (181/197) with ^{68}Ga-SMSa PET/CT , 93% (40/43) with ^{18}F-DOPA PET/CT and 84% (138/164) with ^{18}FDG PET/CT . ^{68}Ga-SMSa-PET/CT detected all the 30 HNPGLs, 16 out of 17 (94%) PHEOs, 10 out of 13 (77%) subdiaphragmatic PGLs and 126 out of 138 (91%) metastases. The 16 false negative of ^{68}Ga-SMSa PET/CT were 5 pulmonary and 5 liver metastases, 4 subdiaphragmatic primaries, 1 subdiaphragmatic and 1 supra-diaphragmatic lymph node. Eight out of 16 (50%) were detected by ^{18}FDG PET/CT as well as 9 out of the 10 lesions (90 %) explored with ^{18}F-DOPA PET/CT.

In the eleven patients who underwent both the 3 exams, ^{18}F-DOPA PET/CT detected significantly more lesions than ^{68}Ga-SMSa PET/CT (95% (38/40) vs 75% (30/40); p = 0,02) and than ^{18}FDG PET/CT (95% (38/40) vs 70% (28/40); p = 0,006).

Conclusion

Our study confirms the high sensitivity of ^{68}Ga-SMSa PET/CT for the exploration of PGL and PHEO and highlights some limits for the detection of lung and liver metastases as well as subdiaphragmatic lesions.

Best performances are obtained by combining nuclear imaging modalities, especially in sporadic diseases, in metastatic or multifocal diseases and subdiaphragmatic PGLs.

Introduction

Following the World Health Organization Classification of Tumor, paragangliomas (PGLs) are chromaffin cell tumors developing from the sympathetic and parasympathetic ganglia throughout head and neck and the abdomen, whereas pheochromocytomas (PHEOs) are chromaffin cell tumors developing within the adrenal medulla (1). Histopathology does not permit to differentiate these two entities: therefore, diagnosis is based on anatomical location (2) and malignancy is defined as the presence of chromaffin tumors in locations where chromaffin cells are not usually present (3).

These are rare tumors with an estimated annual incidence between 4 and 6 per million, with PGLs probably more numerous than PHEOs (3) (4).

These tumors can occur at any age but are more frequently observed in the fourth and fifth decades. Gender distribution seems to be equal. In young patients, PGLs or PHEOs are more oftenly linked to a germline mutation, particularly in the autosomal genes encoding for the Succinate Deshydrogenase (SDH) enzyme: subunits A, B, C and D. Inherited genetic mutations occur in more than 40% of cases and expose patients to multifocal or metastastic disease (especially in cases of SDHB mutation). Many kinds of clinical presentations are observed, depending on tumor location, ability to secrete methoxyamines, and spread of the disease.

Accurate imaging is mandatory at any stage of the disease for an optimal clinical management of affected patients and also for earlier diagnosis and treatment of family members. Functional imaging has been used for several decades for the staging of PHEOs/PGLs, with metaiodobenzylguanidine radiolabeled with the gamma-emitters 131 or 123 iodine (5) (6) or ^{18}F-fluorodeoxyglucose (^{18}FDG) (7) (8) (9) and more recently with ^{18}F-fluorodihydroxyphenylalanine (^{18}F-FDOPA) positron emission tomography/computed tomography (PET/CT) (10) (11) (12) As PGLs overexpress somatostatin receptors (SSTR), especially the subtype 2 (SSTR2) (13), these tumors are targetable by radiolabeled somatostatin analogues (SMSa). Initially radiolabeled with the gamma emitters Indium 111 or pertechnetate, several SMSa radiolabeled with gallium-68, a positron emitter (^{68}Ga-DOTA-TATE, ^{68}Ga-DOTA-NOC and ^{68}Ga-DOTA-TOC) became available for clinical use, and manufactured authorization has been recently obtained in EU and US for ^{68}Ga-DOTA-TOC and ^{68}Ga-DOTA-NOC respectively. In the first reports of literature ^{68}Ga-SMSa PET/CT showed with very promising results in SDHD head and neck PGLs (HNPGL) (14) (15), in metastatic PGL and PHEO (16), and especially SDHx-related metastatic PGL (17). The choice between the different monophotonic and PET tracers may be guided by the tumor location (tightly linked to embryological origin) and the genetic background (18) (19) (20). The revised 2019 European Association of Nuclear Medicine practice guideline/Society of Nuclear Medicine and Molecular Imaging procedure standard has proposed ^{68}Ga-SMSa PET/CT as the first line imaging strategy for PGLs and as the second line imaging strategy for sporadic or inherited PHEOs, after ^{18}FDOPA PET/CT (18).

Our retrospective monocentric study reports our first experience in patients with PGLs and PHEOs explored with ^{68}Ga-SMSa PET/CT in our institution, in complementary to morphological imaging and in many cases, to ^{18}FDG-PET/CT and ^{18}F-DOPA PET/CT. The impact of mutation status, tumoral locations, multifocality or malignancy on the diagnostic performances of the different PET tracers was analyzed.

Methods

1. Patients

Consecutive patients with suspected or histologically proven PGL or PHEO who underwent a ^{68}Ga-SMSa PET/CT at the University Hospital of Nantes, between September 2014 and April 2020 were retrospectively included.

^{68}Ga-SMSa PET/CT were performed in complementary to morphological imaging, including thoraco-abdomino-pelvic CT with contrast injection; head and neck MR angiography and, when indicated, bone and/or liver MR.

The sensitivity of ^{68}Ga-SMSa PET/CT was calculated and compared to the sensitivity of ^{18}FDG PET/CT or ^{18}F-DOPA PET/CT when performed.

For the comparative analysis, the delay accepted between the different PET/CT was adapted to the natural evolution of the disease and to its malignancy. Were included in the intra-individual comparative study only the exams performed in a period without therapeutic modification and with perfect lesional stability on morphological imaging.

Patients were explored before July 2017 with ^{68}Ga-DOTANOC PET/CT as part of a transitional authorization for nominative use (ATU) obtained from the ANSM and, after July 2017, by the manufactured ^{68}Ga-DOTATOC (Somakit®TOC, AAA).

Due to the retrospective nature of this study, ethical approval was given by the local institutional ethics committee. Informed consent was obtained for each patient before genetic analysis (with parental agreement obtained for minors) and surgery. Patient information was de-identified before data analysis.

2. PET/CT procedures

^{68}Ga-DOTANOC was prepared using fully automated synthesis method, with Modular-Lab PharmTracer (Eckert & Ziegler) as previously described (Decristoforo et al. 2007) and ^{68}Ga-DOTATOC is prepared according to the specificities of the SPC of the Advance Accelerator Applications laboratory. The product used is Somakit TOC 40 µg of edotreotide labelled with a gallium chloride solution (^{68}Ga).The generator used is the GalliaPharm 1.85 GBq from Eckert & Ziegler Radiopharma Gmb.

All imagings were performed on a dedicated PET-CT system: Biograph mCT (40 or 64) or Biograph Vision 450 (Siemens Healthcare Molecular Imaging USA, Inc.).

Images were acquired 60 minutes after the injection of 150 MBq of ^{68}Ga-SMSa or 3 MBq/Kg of ^{18}F-DOPA or ^{18}FDG. The time acquisition was 3 min per step, for the 3 tracers. No premedication by Carbidopa was performed before ^{18}F-DOPA PET/CT and a 6-hour fasting was required before intraveinous injection of ^{18}FDG.

If patients were treated by long-acting SMSa, ^{68}Ga-SMSa PET/CT was performed as far as possible from the last injection.

Low-dose CT 3D was performed for attenuation correction, without contrast product injection for all

patients, from vertex to mid-thighs, automatic mA according to the patient weight (80-140 kV) with 3mm slice thickness.
Iterative reconstruction had been applied: OP-OSEM-PSF-TOF HD and TOF: 3 iterations, 21 subsets with a Gaussien 3D filter (FWHM 4 mm).

3. PET/CT analysis

^{68}Ga-SMSa PET/CT, ^{18}F-DOPA PET/CT and ^{18}FDG PET/CT were interpreted independently by two experienced nuclear medicine physicians (CA and CM). If the result between the two physicians was discordant, a third reader was consulted.
Focal uptake was considered to be pathological if it did not correspond to the physiological biodistribution of the tracers (pituitary gland, spleen, adrenals, urinary tract for ^{68}Ga-SMSa; central grey nuclei, pancreas, biliary and urinary tracts for ^{18}F-DOPA and brain, heart, urinary and digestive tracts for ^{18}FDG).
Nine anatomical areas were defined for per-regional analysis. There were, for primary tumors: HNPGL, subdiaphragmatic PGL and PHEO or adrenal-bed recurrence; and for metastases: bone, sub-diaphragmatic lymph nodes, supra-diaphragmatic lymph nodes, lungs, liver and peritoneal carcinomatosis.
In case of spread disease, a maximum of 5 lesions per site involved were considered for sensitivity analysis.
A comparative semi-quantitative analysis between tracers was performed at site level, taking into account tumor maximal standard uptake value (SUVmax) of each pathological site per patient. A ratio was calculated between tumor SUVmax and liver background SUVmean, taken as the reference (measured with a 100cm2 circle in right liver).

4. Statistical analysis

Due to the high frequency of multifocal or metastatic diseases, histological proof could not be obtained for each lesion. Hence, a true positive (TP) was defined as a lesion detected by an imaging method and confirmed by gold-standard, meaning confirmation by another imaging method (anatomical or functional), by histopathology or by follow-up clearly consistent with natural evolution of disease. A false negative (FN) was defined as a negative finding on an imaging method, but positive with the gold standard. A false positive (FP) was defined as a positive finding on an imaging method, but negative with the gold standard. A true negative (TN) was defined as a negative finding on an imaging method, also negative with the other imaging modalities, biology and/or histopathology.
Sensitivity (Se) was calculated for each tracer, in a per-patient and per-lesion level and were compared all together using the Fisher's exact test for count data or McNemar's test if paired data.
The differences between mean SUVmax values were tested using the Wilcoxon signed rank test or Student T test for paired data with normal distribution. P values less than 0.05 were considered to be statistically significant.

Results

1. Population characteristics

A total of 48 patients were explored by ^{68}Ga-SMSa PET/CT: 9 for presymptomatic screening and 39 with histologically proven PGL or PHEO (17 for initial staging and 22 for follow-up).

- Patients explored for presymptomatic screening

Nine patients (5 women and 4 men, median age 40 years) underwent a ^{68}Ga-SMSa PET/CT for screening in a context of a familial SDHx germline mutation (6 SDHB, 2 SDHC, 1 SDHD). Five patients underwent a ^{68}Ga-DOTANOC PET/CT and 6 patients a ^{68}Ga-DOTATOC PET/CT.
Seven of them had a negative exploration and were considered as true negative results. In the 2 other patients, ^{68}Ga-SMSa PET/CT was considered as positive (figure 1).
In the first case, ^{68}Ga-DOTA-TOC PET/CT showed twice, one year apart, an intense and unchanged focal uptake next to carotid bifurcation, in a 26-year-old female, with germline familial SDHD mutation. As this small focus could not be confirmed by two MR-angiography performed in a one-year period, and despite a high clinical presumption of infra radiological PGL, we have decided to consider this focus as uncertain and, consequently, this result as a false positive of SMSa-PET/CT (figure 1).

The second case (patient 31 in table 1) had a positive PET/CT, confirmed as pathological by gold-standard and had been included in the statistical analysis, thus, he is described in the subsequent paragraph.

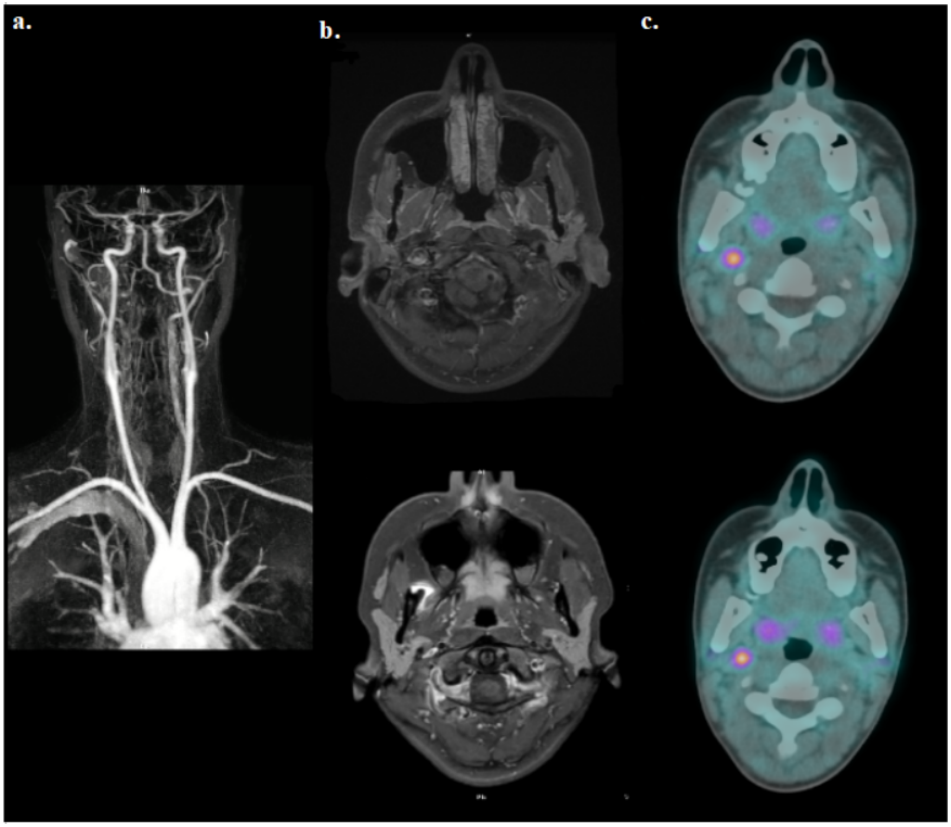

Figure 1: 26 year-old female, with germline familial SDHD mutation.
*MIP 3D coro MR-angiography did not show any anomaly (***a***.)*
*68Ga-DOTATOC PET/CT showed an intense focal uptake next to carotid bifurcation in 2019 and 2020 (***c.***) while contrast-enhanced T1-weighted fat-suppressed did not show any anomaly, one year apart (***b.***)*

- Patients with confirmed PGL/PHEO

The case above-mentioned (patient 31) is a 13-year-old patient with SDHB mutation inherited from his mother, followed annually by biology assessment and whole-body MR. Due to an increase of biological markers, he underwent a ^{68}Ga-DOTATOC PET/CT which found a left para-adrenal focal uptake, confirmed with CT-scan and MRI. The histological analysis confirmed the diagnosis of PGL. He was considered as a true positive and had been included in the statistical analysis.
By adding this patient, a total of 40 patients were included in the analysis: 20 women and 20 men, median age 55 years (from 13 to 85).
32 patients had a histologically proven PGL and 8 a PHEO (1 primary and 7 recurrences).
Methoxyamines secretion was present in 19 patients (45%): 7 patients with a PHEO and 12 patients with a PGL.
Nineteen patients had a localized PGL, 13 patients had a multifocal/ metastatic PGL, 7 had an adrenal-bed or metastatic recurrence of PHEO and 1 patient had a localized PHEO.

The characteristics of these 40 patients are summarized in table 1.

Fourteen patients underwent a ^{68}Ga-DOTANOC PET/CT and 26 patients a ^{68}Ga-DOTATOC PET/CT.
Among the 40 patients, 28 patients (70%) also underwent a ^{18}FDG PET/CT and 14 patients (35%) a ^{18}F-DOPA PET/CT.
Median delay between the modalities was 1 month between ^{68}Ga-SMSa PET/CT and ^{18}FDG PET/CT (from 2 days to 64 months) and 2 months between ^{68}Ga-SMSa PET/CT and ^{18}F-DOPA PET/CT (from 3 days to 40 months).
Only 2 patients (patient 23 and patient 37 in table 1) had a median delay superior to six months between ^{68}Ga-SMSa PET/CT and ^{18}F-DOPA PET/CT or ^{18}FDG PET/CT. We decided to keep their data for the comparative analysis as these two patients had a perfectly stable disease (localized HNPGL for one and multifocal HNPGL for the other) for many years confirmed by both anatomical and functional imaging follow-up.
Genetic testing results were available for 37/40 patients. Mutations on the succinate dehydrogenase complex were identified in 19 patients (48%): 1 SDHA, 12 SDHB, 2 SHDC, 4 SDHD. No germline mutation was identified in 18 patients (45%) and results remained indeterminate in 3 patients (7%).

2. Lesions

A total of 197 lesions were confirmed by the gold standard. There were 59 primary lesions: 30 HNPGLs, 17 PHEOs (1 primary and 16 adrenal-bed recurrences) and 12 subdiaphragmatic PGLs (7 retroperitoneum, 2 para-adrenal, 2 pelvic and 1 gallblader) and 138 metastases: in bone (n = 48), supradiaphragmatic lymph nodes (n = 25), subdiaphragmatic lymph nodes (n = 24), lungs (n = 17), liver (n = 14) and peritoneal carcinomatosis (n = 10).

Table 1: characteristics of patients with confirmed lesions

Patient	Sex	Age	Germline mutation	Location of primary or local recurrence	Location of metastases	Hormone release
1	M	63	Sporadic	L adrenal	SbD lymph node	Adr, Noradr
2	F	66	Sporadic	R jugulo-tympanicum	None	None
3	F	85	Sporadic	L adrenal-bed	PC	Noradr
4	F	60	Sporadic	L carotid body	None	None
5	M	41	Sporadic	L adrenal	SpD & SbD lymph node, liver, bone	Adr, Noradr
6	F	54	Sporadic	Retroperitoneum	None	ChromA
7	M	70	Sporadic	L adrenal-bed	Bone	Noradr, ChromA
8	F	56	Sporadic	L carotid body	None	None
9	M	53	Sporadic	L adrenal-bed, Pelvic	None	None
10	F	72	Sporadic	R jugular foramen	None	ChromA
11	F	70	Sporadic	Pelvic	SubD lymph node	Noradr
12	F	38	Sporadic	R adrenal	Liver	Adr, Noradr
13	F	70	Sporadic	L adrenal-bed	SpD & SbD lymph node, lung, bone	Noradr, ChromA
14	M	58	Sporadic	R jugular foramen	None	None
15	F	84	Sporadic	L jugulo-tympanicum	None	None
16	M	62	Sporadic	Retroperitoneum	SpD & SbD lymph node, lung, bone	Noradr, ChromA
17	F	44	Sporadic	R jugulo-tympanicum	None	None
18	F	54	Sporadic	L jugulo-tympanicum	None	None
19	M	52	SDHA	Retroperitoneum, Pelvic	None	Noradr, ChromA, Dop
20	M	47	SDHB	L carotid body	SpD & SbD lymph node, lung, liver, bone	None
21	M	36	SDHB	R body carotid	Bone	ChromA
22	M	42	SDHB	Retroperitoneum	Bone	ChromA
23	M	77	SDHB	R jugulo-tympanicum	None	ChromA
24	F	48	SDHB	L jugular foramen	None	Adr, Noradr, ChromA
25	M	32	SDHB	Retroperitoneum	SpD & SbD lymph node, PC, bone	ChromA
26	F	34	SDHB	R jugulo-tympanicum	None	None
27	F	47	SDHB	R frontal sinus	Liver	Noradr, ChromA
28	F	28	SDHB	L carotid body	Liver, Bone	None
29	M	46	SDHB	Inferior cervical	None	None
30	M	55	SDHB	R jugular	None	None
31	M	13	SDHB	L para-adrenal	None	Adr, Norad, ChromA
32	M	30	SDHC	L jugular foramen	None	None
33	M	51	SDHC	R jugulo-tympanicum	None	None
34	F	62	SDHD	R&L jugulo-tympanicum, L jugular foramen, L carotid body, Gallblader	Lung, Liver, Bone	None
35	F	57	SDHD	R&L carotid body, Inferior cervical, R para-adrenal	lung	None
36	M	58	SDHD	R vagal, R carotid body	SpD & SbD lymph node	None
37	F	63	SDHD	R jugular foramen, R&L carotid body	None	None
38	F	32	Unknown	R carotid body	None	None
39	M	71	Unknown	R adrenal	None	Noradr, ChromA
40	M	64	Unknown	Retroperitoneum	None	None

Adr Adrenaline *Noradr* Noradrenaline *ChromA* Chromogranine A *Dop* Dopamine *SpD* Supradiaphragmatic *SbD* Subdiaphragmatic *PC* Peritoneal carcinomatosis

3. PET analysis in the population with confirmed lesions

3.1 PET per-patient sensitivities

^{68}Ga-SMSa PET/CT were positive in 38/40 patients (Se = 95%), ^{18}FDG PET/CT in 27/28 patients (Se = 96%) and ^{18}F-DOPA PET/CT in 12/14 patients (Se = 86%).

The two patients false negative in ^{68}Ga-SMSa PET/CT had a metastatic disease with, in the first case, four liver metastases from a PHEO, all confirmed by MRI and per-operative contrast-enhanced ultrasound, three out of four were detected by ^{18}F-DOPA PET/CT and one by ^{18}FDG PET/CT. In the second case, one pelvic PGL plus one external iliac lymph node, confirmed by histopathology, CT-scan, ^{18}FDG PET/CT and ^{18}F-DOPA PET/CT.

The only patient false negative in ^{18}FDG PET/CT had a HNPGL confirmed by histopathology, MR-angiography, CT-scan, ^{68}Ga-SMSa PET/CT and ^{18}FDOPA PET/CT.

The two patients false negative in ^{18}F-DOPA PET/CT had respectively, a right localized PHEO confirmed by histopathology, CT-scan, ^{68}Ga-SMSa PET/CT and ^{18}FDG PET/CT and, in the other case, a right juxta-adrenal PGL, confirmed by histopathology, CT-scan, ^{68}Ga-SMSa PET/CT and ^{18}FDG PET/CT.

3.2 PET per-lesion sensitivities

^{68}Ga-SMSa PET/CT identified 181/197 confirmed lesions (Se = 92%); ^{18}FDG PET/CT identified 139/164 confirmed lesions (Se = 85%) and ^{18}F-DOPA PET/CT identified 40/43 confirmed lesions (Se = 93%).
Combination of 2 or 3 PET modalities increased the sensitivity of detection as indicate in table 2, especially the combination with ^{18}FDOPA PET/CT with a 98% sensitivity for the associations ^{68}Ga-SMSa PET/CT or ^{18}FDG PET/CT and ^{18}FDOPA PET/CT.

In the whole population, there were 16 false negative lesions with ^{68}Ga-SMSa PET/CT: 5 pulmonary metastases, 5 liver metastases, 3 subdiaphragmatic primaries (2 pelvic PGLs and 1 retroperitoneum PGL), 1 adrenal-bed recurrence, 1 subdiaphragmatic and 1 supra-diaphragmatic lymph node.

- All of the 16 ^{68}Ga-SMSa PET/CT false negative lesions were explored with ^{18}FDG PET/CT and 8 (50%) out of them were positive: 2/5 liver metastases, 4/5 lung metastases, 1/2 pelvic PGL, and 1/1 subdiaphragmatic lymph node.
- 10 out of these 16 lesions were explored with ^{18}F-DOPA PET/CT, and 9 (90%) were detected (3/3 subdiaphragmatic primaries, 1/1 adrenal-bed recurrence, 4/5 liver metastases and 1/1 subdiaphragmatic lymph node) (figure 2 & 3).

There were 25 ^{18}FDG PET/CT false negative lesions: 3 subdiaphragmatic PGLs (2 retroperitoneum and 1 pelvic), 4 recurences in adrenal-bed, 6 HNPGLs, 7 lung metastases, 4 liver metastases and 1 supradiaphragmatic lymph node.

- ^{68}Ga-SMSa PET/CT detected 17 of them (68%): 1/3 subdiaphragmatic PGL and 4 adrenal-bed recurrences, 6/6 HNPGLs, 6/7 lung metastases, 1/4 liver metastases and 0/1 supradiaphragmatic lymph node.
- 12 lesions were explored by ^{18}F-DOPA PET/CT, and 11 were detected (92%): 4/4 subdiaphragmatic PGLs (2 retroperitoneum PGL and 2 pelvic PGL), 2 recurrences in adrenal-bed, 2/2 HNPGLs, 1/1 lung metastasis and 2/3 liver metastases.

There were 3 ^{18}F-DOPA PET/CT false negative lesions: 1 PHEO, 1 para-adrenal PGL and 1 liver metastasis.

- ^{68}Ga-SMSa PET/CT detected the 2 subdiaphragmatic primaries but not the liver metastasis.
- ^{18}FDG PET/CT explored 1 PHEO and the liver metastasis and detected only the PHEO.

4. Subgroup analysis

4.1 Patients who underwent 2 or 3 PET explorations

Fourteen patients with a total of 43 lesions underwent both ^{68}Ga-SMSa PET/CT and ^{18}F-DOPA PET/CT. ^{68}Ga-SMSa PET/CT per-patient sensitivity was similar to ^{18}F-DOPA PET/CT : 86% (12/14) vs 86% (12/14). In per-lesion analysis, ^{68}Ga-SMSa PET/CT showed a lower sensitivity than ^{18}F-DOPA PET/CT : 77% (33/43) vs 93% (40/43). Nontheless, this difference was not significant ; $p = 0,06$.

Twenty-eight patients with a total of 164 lesions underwent both ^{68}Ga-SMSa PET/CT and ^{18}FDG PET/CT (n = 164 lesions). ^{68}Ga-SMSa PET/CT and ^{18}FDG PET/CT showed similar efficiency in per-patient analysis: 93% (26/28) vs 96% (27/28) and ^{68}Ga-SMSa PET/CT showed a significant higher per-lesion sensitivity : 90% (148/164) vs 85% (139/164) $p < 0,0001$.

Eleven patients underwent the 3 PET explorations (patients 2, 3, 4, 9, 11, 12, 19, 21, 27, 35 and 39 in table 1).

There were: 3 patients with localized disease (2 HNPGLs and 1 PHEO) and 8 patients with multifocal/metastatic disease (3 metastatic HNPGLs, 1 multifocal retroperitoneum PGL, 1 metastatic pelvic PGL and 3 recurrent PHEO).

Six of these patients had a sporadic disease, 4 had a SDHB mutation and 1 remained indeterminate.

Fourty lesions were identified in the 11 patients. There were 23 primaries: 13 PGLs (6 HNPGLs, 4 retroperitoneum PGLs, 2 pelvic PGLs and 1 para-adrenal PGL), 1 PHEO and 9 adrenal-bed recurrences and 17 metastases (5 liver metastases, 5 bone metastases, 5 peritoneal carcinomatosis lesions, 1 lung metastasis and 1 subdiaphragmatic lymph node).

^{18}F-DOPA PET/CT and ^{18}FDG PET/CT were negative in 1 patient each, and ^{68}Ga-SMSa PET/CT in 2 patients corresponding to a per-patient sensitivities of 91%, 91%, and 82% respectively ; p = 1,00 (table 2).

On a per-lesion basis, ^{18}F-DOPA PET/CT [1] detected significantly more lesions than ^{68}Ga-SMSa PET/CT [2] and ^{18}FDG PET/CT [3], respectively 95% (38/40) vs 75% (30/40) and 70% (28/40): [1] vs [2] p = 0,02 ; [1] vs [3] p = 0,006 ; [2] vs [3] p = 0,8.

Indeed, 10 ^{68}Ga-SMSa PET/CT false negative lesions were found in 5 patients, corresponding to 3 subdiaphragmatic PGLs (2 pelvic PGLs and 1 retroperitoneum PGL), 1 recrurrent PHEO, 5 liver metastases and 1 subdiaphragmatic lymph node. These 5 patients presented several mutation status: 1 SDHA, 1 SDHB and 3 not mutated.

^{18}FDG PET/CT missed 12 lesions: 2 HNPGLs, 3 subdiaphragmatic PGLs (1 pelvic PGL and 2 retroperitoneum PGLs), 3 recurrent PHEOs, 3 liver metastases, and 1 lung metastase; while ^{18}F-DOPA PET/CT missed only 2 lesions: 1 PHEO and 1 liver metastase. The higher sensitivity was obtained when combining ^{18}F-DOPA PET/CT with ^{68}Ga-SMSa PET/CT or ^{18}F-DOPA PET/CT with ^{18}FDG PET/CT [1]. These associations had led to obtain a 98% detection rate on per-lesion basis (9 more lesions detected in comparison with ^{68}Ga-SMSa PET/CT alone) and 100% on per-patient basis; whereas the association of ^{68}Ga-SMSa PET/CT with ^{18}FDG PET/CT [2] detected only 4 more lesions than ^{68}Ga-SMSa PET/CT alone (figure 4). [1] vs [2] p = $2{,}3.10^{-5}$

The only lesion which is not detected by any tracer was a millimetric liver metastase in segment IV, only seen with specific MRI sequences and with per-operative contrast-enhanced ultrasound (during radiofrequency ablation). The three other liver metastases in this patient are detected with ^{18}F-DOPA PET/CT (figure 2).

Table 2: PET per-patient and per-lesion analysis in the whole population and in the 11 patients who underwent the three PET/CT explorations.

	Whole population		Eleven patients subgroup	
	Per-patient Se	Per-lesion Se	Per-patient Se	Per-lesion Se
^{68}Ga-SMSa	95% (38/40)	92% (181/197)	82% (9/11)	75% (30/40)
^{18}F-DOPA	86% (12/14)	93% (40/43)	91% (10/11)	95% (38/40)
^{18}FDG	96% (27/28)	85% (139/164)	91% (10/11)	70% (28/40)
^{68}Ga-SMSa + ^{18}F-DOPA	100% (14/14)	98% (42/43)	100% (11/11)	98% (39/40)
^{68}Ga-SMSa + ^{18}FDG	100% (28/28)	95% (156/164)	100% (11/11)	85% (34/40)
^{18}F-DOPA + ^{18}FDG	100% (11/11)	98% (39/40)	100% (11/11)	98% (39/40)
^{68}Ga-SMSa + ^{18}F-DOPA + ^{18}FDG	100% (11/11)	98% (39/40)	100% (11/11)	98% (39/40)

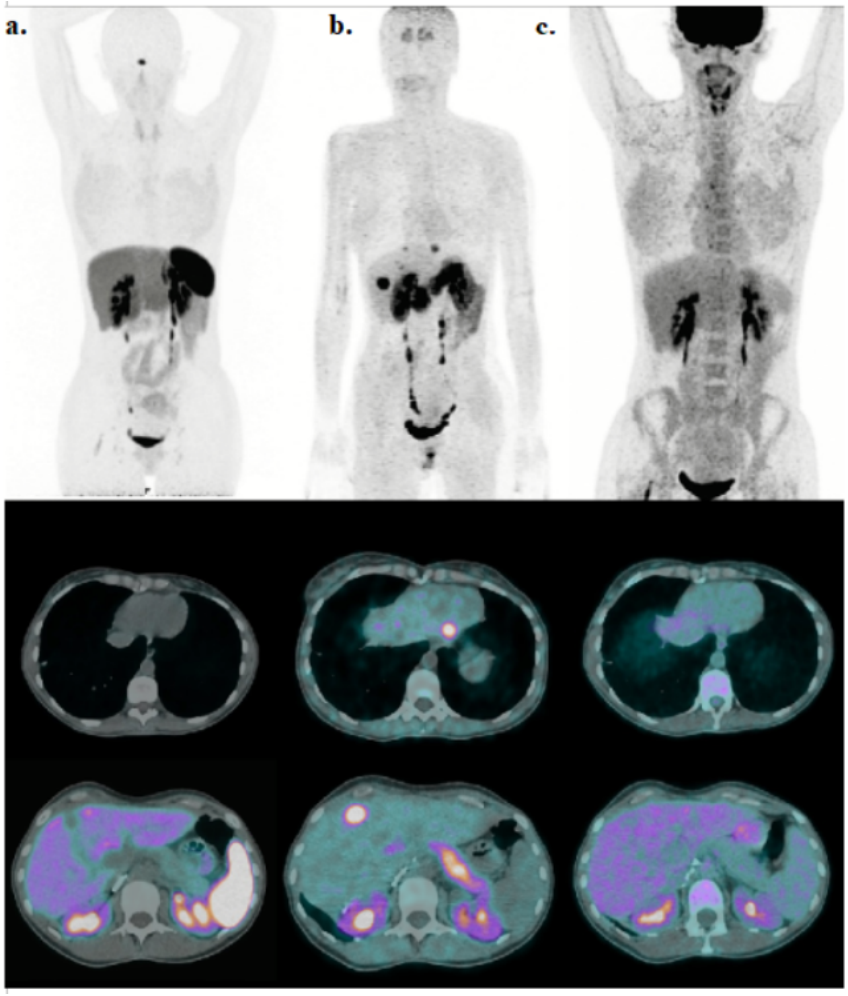

Figure 2: 38-year-old female with liver metastases from a sporadic PHEO (patient 12 in table 1).
a. *^{68}Ga-DOTATOC PET/CT maximal intensity projection (MIP) and axial-slice failed to show any uptake in pathological area.*
b. *^{18}F-DOPA PET/CT MIP and axial-slice showed intense focal uptakes corresponding to liver metastases.*
c. *^{18}FDG PET/CT MIP and axial-slice was barely normal with only a heterogenous uptake in the pathological area.*

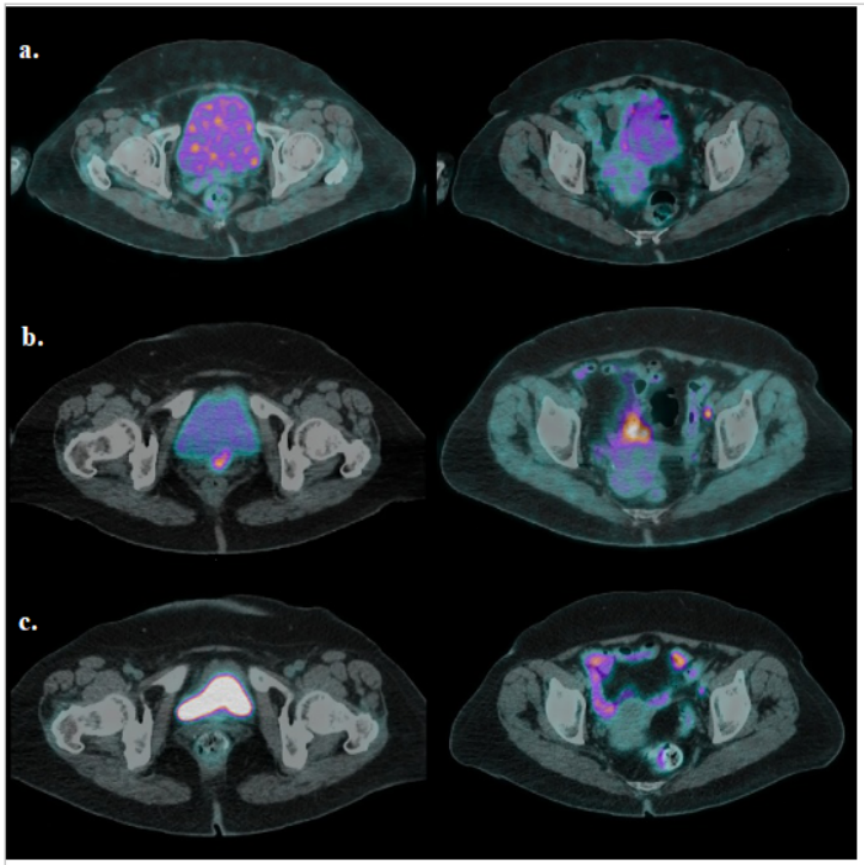

Figure 3: 70-year-old female with a sporadic retrovesical PGL and one external iliac lymph node (patient 11 in table 1).
a. *^{68}Ga-DOTANOC PET/CT axial-slices failed to show any uptake in bladder and in external iliac area.*
b. *^{18}F-DOPA PET/CT axial-slices clearly showed an intense uptake in posterior bladder wall and in external iliac lymph node.*
c. *^{18}FDG PET/CT did not detected the bladder lesion but was positive in external iliac lymph node with low intense uptake.*

4.2 Analysis according to the lesional location

Sensitivities of the tracers according to the lesions location are summarized in table 3.

^{68}Ga-SMSa PET/CT as well as ^{18}F-DOPA PET/CT detected all the HNPGLs explored and showed higher sensitivity than ^{18}FDG PET/CT in this indication (Se = 74%).

In patient with an initial diagnosis of PHEO, ^{68}Ga-SMSa PET/CT detected 16/17 PHEO or adrenal-bed recurrences, corresponding to a sensitivity of 94%, similar to ^{18}F-DOPA PET/CT (Se=90% ; 9/10). ^{18}FDG PET/CT detected fewer lesions, with a sensitivity of 76% (13/17).

The lowest detection rate of ^{18}Ga-SMSa PET/CT and ^{18}FDG PET/CT were observed for pelvic PGLs and for lung and liver metastases.

Table 3: Per-regional analysis

	^{68}Ga-SMSa	^{18}F-DOPA	^{18}FDG
HNPGL	100% (30/30)	100% (6/6)	74% (17/23)
Subdiaphragmatic PGL	77% (10/13)	89% (8/9)	70% (7/10)
Retroperitoneum	83% (5/6)	100% (10/10)	60% (3/5)
Para-adrenal	100% (2/2)	50% (1/2)	100% (1/1)
Pelvic	33% (1/3)	100% (2/2)	66% (2/3)
Gallblader	100% (1/1)	NA	100% (1/1)
PHEO or local recurrence	94% (16/17)	90% (9/10)	76% (13/17)
Metastases	91% (126/138)	94% (17/18)	89% (102/114)
SpD lymph nodes	96% (24/25)	NA	95% (19/20)
SbD lymph nodes	96% (23/24)	100% (2/2)	100% (18/18)
Bone	100% (48/48)	100% (5/5)	100% (38/38)
Liver	64% (9/14)	80% (4/5)	64% (7/11)
Lung	71% (12/17)	100% (1/1)	59% (10/17)
Peritoneal carcinomatosis	100% (10/10)	100% (5/5)	100 (10/10)
All lesion	92% (181/197)	93% (40/43)	85% (139/164)

NA Not available

4.3 Analysis depending on the mutation status

A 100% per-patient sensitivity was obtained with ^{68}Ga-SMSa PET/CT and ^{18}FDG PET/CT in pooled SDHx-mutated patients. At the lesion level, ^{68}Ga-SMSa PET/CT and ^{18}F-DOPA PET/CT showed higher sensitivities than ^{18}FDG PET/CT: 97% and 94% vs 85% (table 4).

In the SDHB subgroup, and especially in the 6 patients with metastatic SDHB-related disease, all three

tracers showed very high per-patient and per-lesion sensitivities: ^{68}Ga-SMSa PET/CT per-patient Se = 100% (6/6), per-lesion Se = 98% (59/60); ^{18}F-DOPA PET/CT per-patient Se = 100% (2/2), per-lesion Se = 100% (7/7) and ^{18}FDG PET/CT per-patient Se = 100% (5/5), per-lesion Se = 100% (53/53). The only ^{68}Ga-SMSa PET/CT false negative was a liver metastasis.

In sporadic cases, ^{18}F-DOPA PET/CT had better per-patient and per-lesion sensitivities than ^{68}Ga-SMSa PET/CT and ^{18}FDG PET/CT: respectively 100% (7/7) and 96% (22/23) vs 89% (16/18) and 85% (73/86) vs 91% (10/11) and 84% (54/64).

No significant difference was observed with ^{68}Ga-SMSa PET/CT between sporadic and SDHx-mutated populations (p = 0,24).

Table 4 : Per-patient analysis according to mutation status.

	Sporadic cases		SDHx mutated	
	Per-patient Se	Per-lesion Se	Per-patient Se	Per-lesion Se
^{68}Ga-SMSa	89% (16/18)	85% (73/86)	100% (19/19)	97% (105/108)
^{18}F-DOPA	100% (7/7)	96% (22/23)	80% (4/5)	94% (17/18)
^{18}FDG	91% (10/11)	84% (54/64)	100% (16/16)	85% (84/99)
^{68}Ga-SMSa + ^{18}F-DOPA	100% (7/7)	96% (22/23)	100% (5/5)	100% (18/18)
^{68}Ga-SMSa + ^{18}FDG	100% (11/11)	91% (58/64)	100% (16/16)	98% (97/99)
^{68}Ga-SMSa + ^{18}F-DOPA + ^{18}FDG	100% (6/6)	95% (21/22)	100% (4/4)	100% (17/17)

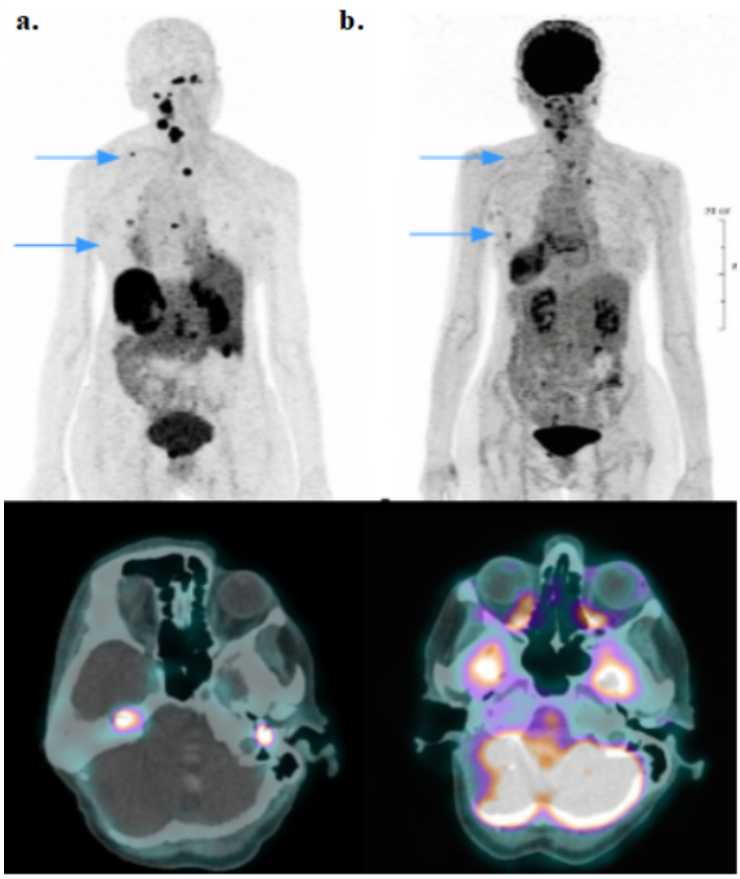

Figure 4: 62-year-old female with metastatic PGL (lungs, liver, bone) related to SDHD mutation (patient 34 in table 1). She underwent both ^{68}Ga-DOTANOC PET/CT (left) and ^{18}FDG PET/CT (right).

a. b. *Several lesions are observed on ^{68}Ga-DOTANOC PET/CT and ^{18}FDG PET/CT MIP, more or less well seen. Some lesions are detectable with one tracer but not with the other (arrows show 2 bone metastases on ribs, each tracer only detected one out of these two lesions, not detected by the other tracer).*

*This patient had, bilateral jugulo-tympanicum PGL, clearly positive with ^{68}Ga-DOTANOC PET/CT (**c.**) and negative with ^{18}FDG PET/CT (**d.**)*

For this kind of patient, tracers combination is relevant and even essential.

5. PET semi-quantitative analysis

The mean SUVmax per site was significantly higher with ^{68}Ga-SMSa PET/CT than with ^{18}FDG, respectively at 53,7 [range 1,0 – 344,0] vs 16,6 [range 2,8 – 53,6] ; p = 0,00019. We observed a difference between ^{68}Ga-SMSa and ^{18}F-DOPA : 53,7 [range 1,0 – 344,0] vs 19,0 [range 2,1 – 103,2] although it is non significant: p = 0,232 (table 5).

In HNPGL, ^{68}Ga-SMSa PET/CT and ^{18}F-DOPA PET/CT showed a 100% sensitivity, superior to ^{18}FDG PET/CT (74%). The mean SUVmax was significantly higher with ^{68}Ga-SMSa PET/CT than ^{18}F-DOPA PET/CT (84,9 vs 15,5; p = 0,0015) and than ^{18}FDG PET/CT (84,9 vs 13,0; p = $7{,}5.10^{-4}$).

In PHEO or adrenal-bed recurrence, ^{68}Ga-SMSa PET/CT showed a higher mean SUVmax than ^{18}F-DOPA PET/CT: 32,9 vs 19,5 ; and than ^{18}FDG PET/CT: 32,9 vs 11,4 even though it was not significant : p = 0,305 and p = 0,056 respectively.

A significantly higher liver background was noted with ^{68}Ga-SMSa PET/CT than with ^{18}F-DOPA PET/CT (5,4 vs 1,6 ; p = $1{,}3.10^{-8}$) and than with ^{18}FDG PET/CT (5,4 vs 2,3; p = 0,0084).

Nevertheless, when they are detected, no significant difference was found between the ratios [SUVmax of liver metastases / SUVmean of liver background], in particular between ^{68}Ga-SMSa PET/CT and ^{18}F-DOPA PET/CT (5,7 vs 4,7 ; p = 0,69) nor between ^{68}Ga-SMSa PET/CT and ^{18}FDG PET/CT (5,7 vs 6,0 ; p = 0,94).

Table 5: Semi-quantitative analysis depending on the lesions locations

	^{68}Ga-SMSa (1)	^{18}F-DOPA (2)	^{18}FDG (3)	
All sites involved mean SUVmax	53,7	19	16,6	(1) vs (2) p = 0,232 (1) vs (3) p = $1{,}9.10^{-4}$
HNPGL mean SUVmax	84,9	15,5	13,0	(1) vs (2) p = 0,001 (1) vs (3) p = $7{,}5.10^{-4}$
PHEO/adrenal-bed mean SUVmax	32,9	19,5	11,4	(1) vs (2) p = 0,305 (1) vs (3) p = 0,056
Liver metastases mean SUVmax	19,0	5,3	10,6	(1) vs (2) p = 1,00 (1) vs (3) p = 0,39
Liver background mean SUVmax	5,4	1,6	2,3	(1) vs (2) p = $1{,}3.10^{-8}$ (1) vs (3) p = 0,008
Ratio liver metastases / liver background	5,7	4,7	6,0	(1) vs (2) p = 0,690 (1) vs (3) p = 0,940

Discussion

Nuclear imaging modalities as ^{68}Ga-SMSa PET/CT, ^{18}F-DOPA PET/CT and ^{18}FDG PET/CT are accurate exams in PGLs and PHEOs allowing a whole-body exploration and providing both anatomical and functional information.

^{18}FDG is a very sensitive tracer for the detection of high carbohydrates consumption areas. This is commonly considered as the reflect of metabolic activity and biologic aggressiveness in oncology and haematology. Its interest for the exploration of PGLs and PHEO has been published since the 1990s (7), reaffirmed in the beginning of the previous decade (8) and its performances can, in some cases, compete with other PET/CT tracers (21). However, ^{18}FDG may lack of specificity particularly to differentiate between tumoral and inflammatory diseases or to identify a specific tumoral histotype. ^{18}F-DOPA and, more recently, ^{68}Ga-SMSa are both specific tracers for neuroendocrine tumors including those derived from chromafin cells as PGLs and PHEOs. These two tracers have very different mechanisms of cellular uptake and pharmacokinetics, explaining different physiological uptakes and thus different detection efficiencies depending on the tumor location and characteristics. ^{18}F-DOPA penetrates in chromaffin cells via amino acid membrane transporter and, is then transformed in ^{18}F-FDA by the L-aromatic amino acid decarboxylase, to be stored in catecholamine vesicles. Uptake and retention depend on all these players.

PGLs overexpress somatostatin receptors (SSTR), especially SSTR2 (13). SMSa tracers uptake and retention depend on the density of SST receptors on the cell membrane and the SSTR subtype expression. Despite some differences in terms of SSTRs affinities, the different SMSa available for imaging (DOTATOC, DOTANOC and DOTATE) are all characterized by a high affinity for the subtype SSTR2 (the mainly express SST among the 5 SST subtypes) without demonstrated clinical difference between them (22).

These different mechanisms mean different physiological uptakes and thus differences for interpretation criteria. For example, ^{68}Ga-SMSa PET/CT might be less efficient for detection of PHEO due to the high physiological uptake in adrenals, which is not the case with ^{18}F-DOPAPET/CT, more hamper in pancreas and biliary areas due to its pharmacokinetics.

Moreover, and despite the high specificity of these tracers, false positives had been described, particularly with ^{68}Ga-SMSa PET/CT due to inflammation, other solid tumors, hemopathies, meningiomas, oncogenic osteomalacia or simply due to physiological uncinate process of pancreas uptake (23) (24) (25)

The interest of somatostatin receptors imaging in PGL and PHEO has been documented in the past with 111n-pentetreotide (Octreoscan®). In particular, Gimenez-Roqueplo et al. (26) has explored prospectively the efficiency of Octreoscan® in presymptomatic screening for SDHx mutations, comparatively to MIBG scintigraphy and morphological imaging (head and neck MR-angiography and TAP-CT scan). They showed a lower sensitivity with somatostatin receptor scintigraphy in abdominal and pelvic PGL than with MIBG or anatomical imaging and concluded to the interest of combining functional and anatomical imaging for a better detection rate.

PET imaging with ^{68}Ga-SMSa has demonstrated higher accuracy in the detection of neuroendocrine tumors compared with Octreoscan® (27) (28). Relatively few studies have been conducted in PGL/PHEO with ^{68}Ga-SMSa, but showed very promising results. In particular, a clear superiority of ^{68}Ga-SMSa PET/CT on

^{18}F-DOPA PET/CT has been demonstrated in metastatic PGLs/PHEOs (16,29), especially in SDHB-associated metastatic ones (30) and also in HNPGLs (14,15). A clear superiority of ^{68}Ga-SMSa PET/CT was also noted when compared to ^{18}FDG PET/CT in metastatic PGL/PHEO with germline mutation (17).

Our study reports our first experience of ^{68}Ga-SMSa PET/CT in the exploration PGL and PHEO and is, to our knowledge, the first series that compare in the same patients ^{18}FDG PET/CT, ^{18}F-DOPA PET/CT and ^{68}Ga-SMSa PET/CT. We confirm the high diagnostic performances of the 3 PET tracers in the whole population, with a per-lesion sensitivity of 92%, 93% and 84%, for ^{68}Ga-SMSa PET/CT, ^{18}F-DOPA PET/CT and ^{18}FDG PET/CT respectively.
When compared with the others tracers, ^{68}Ga-SMSa PET/CT showed a significant higher per-lesion sensitivity than ^{18}FDG PET/CT (90% vs 85%) in 28 patient, but a lower per-lesion sensitivity when compared to ^{18}F-DOPA PET/CT (77% vs 93% ; p = 0,06) in 14 patients who underwent both exams, indicating that ^{68}Ga-SMSa PET/CT is not always the more accurate tracer for PGL/PHEO exploration.

Our results are nevertheless consistent with the recommendation of the Guideline for radionuclide imaging of pheochromocytoma and paraganglioma (EANM 2019) (18) situating ^{68}Ga-SMSa PET/CT as the first-choice of imaging procedure for HNPGLs. Indeed, we confirmed the excellent per-lesion sensitivity of ^{68}Ga-SMSa PET/CT in HNPGL (Se = 100%) that was, nevertheless, similar to ^{18}F-DOPA PET/CT sensitivity, but with a significantly higher uptake for ^{68}Ga-SMSa PET/CT (meanSUV max = 84,9 vs 15,5, p = 0,0015). Among the 3 tracers, ^{18}FDG was clearly the less accurate, in terms of sensitivity and uptake intensity for HNPGL exploration. Moreover, in our series, we have considered as a false positive of ^{68}Ga-SMSa PET/CT result a focal uptake next to carotid bifurcation, that was not confirmed by 2 MR-angiographies in a 26-year-old female carrying a germline SDHD mutation. Nevertheless, the probability of a sub-clinical and sub-radiological PGL is very high in this case because of the high frequency of HNPGL associated with SDHD mutation and the persistence of this focus in a one-year interval (figure 1).

Our study pointed out some limits of ^{68}Ga-SMSa PET/CT in the detection of subdiaphragmatic lesions as already observed in the “PGL.EVA” study with Octreoscan® (26) as well as in the detection of pulmonary and liver metastases. Our results demonstrate a complementarity with others PET/CT tracers and encourage association between them.
Indeed, half of ^{68}Ga-SMSa PET/CT's false negative lesions were detected by ^{18}FDG PET/CT and most of those explored with ^{18}FDOPA PET/CT were detected too.
In the subgroup of patients who underwent the 3 PET/CT exams, ^{18}F-DOPA PET/CT demonstrated the best per-lesion sensitivity and the combination ^{18}F-DOPA PET/CT plus ^{68}Ga-SMSa PET/CT or ^{18}FDG PET/CT showed equal performances in terms of lesion detection rate.

It is difficult to confirm the superiority of ^{18}F-DOPA PET/CT over ^{68}Ga-SMSa PET/CT because of the retrospective design of the study and the potential bias in the selection of patients, with an overestimation of ^{68}Ga-SMSa PET/CT false results in the patients who underwent the 3 PET/CTs. Nevertheless, these data

illustrated the complementarity of ^{68}Ga-SMSa with the others PET tracers and especially with ^{18}F-DOPA, particularly in patients with subdiaphragmatic primaries or metastases.

It is well recognised that genetic status has an impact on imaging in PGL and PHEO, with higher SUV max observed in cluster 1-related gene mutations including SDHx mutations (8) (9). Furthermore, better detection rate of ^{68}Ga-SMSa PET/CT over ^{18}FDG PET/CT had been described in metastastic SDHB-mutated patients (30) (17).
That was not verifiable in our series in SDHB-mutated patients, with very high and similar sensitivities observed with the 3 tracers. Only ^{68}Ga-SMSa PET/CT missed a liver metastasis on the 60 lesions explored.

In the sporadic cases of our series, ^{18}F-DOPA PET/CT trended to have a higher per-patient and per-lesion sensitivity than ^{68}Ga-SMSa PET/CT and ^{18}FDG PET/CT (respectively 96% vs 87% vs 83%). These different results should be taken with caution because ^{18}F-DOPA PET/CT were less frequently performed than ^{18}FDG PET/CT or ^{68}Ga-SMSa PET/CT in the analyzed populations. Nevertheless, in the eleven patients who underwent both the 3 exams, 60% of patients with ^{68}Ga-SMSa PET/CT false negative lesions had a sporadic disease. This trend was not highlighted by Archier et al. (15) in their emphasis on sporadic cases.

In their studies, Archier et al. made the hypothesis that ^{68}Ga-SMSa PET/CT might be inferior to ^{18}F-FDOPA PET/CT in the detection of primary PHEOs and adrenal-bed recurrences, with respectively 8 and 11 lesions detected with each tracer. Our results do not confirm that trend: ^{68}Ga-SMSa PET/CT showed a high sensitivity by detecting 16 out of 17 PHEOs (1 primary and 15 adrenal-bed recurrences) (Se = 94%), similar to ^{18}F-DOPA (Se=90% ; 9/10) and superior to ^{18}FDG PET/CT (Se = 76% ; 13/17). However, our population in more heterogeneous, with much more local recurrences than primaries, and a different number of lesions explored with each tracers.

One of the advantage of nuclear medicine exams is that they allow a precise quantification of uptake intensities, which can be very informative. In the second time of our study, we performed a semi-quantitative analysis between tracers. This analysis showed a significantly higher liver background with ^{68}Ga-SMSa PET/CT compared to ^{18}F-DOPA PET/CT or ^{18}FDG PET/CT (mean SUVmean at 5,4 vs 1,6 vs 2,3 respectively). Nevertheless, and despite this higher liver background, the tumor-to-liver ratio in liver metastases were not significantly different between the 3 tracers: 5,7 with ^{68}Ga-SMSa PET/CT versus 4,7 with ^{18}F-DOPA PET/CT and versus 6,0 with ^{18}FDG PET/CT, due to higher SUVmax of liver metastases with SMSa. These results do not explain low ^{68}Ga-SMSa PET/CT's sensitivity in liver metastases detection but concerns only detected lesions. PGLs and PHEOs are inter and intra-individual heterogeneous diseases (19) with a heterogeneity in size and potentially in SSTR expression within pathological sites. The ratios had been calculated taking into account the liver background and the most intense lesion per site, but, there was frequently an intra-individual heterogeneity in size and uptake intensity between metastases. We couldn’t reasonably exclude that the higher liver background is not responsible for a lower detection rate of small or moderate expressing SSTR liver metastasis in our patients. The very low ^{18}F-DOPA PET/CT liver

background is probably an advantage for liver lesion detection. Yet again, tracers association with ^{68}Ga-SMSa and ^{18}F-DOPA appears relevant in these cases.

Our study presents some limitations, such as the retrospective nature of the analysis, the limited number of patients and the heterogeneous characteristics of the population analyzed (with localized and metastatic diseases, and different genetic status). Nevertheless, our population reflects the real life and the usual indications for imaging in these rare and heterogeneous diseases. Two different SMSa tracers had been used depending on their availability in time: ^{68}Ga-DOTANOC and ^{68}Ga-DOTATOC. In our serie, several patients underwent repeated ^{68}Ga-SMSa PET/CT with the two radiopharmaceuticals and no evident differences were noted, as previously reported in literature (22).

As all patients did not underwent the 3 PET exams, bias in the tracers selection and the number of PET performed were not excluded, with especially more imaging methods performed in multifocal or metastastic PGL/PHEO and in case of ^{68}Ga-SMSa PET/CT false negative. The comparative PET analysis was almost pertinent in the patients who underwent the 3 PET/CTs, but the small number of lesions might limit the results.

Prospective studies with larger and more homogeneous populations are requested to obtain more robust and reliable findings, especially to evaluate the clinical impact of performing several PET imaging in the staging and follow-up for patients with PGL/PHEO. If documented, an inter-lesional heterogeneity may have an impact on the selection of patients for therapy, and especially for peptide receptor radionuclide therapy with radiolabelled SMSa.

Conclusion

Our study confirms the accuracy of ^{68}Ga-SMSa PET/CT for the exploration of paragangliomas and pheochromocytomas.

Nevertheless, and as already reported with ^{18}FDG PET/CT and ^{18}F-DOPA PET/CT, ^{68}Ga-SMSa PET/CT alone does not detect all the lesions. Best performances are obtained by combining nuclear imaging modalities, particularly in sporadic diseases, in metastatic or multifocal diseases and subdiaphragmatic PGLs.

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Titre de Thèse : La TEP/TDM aux analogues de la somatostatine marqués au gallium-68 dans l'exploration des paragangliomes et phéochromocytomes.
Intérêt de l'association avec d'autres traceurs TEP : retour d'expérience du CHU de Nantes.

RESUME

Introduction
La TEP/TDM aux analogues de la somatostatine marqués au gallium-68 (^{68}Ga-SMSa) est recommandée chez les patients porteurs de paragangliome (PGL) et de phéochromocytome (PHEO). Notre étude rétrospective a analysé la sensibilité de la TEP-^{68}Ga-SMSa réalisée pour l'exploration des PGL et PHEO au CHU de Nantes entre septembre 2014 et avril 2020.

Matériels et méthodes
Ont été inclus consécutivement les patients explorés dans le cadre de l'évaluation initiale ou du suivi de leur maladie. La TEP-^{68}Ga-SMSa était systématiquement réalisée en complément d'un examen d'imagerie morphologique et souvent en association à une TEP/TDM à la ^{18}F-DOPA et/ou au ^{18}FDG. Le cas échéant, les données des différents examens TEP ont été comparées. Les foyers ne correspondant pas à des zones de captation physiologique des différents traceurs étaient considérés comme pathologiques et confirmés par l'étalon de vérité (anatomopathologie, positivité d'au moins une autre modalité d'imagerie ou évolution au cours du suivi).

Résultats
40 patients ont été inclus: 32 porteurs d'un PGL et 8 d'un PHEO. 20 maladies étaient localisées et 20 métastatiques ou multifocales.
19 de ces 40 patients étaient porteurs d'une mutation génétique (1 SDHA, 12 SDHB, 2 SDHC, 4 SDHD).
Au total, 197 lésions étaient confirmées par l'étalon de vérité, correspondant à 59 primitifs ou récidives locales et 138 métastases.
Dans l'ensemble de la population, les sensibilités par patient des examens TEP/TDM étaient de 95% (38/40) pour le ^{68}Ga-SMSa, 86% (12/14) pour la ^{18}F-DOPA et 96% (27/28) pour le ^{18}F-FDG. Les sensibilités par lésion étaient respectivement de 92% (181/197), 93% (40/43) et 84% (138/164).
La TEP-^{68}Ga-SMSa détectait l'ensemble des 30 PGL de la tête et du cou, 16 sur 17 (94%) PHEO primitifs ou récidives locales, 10 sur 13 (77%) PGL sous-diaphragmatiques et 126 sur 138 (91%) métastases.
Les 16 faux négatifs correspondaient à 5 métastases pulmonaires, 5 métastases hépatiques, 4 primitifs sous-diaphragmatiques, 1 adénopathie sus et 1 adénopathie sous-diaphragmatique. Huit de ces 16 faux négatifs (50%) étaient détectés par la TEP-^{18}FDG de même que 9 des 10 faux négatifs (90%) explorés par la TEP-^{18}F-DOPA.
Parmi les 11 patients qui avaient été explorés par les trois traceurs, la TEP-^{18}F-DOPA détectait significativement plus de lésions que la TEP-^{68}Ga-SMSa (95% (38/40) vs 75% (30/40); p = 0,02) et que la TEP-^{18}FDG (95% (38/40) vs 70% (28/40); p = 0,006).

Conclusion
Notre expérience préliminaire confirme la très bonne sensibilité de la TEP/TDM au ^{68}Ga-SMSa pour l'exploration des PGL et des PHEO. Toutefois, comme il a déjà été rapporté pour les TEP/TDM au ^{18}FDG et à la ^{18}F-DOPA, la TEP-^{68}Ga-SMSa seule ne détecte pas toutes les lésions. Les meilleures performances sont obtenues en combinant plusieurs traceurs TEP notamment pour les maladies sporadiques, pour les maladies métastatiques ou multifocales et pour les paragangliomes sous-diaphragmatiques.

Mots clés: *^{68}Ga-DOTA-NOC; ^{68}Ga-DOTA-TOC; ^{18}F-DOPA; ^{18}FDG; Paragangliome; Phéochromocytome; PET/CT*