Role of ^{18}F -FDG PET/CT, ^{123}I -MIBG SPECT, and CT in Restaging Patients Affected by Malignant Pheochromocytoma

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Abstract

Purpose Pheochromocytoma (PH) is a rare catecholamine-secreting tumor that arises from chromaffin tissue within the adrenal medulla and extra-adrenal sites; commonly it is sporadic, and malignant PH accounts for about 10% of all cases. Several imaging modalities have been used for the diagnosis and staging of this tumor: functional imaging using radio-labelled metaiodobenzylguanidine and, more recently, ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET/CT), which offers substantial sensitivity and specificity to correctly detect metastatic PH and helps to identify patients suitable for treatment with radiopharmaceuticals. The aim of our study was to compare CT, ^{18}F -FDG PET/CT, and ^{123}I -metaiodobenzylguanidine single photon emission tomography (^{123}I -MIBG SPECT) as feasible methods to restage patients diagnosed histologically with PH.

Methods We retrospectively evaluated 38 patients (27 females and 11 males; mean age: 44 ± 15 years) with malignant PH documented histologically after surgical intervention. These patients underwent CT, ^{18}F -FDG PET/CT, and ^{123}I -MIBG SPECT.

Results ^{18}F -FDG PET/CT showed positive results for neoplastic tissue in 33/38 patients (86.8%) and negative in 5/38 (13.2%), in concordance with CT alone. ^{123}I -MIBG SPECT was positive in 30/38 patients (78.9%) and negative in 8/38 (21.1%). No differences in lesion numbers were found between ^{18}F -FDG PET/CT and CT, whereas a difference could be demonstrated between ^{18}F -FDG PET/CT and ^{123}I -MIBG SPECT.

Conclusion ^{18}F -FDG PET/CT could more accurately restage patients with PH than CT and ^{123}I -MIBG SPECT, also in the absence of a staging study.

Keywords PET · Pheochromocytoma · Paraganglioma · MIBG · SPECT

Introduction

First described in 1886 by Fränkel, pheochromocytomas (PH) are rare catecholamine-secreting tumors derived from the chromaffin cells of the embryonic neural crest [1] and arise from the adrenal medulla [2]. The incidence in the general population is estimated to be less than 1 per 100,000 people per year [3]. The majority of PH are benign, while malignant tumors occur in about 10% of PH [4]. The most common metastatic sites for chromaffin cell tumors are local lymph nodes, bone, liver, and lung [5, 6]. Diagnosis is based on clinical data, laboratory findings, anatomical imaging [magnetic resonance imaging (MRI) and computed tomography (CT)], and functional imaging such as ^{123}I -metaiodobenzylguanidine single photon emission tomography (^{123}I -MIBG) SPECT and ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET)/CT. In particular, some studies, comparing both modalities, demonstrated that ^{18}F -FDG

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PET/CT has a higher sensitivity and specificity than ^{123}I -MIBG SPECT for detecting PH, even if a direct relationship between malignancy and ^{18}F -FDG uptake cannot be demonstrated [7, 8]. Another possible application for ^{123}I -MIBG and ^{18}F -FDG PET/CT is the evaluation of a possible ^{131}I -MIBG radiometabolic treatment, which can be the only therapeutic option in cases where surgical resection is not possible. In addition, because of waiting lists, department workloads, and urgent clinical necessity, a staging study cannot always be performed on time. Furthermore, during follow-up, treatment may be delayed while waiting for laboratory, anatomical, and functional findings. The aim of our study was to determine the feasibility of using ^{18}F -FDG PET/CT as a single restaging study in patients affected by previously histologically confirmed PH, comparing this technique with CT alone and ^{123}I -MIBG SPECT.

Materials and Methods

Patients

We have retrospectively evaluated 38 patients (27 females and 11 males; mean age: 44 ± 15 years) from a multicenter database. These patients, after a standard staging study using CT, underwent a surgical resection for PH between March 2006 and March 2010. On the staging study, no patients had evidence of hematogenous metastases: 7 out of 38 (18.4%) were stage 1, 18 (47.3%) stage 2, and 13 (34.3%) stage 3. Written consent was obtained from all patients before our study. Surgery and chemotherapy (using a combination of cyclophosphamide, vincristine, and decarbazine) were the treatment in 31 out of 38 patients (81.6%) and surgery only in the 7 patients assigned to stage 1 (18.4%). Six months after surgical resection, all patients underwent a thorax-abdomen CT with contrast medium injection and a total body ^{18}F -FDG PET/CT for restaging purposes; a ^{123}I -MIBG SPECT study was also performed in order to evaluate the feasibility of a radiometabolic treatment. Moreover, 10 out of 38 patients underwent a second ^{18}F -FDG PET/CT and a second ^{123}I -MIBG SPECT after a cycle of radiometabolic treatment in order to evaluate the response to treatment.

PET/CT Imaging

^{18}F -FDG PET/CT was performed after a fast lasting at least 6 h and when glucose levels were lower than 120 mg/dl. An ^{18}F -FDG dose of 5.5 MBq/kg was administered intravenously, and images were acquired 60 min after injection on a Discovery ST PET/CT tomograph (GE®, Milwaukee, WI, USA) with standard CT parameters (80 mA, 120 kV without contrast; 4 min per bed-PET-step of 15 cm) and

processed with 2D ordered-subset-expectation-maximization (OS-EM) imaging. The reconstruction was performed in a 128×128 matrix and 60 cm field of view. The PET images were analyzed visually by two experienced physicians and semiquantitatively by measuring the maximum standardized uptake value (SUVmax), automatically calculated by the software (Volumetrix for PET/CT; Xeleris™ Functional imaging workstation; GE®).

SPECT Imaging

All patients underwent a washout from confounding treatment, according to EANM guidelines (www.eanm.org). A dual-headed hybrid SPECT/CT system at the 90° setting (Infinia™ VC Hawkeye® 4, General Electric Healthcare), equipped with high resolution and low energy collimators was used. After intravenously administering 400 MBq of ^{123}I -MIBG, planar images were obtained after 6 and 24 h at 5 cm/s both in anterior and posterior projections. Tomographic images were obtained after 24 h in a 128×128 matrix, with a zoom factor of 1.3 over a 180° orbit, at 5 cm/s. Reconstructed images were visually analyzed by other two experienced physicians, blind to PET/CT results. The ^{123}I -MIBG SPECT study was performed within 10 days of the PET/CT study.

^{18}F -FDG PET/CT Image Interpretation

PET images were analyzed visually by two experienced physicians and semiquantitatively by measuring the maximum standardized uptake value (SUVmax), considering an SUVmax value higher than 2.5 to be significant, as a cut-off value of 2.5 is widely accepted for differentiation between benign and malignant lesions [2]. The lesions eventually found were categorized as follows: most likely metastatic, ambiguous, and most likely benign. Only the first two kinds of lesions were considered for restaging purpose. This evaluation was based on SUVmax, dimensions, form, and location criteria (Table 1). In case of disagreement, a final decision was obtained by consensus after consulting with an experienced oncologist. Signs of malignancy included the presence of high ^{18}F -FDG uptake in lymph node or hematogenous sites normally involved during the metastatic process (Table 2), nodular form and, in the patients who underwent also a second study, growth on follow-up examination. No histopathological examination of the suspected metastases was performed, considering the histopathologically proven presence of a malignant pheochromocytoma.

^{123}I -MIBG SPECT Image Interpretation

Images were evaluated by two other experienced physicians, blind to PET/CT data. The lesions accumulating ^{123}I -

Table 1 Criteria for visual assessment of ^{18}F -FDG PET/CT applied to distinguish lesions as most likely positive or ambiguous/unclear

Attribute	Criteria
Form	Most likely positive: round/nodular shape, regular or irregular; ambiguous/unclear: apparently round, but not perfectly defined because of small dimensions or too close to other lesions
Dimension	Most likely positive: ≥ 1 cm; ambiguous/unclear: 0.9–0.99 cm
Location	Most likely positive: sites normally involved in metastatic process, with optimal contrast between the lesion and its immediate surroundings (see also Table 2); ambiguous/unclear: sites normally involved in metastatic process, with suboptimal contrast between the lesion and its immediate surroundings
SUVmax	Both most likely positive and ambiguous: ≥ 2.5
Other attributes considered	Correlation with patient history; comparison with other imaging modalities; physical examination

MIBG were considered as most likely positive for metastases if not proximal to sites physiologically accumulating ^{123}I -MIBG and if the uptake was clearly superior to the background.

CT Image Interpretation

Images were evaluated visually by two experienced radiologists, blind to clinical data. Lesions were categorized as most likely positive, ambiguous, or benign on the basis of dimension, form, location, and enhancement after injection of contrast medium.

Radiometabolic Therapy

Ten out of 38 patients underwent a cycle of radiometabolic therapy using ^{131}I -MIBG. After a wash-out from confounding therapy, ^{131}I -MIBG, diluted in compliance with the manufacturer's instructions, was administered by slow intravenous infusion (45 min to 4 h) via an indwelling cannula or central venous line using a lead-shielded infusion system. Vital signs were checked before and after the infusion and at least twice daily afterwards, as ^{131}I -MIBG administration may result in unstable blood pressure. To avoid possible drug interaction, Ondansetron was the anti-emetic of choice. Single-administered activities ranged

between 3.7 GBq (100 mCi) and 11.1 GBq (300 mCi), depending on tumor size and metastatic involvement and also considering myelosuppression and impaired renal function. Hematological monitoring was performed post-therapy to anticipate significant myelosuppression and to plan subsequent treatment cycles. All procedures were undertaken according to EANM guidelines.

Statistical Analysis

SPSS Software (Version 16.0) was used to perform statistical analysis. Values of sensitivity and specificity were obtained on χ^2 test. The comparison between ^{18}F -FDG PET/CT and ^{123}I -MIBG SPECT during follow-up was performed by paired *t*-test.

Results

^{18}F -FDG PET/CT identified pathologic uptakes and indicated positive lymph node and hematogenous metastases in 33 out of 38 patients (86.8%). All 33 positive patients had bone metastatic involvement, and 7 out of 33 also had pathologic uptakes involving abdominal lymph nodes (Fig. 1). One out of 33 had pulmonary lesions and one had a voluminous lesion involving the right adrenal gland,

Table 2 Staging criteria for pheochromocytoma (modification from INSS staging system)

Stage	Criteria
1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with primary tumor may be positive)
2	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative or positive for tumor microscopically
3	Unresectable unilateral tumor infiltrating across the midline (vertebral column) with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement
4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs (except as defined for stage 4S)
4S	Localized primary tumor (as defined for stage 1, 2) with dissemination limited to skin, liver, and/or bone marrow (limited to infants <1 year of age)

Fig. 1 ^{18}F -FDG PET/CT images of a patient with various bone and lymph node metastases are reported and a voluminous abdominal lymph node is shown. Coronal, sagittal, and transaxial fused images are shown

characterized by a central necrosis (Fig. 2). This finding was quite surprising, since the primary site of PH in this patient was the left adrenal gland.

All patients positive on ^{18}F -FDG PET/CT were also positive on CT imaging, and the 5 patients who were negative on ^{18}F -FDG PET/CT were also negative on CT imaging (with negative considered the absence of lesions). An evaluation with ^{123}I -MIBG SPECT was performed in all patients to determine ^{123}I -MIBG uptake for an eventual radiometabolic treatment. After surgical resection, 30 out of the 33 positive patients showed various degrees of ^{123}I -MIBG uptake, not always corresponding to the lesions revealed by CT and ^{18}F -FDG PET/CT (Fig. 3). In particular, only two out of seven patients with abdominal lymph node involvement detected by ^{18}F -FDG PET/CT and

CT had a corresponding ^{123}I -MIBG uptake, and in 3 out of 33 patients ^{123}I -MIBG SPECT was completely negative (Table 3).

According to the locations of the lesions revealed by CT, ^{18}F -FDG PET/CT, and ^{123}I -MIBG SPECT, all patients were restaged, considering as metastases only the lesions described as most likely positive for metastases and not the ambiguous ones.

Location criteria for restaging are shown in Table 1. Using CT, 7 out of 38 patients were assigned to stage 1, 11 to stage 2, 6 to stage 3, and 14 to stage 4. ^{18}F -FDG PET/CT assigned 5 out of 38 patients to stage 1 and 33 to stage 4. ^{123}I -MIBG SPECT assigned 8 out of 38 patients to stage 1, 1 to stage 3, and 29 to stage 4 (Table 4). ^{18}F -FDG PET/CT showed 86% sensitivity and 100% specificity ($P=0.007$),

Fig. 2 ^{18}F -FDG PET/CT images of a patient with a voluminous lesion with a central necrosis involving the right adrenal gland are shown. The original site of the tumor was the left adrenal gland. Coronal, sagittal, and transaxial fused images are shown

Fig. 3 ^{18}F -FDG PET/CT fused images (a) of a patient with a lesion involving the 7th cervical vertebra are shown in comparison with CT images (b) and ^{123}I -MIBG SPECT findings (c). The lesion is not evident on ^{123}I -MIBG SPECT, suggesting an early dedifferentiation has occurred

while ^{123}I -MIBG SPECT showed 65% sensitivity and 94% specificity ($P=0.005$). After a cycle of radiometabolic therapy, following EANM procedure guidelines, 10 out of 33 positive patients underwent a second ^{18}F -FDG PET/CT and a second ^{123}I -MIBG SPECT. At the second ^{18}F -FDG PET/CT, unchanged neoplastic uptakes were revealed in 4 out of 10 patients and persistent but reduced uptakes in 6 out of 10, whereas at the second ^{123}I -MIBG SPECT unchanged uptakes were revealed in 2 out of 10 and reduced uptakes in 8 out of 10. The differences in radiopharmaceutical uptake between ^{18}F -FDG PET/CT and ^{123}I -MIBG SPECT were still present, in particular for lesion numbers and growth, although no statistical significance was found ($P=0.89$, Table 5).

Discussion

The role of ^{18}F -FDG PET/CT in staging patients affected by PH is well established as these tumors have shown high glucose metabolism [9–16], although, unfortunately, a correlation between ^{18}F -FDG uptake and malignant potential or prognosis has never been demonstrated [7, 8]. In particular, a study reported that there is not a significant difference between ^{18}F -FDG uptake in benign and malignant PH and that the uptake is not influenced by the secretory status [17]. Other PET tracers have also been used, but none showed a better correlation between tumor activity and radiopharmaceutical uptake [9, 12, 14, 18]. Data from related literature support two explanations: either that an early metabolic switch related to genetic defects occurs (the pseudohypoxia model) or that there is an adaptive response to hypoxia. These possibilities could

explain why ^{18}F -FDG avidity of PH seems to be different from other neuroendocrine tumors in which ^{18}F -FDG uptake seems to be related to tumor aggressiveness. A definite answer to this question has not been found yet, although an interesting study hypothesized that the amount of glucose uptake in chromaffin-derived tumors results from the severe impairment of oxidative phosphorylation in tumor cells [8]. Relatively few studies about restaging, follow-up, and treatment response monitoring have been performed, since the majority of studies comparing ^{18}F -FDG PET/CT and ^{123}I -MIBG SPECT either to MRI [10], ^{18}F -DOPA PET/CT [9, 12], or CT are about diagnosis and detection of metastases.

In our study, we selected patients already diagnosed with histologically proven malignant PH to compare CT alone, ^{18}F -FDG PET/CT, and ^{123}I -MIBG SPECT as techniques for follow-up and for monitoring treatment response. In all patients, we found a full correspondence between the number of lesions revealed by radiologic imaging (CT) and the pathological uptakes revealed by ^{18}F -FDG PET/CT. The majority of the ambiguous lesions revealed by CT were confirmed as positive on ^{18}F -FDG PET/CT; our findings are quite similar to what was observed in other studies about PH [7, 8, 13, 14] confirming ^{18}F -FDG PET/CT accuracy even in restaging and follow-up. Other studies have also demonstrated that ^{18}F -FDG PET/CT is superior to ^{123}I -MIBG SPECT for evaluating treatment response, considering its more accurate spatial resolution and the possible presence of MIBG-confounding treatment [19, 20]. This opinion seems reasonable, since even in our patients, all negative lesions on ^{123}I -MIBG scintigraphy were detected by ^{18}F -FDG PET/CT, suggesting that an early dedifferentiation can often be observed in malignant PH

Table 3 Number of lesions revealed by CT, ^{18}F -FDG PET/CT, and ^{123}I -MIBG SPECT in each patient. For each investigation it is stated whether a lesion was certain (pos.) or ambiguous (ambig.). The total number of lesions in each investigation is also indicated (tot.)

Pt	CT			PET/CT			^{123}I -MIBG SPECT		
	Pos.	Ambig.	Tot.	Pos.	Ambig.	Tot.	Pos.	Ambig.	Tot.
1	1	2	3	2	1	3	2	1	3
2	5	2	7	5	2	7	5	2	7
3	5	4	9	8	1	9	8	1	9
4	3	1	4	4	0	4	4	0	4
5	1	2	3	3	0	3	3	0	3
6	1	1	2	2	0	2	2	0	2
7	1	0	1	1	0	1	1	0	1
8	2	1	3	2	1	3	2	1	3
9	0	0	0	0	0	0	0	0	0
10	3	1	4	4	0	4	4	0	4
11	0	2	2	1	1	2	1	1	2
12	7	4	11	9	2	11	9	2	11
13	1	2	3	1	2	3	1	2	3
14	0	0	0	0	0	0	0	0	0
15	1	1	2	2	0	2	2	0	2
16	2	5	7	4	3	7	4	3	7
17	1	1	2	2	0	2	0	0	0
18	3	2	5	4	1	5	4	1	5
19	2	0	2	2	0	2	2	0	2
20	2	2	4	4	0	4	4	0	4
21	0	1	1	1	0	1	1	0	1
22	3	1	4	4	0	4	0	0	0
23	2	1	3	3	0	3	2	0	2
24	2	0	2	2	0	2	2	0	2
25	0	2	2	2	0	2	1	0	1
26	3	1	4	3	1	4	3	1	4
27	0	0	0	0	0	0	0	0	0
28	3	0	3	3	0	3	3	0	3
29	0	0	0	0	0	0	0	0	0
30	2	1	3	3	0	3	3	0	3
31	2	3	5	3	2	5	0	0	0
32	3	5	8	4	4	8	4	4	8
33	6	5	11	9	2	11	10	0	10
34	4	1	5	5	0	5	5	0	5
35	0	0	0	0	0	0	0	0	0
36	1	3	4	4	0	4	4	0	4
37	1	2	3	3	0	3	3	0	3
38	1	2	3	3	0	3	3	0	3

cells with consequent cellular inability to take up MIBG. Since an early dedifferentiation can also be considered as a sign of tumor aggressiveness, that might also explain why none of our patients had evidence of hematogenous metastases at diagnosis, whereas 86.8% of our patients

Table 4 Stage assignment using CT, ^{18}F -FDG PET/CT, and ^{123}I -MIBG SPECT with percentages

	Patients (n)		
	CT	^{18}F -FDG PET/CT	^{123}I -MIBG SPECT
Stage 1	7/38 (18.4%)	5/38 (13.1%)	8/38 (21%)
Stage 2	11/38 (29%)	0/38 (0%)	0/38 (0%)
Stage 3	6/38 (15.8%)	0/38 (0%)	1/38 (2.6%)
Stage 4	14/38 (36.8%)	33/38 (86.9%)	29/38 (76.4%)

showed diffuse metastatic lesions only 6 months after surgical resection.

Data from the literature [14] and from our study suggest that ^{18}F -FDG PET/CT has an 86–100% sensitivity and 100% specificity in detecting PH metastases, while ^{123}I -MIBG SPECT has a 57–90% sensitivity and 94% specificity [9]. In our study, these data are supported by the fact that only lesions with characteristics typical of metastases in terms of dimension, form, location, and radiopharmaceutical uptake were considered positive. Obviously, ^{18}F -FDG PET/CT imaging can have false positive findings like other imaging modalities, but sensitivity and specificity are very high and a certain diagnosis could be obtained only on a histopathological examination, which cannot be always after performed; moreover, in evaluating a metastatic disease, the target should be the assignment to the correct stage (Table 2), which was more accurate using ^{18}F -FDG PET/CT. Sensitivity of ^{123}I -MIBG SPECT seemed to be similar before and after radiometabolic treatment, even if the small patient sample of our study cannot allow any firm conclusions. Possible applications of ^{18}F -FDG PET/CT in PH include initial disease staging and early monitoring of ^{131}I -MIBG treatment, residual viable disease assessment post-surgery and post ^{131}I -MIBG treatment, detection of acquired resistance to ^{131}I -MIBG and disease recurrence, detection of synchronous and metachronous malignancies, evaluation of restaging, and guidance regarding future directions for ^{18}F -FDG PET/CT-guided personalized management.

According to our results, the restaging process could be safely based on ^{18}F -FDG PET/CT imaging, which has been demonstrated to be superior to CT only and to ^{123}I -MIBG SPECT both by our study and also by other authors [14]. The concordance between ^{18}F -FDG PET/CT results and CT

Table 5 Results of ^{18}F -FDG PET/CT and ^{123}I -MIBG SPECT after radiometabolic therapy in comparison to basal studies

	Unchanged	Persistent but reduced
PET/CT	4/10	6/10
^{123}I -MIBG SPECT	2/10	8/10

imaging seems to confirm ^{18}F -FDG PET/CT accuracy and reliability suggesting the opportunity to use only one total body study to reduce costs and doses to patients. Not infrequently in clinical practice, the impossibility of acquiring a staging study of patients because of waiting lists, department workloads, and clinical necessities could lead the referring physician to start treatment in the absence of initial evaluation. The possibility of using a single study to restage patients could reduce absorbed doses, optimize clinical management to reduce time from relapse diagnosis to treatment, and reduce costs. Moreover, these studies could be safely considered the new baseline to assess subsequent ^{131}I -MIBG radiometabolic treatment efficacy.

In conclusion, despite the relatively small number of cases in our study, justified by the low prevalence of malignant PH, we confirm the role of ^{18}F -FDG PET/CT as a single study for restaging and its better accuracy in comparison to CT alone and ^{123}I -MIBG SPECT, also in the absence of a staging study.

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