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Current and Future Anatomical and Functional Imaging Approaches to Pheochromocytoma and Paraganglioma

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Abstract

After establishing a biochemical diagnosis, pheochromocytomas and extra-adrenal paragangliomas (PPGLs) can be localized using different anatomical and functional imaging modalities. These include computed tomography, magnetic resonance imaging, single-photon emission computed tomography (SPECT) using ^{123}I-metaiodobenzylguanidine or ^{111}In-DTPA-pentetreotide, and positron emission tomography (PET) using 6-[^{18}F]-fluorodopamine (^{18}F-FDA), 6-[^{18}F]-fluoro-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA), and 2-[^{18}F]-fluoro-2-deoxy-D-glucose. We review the currently available data on the performance of anatomical imaging, SPECT, and PET for the detection of (metastatic) PPGL as well as parasympathetic head and neck paragangliomas. We show that there appears to be no 'gold-standard' imaging technique for all patients with (suspected) PPGL. A tailor-made approach is warranted, guided by clinical, biochemical, and genetic characteristics. In the current era of a growing number of PET tracers, PPGL imaging has moved beyond tumor localization towards functional characterization of tumors.

Keywords

FDG PET; MIBG scintigraphy; FDOPA PET; FDA PET

Introduction

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors that derive from sympathetic chromaffin tissue in the adrenal medulla and from the extra-adrenal paraganglial system of the thorax and abdomen [1]. PPGLs arising from the adrenal medulla are commonly referred to as pheochromocytomas. Typical locations for extra-adrenal abdominal and thoracic PPGLs are: 1. the Zuckerkandl body, a sympathetic ganglion located

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at the root of the inferior mesenteric artery, 2. the sympathetic plexus of the urinary bladder, the kidneys and the heart, and 3. the sympathetic ganglia or the aortopulmonary body in the mediastinum. Head and neck paragangliomas (HNPGLs), also called glomus tumors, arise from parasympathetic paraganglia, mainly from the glomus caroticum, glomus jugulare, glomus tympanicum, and glomus vagale.

The majority of PPGLs synthesize, metabolize, store, and secrete catecholamines, whereas HNPGLs usually do not. Most common symptoms and signs of catecholamine excess due to PPGLs include headache, palpitations, diaphoresis, and sustained or paroxysmal hypertension. Symptoms and sign of HNPGLs rather relate to the tumor's space-occupying effects, including cranial nerve damage.

PPGLs occur sporadically or in association with familial poly-tumor syndromes: multiple endocrine neoplasia type 2 (MEN2); von Hippel-Lindau (VHL) syndrome; neurofibromatosis type 1 (NF1); and paraganglioma syndromes associated with mutations of genes encoding subunits of the succinate dehydrogenase (SDH) complex, in particular subunits B (SDHB) and D (SDHD) [2, 3]. Reported frequencies of germline mutations of the above genes among patients with PPGLs range from 27 % to 32 % [4], and are likely to increase as further tumor susceptibility genes are identified. Most recently, mutations of genes encoding the SDH complex assembly factor 2 (SDHAF2), transmembrane protein 127 (TMEM127), SDHA, and MYC associated factor X (MAX) have been identified as further hereditary causes of PPGLs, ranking PPGLs as tumors most commonly associated with known gene mutations [5 – 7]. It is important to note that PPGLs with an underlying SDHB mutation are strongly associated with an aggressive behavior and the development of metastatic disease [8].

Before any localization of these tumors is initiated, it is now well accepted that the presence of these tumors needs to be proven biochemically first. It is recommended that plasma and/or 24-hour urine concentrations of metanephrines are measured since their sensitivity is more than 97 % for detecting PPGLs [9].

In patients with a biochemically established diagnosis of PPGL, anatomical and functional imaging are critical for a) primary tumor localization; b) the detection of multiple primary tumors that often come with above mentioned genetic disorders; and c) the detection of metastases commonly seen in SDHB-related PPGLs, guiding the optimal choice between curative surgery and palliative treatment options. First line anatomical imaging modalities for PPGL imaging include computed tomography (CT) or magnetic resonance imaging (MRI). MRI is a preferred method in children, young adults, pregnant women, and in those with cardiac PPGLs. CT and MRI provide a high sensitivity and allow precise tumor delineation, which is critical for pre-surgical evaluation. The specificity of these techniques is limited, however, and often must be coupled with the use of PPGL specific functional imaging. The exception to such a rule would be epinephrine-secreting tumors, since these are almost always located in adrenal glands and a positive CT or MRI points towards these tumors without the need of any functional imaging. However, it should be noted that in tumors with size over 5–6 cm, the likelihood of metastases at initial presentation is high and the whole body PPGL-specific functional imaging is recommended.

PPGLs possess unique characteristics regarding the uptake of highly specific radiotracers. Functional imaging is complimentary to anatomical imaging and provides specific information about the tumor's functional characteristics. Nuclear medicine scanning techniques include planar scintigraphy, single-photon emission computed tomography (SPECT) and positron emission tomography (PET). These imaging modalities involve the use of radiotracers, which are taken up by the tumor cells through the targeting of specific transporter systems or peptide receptors on the cell membrane. The most widely used radiotracers for PPGL and HNPGL scintigraphy are ^{123}I-labeled metaiodobenzylguanidine (^{123}I-MIBG) and ^{111}In-DTPA-pentetreotide scintigraphy. They have long been considered as the 'gold standard' modalities. However, novel PET tracers have become available in the recent years, some of which have been proven to be very useful for the functional and highly specific imaging of PPGL. These include 6-[^{18}F]-fluorodopamine (^{18}F-FDA), 6-[^{18}F]-fluoro-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA), and 2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG).

We provide a review of the techniques that are currently available for the anatomical and functional imaging of PPGs and compare the diagnostic performance of these techniques for the detection of nonmetastatic and metastatic PPGLs as well as HNPGLs. We also explore the links between genotype-specific tumor biology and functional imaging results and address the future role of nuclear medicine in the localization and characterization of PPGs and HNPGs. Based on the available data, we provide recommendations for the optimal approach to PPGL imaging in clinical practice.

Anatomical Imaging

There are no large comparative studies on the performance of CT vs. MRI for the localization of PPGL. From our own experience, extra-adrenal PPGLs of the chest and abdomen may be better detected by CT than by MRI. Potential disadvantages of CT, however, include radiation exposure and the risk of contrast nephropathy. For the localization of HNPGL, it is well established that MRI is the preferred anatomical imaging technique.

Functional Imaging

In conjunction with planar imaging, SPECT provides cross sectional functional imaging data. The SPECT data can be fused with CT images for anatomic correlation, which are now routinely obtained on hybrid SPECT/CT instruments. In recent years, SPECT/CT has become more widely available and has the advantage of simultaneous acquisition of both morphological and functional data, increasing diagnostic confidence in image interpretation and enhancing sensitivity in some cases. However, these examinations are associated with practical constraints such as long imaging times, protection of the thyroid with non-radioactive iodine and need for withdrawals of interfering medications and gastrointestinal tract artifacts requiring bowel cleansing in some cases. The main disadvantage is probably the still low-resolution of the SPECT image, which is prone to artifacts and attenuation, limiting the ability to detect tiny lesions. SPECT also does not provide a quantifiable estimate of the tumor metabolism (tracer uptake). Thus, PET imaging has been growing

rapidly in the imaging of PGLs, paralleled by great efforts towards the development of new tracers. The sensitivity and resolution of PET is superior to that of SPECT scintigraphy (the current theoretical resolution on phantoms is 4–5 mm, and in true clinical setting close to 7–10 mm). PET is also a quantitative imaging technique. Most commonly, the Standardized Uptake Value (SUV) is used to estimate the degree of tracer concentration in a defined region. In cases of small lesions, the partial volume phenomenon affects images both qualitatively and quantitatively with underestimation of the SUV, and sometimes missing such lesions. However, detectability of sub-centimetric lesions remains possible in case of high tracer avidity with favorable signal-to-noise ratio. Similar to SPECT-CT, PET is combined with CT for attenuation correction and co-localization.

Functional Imaging Targets in PPGL

Lesions detected by anatomical imaging can be specifically identified as PPGL by functional imaging agents that target the catecholamine synthesis, storage, and secretion pathways of chromaffin tumor cells [10]. These techniques include $^{123/131}$I-MIBG SPECT and ^{18}F-FDA PET. $^{123/131}$I-MIBG and ^{18}F-FDA target the norepinephrine transporter of the PPGL cell membrane and the vesicular monoamine transporters in the membrane of intracellular vesicles. These transporters facilitate the re-uptake and storage of catecholamines, respectively. The PET tracers ^{11}C-epinephrine and ^{11}C-hydroxyephedrine are alternatives that accumulate in tumor cells through the same mechanisms, but are of limited use for clinical imaging because of their (very) short half-life [11, 12].

^{18}F-DOPA PET can be used for the imaging of the striatal system and neuroendocrine tumors such as carcinoids, but also for PPGL and HNPGL. The target of ^{18}F-DOPA is the large amino acid transporter involved in the uptake of amine precursors.

Other, less-specific targets for PPGL imaging are the somatostatin receptors and glucose transporters. For somatostatin receptor-based imaging, ^{111}In-DTPA-pentetreotide is available for SPECT and ^{68}Ga-DOTA-TOC/TATE/NOC for PET/(CT). ^{18}F-FDG PET provides an index of intracellular glucose metabolism. ^{18}F-FDG is taken up by the tumor cell through the glucose transporters (6–8).

Sensitivity and Specificity

The use of ^{123}I-MIBG is preferred over ^{131}I-MIBG because of its higher sensitivity, lower radiation exposure, and improved imaging quality with SPECT [13]. The energy of ^{123}I photons is better suited to detection with gamma cameras and, the absence of emission of beta particles, as well as the shorter isotope half-life (13 h vs. 8 days), lead to reduced dosimetry and authorize the administration of higher activity. Reported sensitivities of ^{123}I-MIBG scintigraphy for localizing nonmetastatic PPGL vary between 77 and 98 % [14 – 16]. MIBG uptake by normal adrenal gland tissue might obscure small lesions. Overall, the sensitivity of MIBG imaging appears to be lower in extra-adrenal PGLs. The specificity of ^{123}I-MIBG SPECT approaches 100 % [17]. Normal adrenal medulla is visualized with ^{131}I-MIBG in about 10 % of cases and with ^{123}I-MIBG in 50–80 % of cases. For the detection of metastatic lesions of PPGL, the sensitivity of ^{123}I-MIBG is much lower, that is, only 50–79 % [14, 18]. Despite the low sensitivity for detecting PPGL metastases, a very

important advantage of using ^{123}I-MIBG scintigraphy in the setting of metastatic disease is the fact that it can identify patients who possibly benefit from palliative treatment with therapeutic doses of ^{131}I-MIBG [19].

^{18}F-DOPA PET has a high sensitivity for the localization of nonmetastatic PPGL [14, 20 – 22] and HNPGL [23 – 25]. Reported sensitivities vary between 81–100 %. No specificity data are available. The diagnostic accuracy of ^{18}F-DOPA PET is improved when using carbidopa, an inhibitor of DOPA decarboxylase. Carbidopa enhances the sensitivity of ^{18}F-DOPA PET for PPGL by increasing the tumor-to-background ratio of tracer uptake [26]. The performance of ^{18}F-DOPA PET appears to be disappointing, however, in case of metastatic PPGL, especially SDHB-related cases, with sensitivities of only 45 % and 20 %, respectively (lesion-based analysis) [14].

For ^{18}F-FDG PET, sensitivities up to 88 % for primary nonmetastatic PPGL were reported. When using a radiotracer that targets any tissue with an increase glucose metabolism, specificity might be of concern. Specificity in the context of PPGL imaging, however is as high as ~ 90 % and is similar to the specificity of ^{123}I-MIBG SPECT and ^{18}F-DOPA PET (unpublished results). ^{18}F-FDG PET is highly sensitive for the detection of PPGL metastases, especially SDHB-related cases (region-based sensitivity 97 % in reference to CT/MRI) [18] (Fig. 1).

^{18}F-FDA was initially developed at the National Institutes of Health for functional imaging of the sympathetic nervous system and later evaluated as a new imaging tool for PPGL. ^{18}F-FDA PET was shown to have a high sensitivity for both primary tumors (77–100 %) and metastases (77–90 %) [14, 17, 27]. The specificity of ^{18}F-FDA PET exceeds 90 % [17]. The distinction between adrenal PPGL and normal adrenal glands is facilitated by the quantification of ^{18}F-FDA uptake using SUVs [28]. So far, ^{18}F-FDA is only available as an experimental imaging agent at the National Institutes of Health.

The sensitivity of somatostatin receptor scintigraphy with ^{111}In-DTPA-pentetreotide is lower than that of ^{123}I/^{131}I-MIBG in PPGLs [29 – 31]. However, considering HNPGLs, several studies have demonstrated the superiority of ^{111}In-DTPA-pentetreotide scintigraphy as compared to ^{123}I/^{131}I-MIBG, with sensitivities of 89–100 % and 18–50 %, respectively [32 – 37]. SPECT imaging with ^{111}In-DTPA-pentetreotide is currently the most widely available scintigraphy modality for HNPGLs. However, its sensitivity needs to be revised downwards in patients with hereditary syndromes because some additional lesions can be at the millimeter stage and may not be detectable by conventional scintigraphy. For PET imaging of HNPGL, ^{18}F-DOPA has been shown to be superior to other tracers [25].

The results of our previously reported study with a head-to-head comparison of the sensitivities between different functional imaging modalities [14] are presented in Table 1.

Imaging across Hereditary Syndromes

Imaging results appear to be largely determined by the underlying genotypes and related tumor cell characteristics. There is evidence of differential expression of cellular targets for radiopharmaceuticals. For example, it was shown that there is lower expression of the cell

membrane norepinephrine transporter system in VHL-related PPGL cells than in MEN2-related tumor cells [38]. Considering a higher affinity of ^{18}F-FDA than ^{123}I-MIBG for these transporters, it is no surprise that ^{18}F-FDA PET is superior to ^{123}I-MIBG SPECT in the context of VHL syndrome [39].

There also appears to be a link between tumor biology and imaging. *SDHB* -mutations are associated with PPGLs of a parti cularly high malignant potential. ^{18}F-FDG PET has an excellent sensitivity for *SDHB*-associated metastatic PPGL [40, 41] (Fig. 2). ^{18}F-FDG accumulation is an index of increased tissue glucose metabolism and, as a marker of tumor viability, the degree of ^{18}F-FDG uptake usually reflects tumor aggressiveness. ^{18}F-FDG uptake by PPGL does not appear to be merely an indicator of a high metabolic rate due to malignancy per se, but may rather be directly linked to *SDHB* -specific tumor biology [14]. The *SDHB* gene encodes for subunit B of the mitochondrial SDH complex II, a key enzyme in oxidative phosphorylation. *SDHB* mutations can lead to complete loss of SDH enzymatic activity in malignant PPGL, with upregulation of hypoxic-angiogenetic responsive genes [42]. Impairment of mitochondrial function due to loss of *SDHB* function may cause tumor cells to shift from oxidative phosphorylation to aerobic glycolysis, a phenomenon known as the “Warburg effect” [43]. Higher glucose requirement because of a switch to less efficient pathways for cellular energy production may perhaps explain the increased ^{18}F-FDG uptake by malignant *SDHB* -related PPGL.

Recommendations for Clinical practice

The current review shows that there appears to be no ‘gold-standard’ imaging technique for all patients with (suspected) PPGL and/or (suspected) HNPGL. A tailor-made approach to the anatomical and functional imaging of the individual patient is clearly warranted. The choices to be made by the practicing physician depend on many factors, including the aim of the investigation, clinical parameters including age and known hereditary syndrome, renal function (contrast nephropathy), (anticipated) radiation burden, the results of previous imaging (tumor size and location, suspicion of metastases), biochemical findings, preference of the patient, local availability of scanning systems and insurance issues. Based on the currently reviewed data and our own experience, we recommend the following principles for the approach to imaging. In patients with a biochemically established diagnosis of PPGL and a low likelihood of metastases (small tumors, adrenal location, adrenergic phenotype, non-SDHB) we recommend to perform a CT scan of the abdomen alone. In addition, ^{18}F-FDG PET can be useful for functional tumor characterization, providing clues for an underlying hereditary syndrome. ^{18}F-FDG uptake appears to be particularly high in SDHx and VHL-related PPGLs. In patients with a biochemically established diagnosis, when the aim is to rule out metastases, we recommend to perform a CT of the neck, chest, abdomen and pelvis in combination with ^{18}F-FDG PET or ^{18}F-FDA PET. ^{123}I-MIBG SPECT needs to be performed in patients with established metastatic disease in order determine whether the tumor lesions are ^{123}I-MIBG avid and whether the patient qualifies for palliative ^{131}I-MIBG treatment. We do not recommend the use of ^{111}In-DTPA-pentetreotide scintigraphy as a first-line imaging tool for PPGL due to lack of sensitivity. The role of novel somatostatin receptor-based PET scanning such as ^{68}Ga-DOTA-peptides awaits further evaluation.

For patients in whom a HNPGL is suspected or needs to be ruled out (SDHx mutation carriers), an MRI of the head and neck is the scan of choice. For functional imaging of HNPGL, ^{18}F-DOPA PET and somatostatin-receptor based imaging such as ^{111}In-DTPA-pentetreotide appear to be most effective.

Future Perspectives

As outlined above current imaging approaches using either anatomical or functional imaging are directed towards the precise localization of PPGLs. However, with exciting recent introductions of new radiopharmaceuticals a new era is approaching for imaging cancer, including neuroendocrine tumors such as PPGLs. Soon it is expected that we will move from classic tumor localization towards tumor characterization. This is well supported by recent discoveries about how to assess angiogenesis [44], apoptosis [45], hypoxia [46], and other tumor specific cellular characteristics. The information obtained from these studies will serve to facilitate choice of appropriate drug regimens. This includes predicting therapeutic responses and discontinuation of treatment if no “targeted” pathway is affected. This will secure a cost-effective approach, minimize side effects, and “buy” valuable time for any patient in need of transfer to another form of treatment. Lack of response to indicate the latter can be expected to be revealed much earlier than by CT or MRI (usually 3–6 months). Personalized medicine will become a reality supported to the greatest extent by the use of functional imaging directed towards the characterization of any tumors including PPGLs. This at least initially requires a multi-institutional effort tightly coupled to close collaboration with the radiopharmaceutical industry as well as patient support groups. The future of new functional imaging is bright and it is very close to realization.

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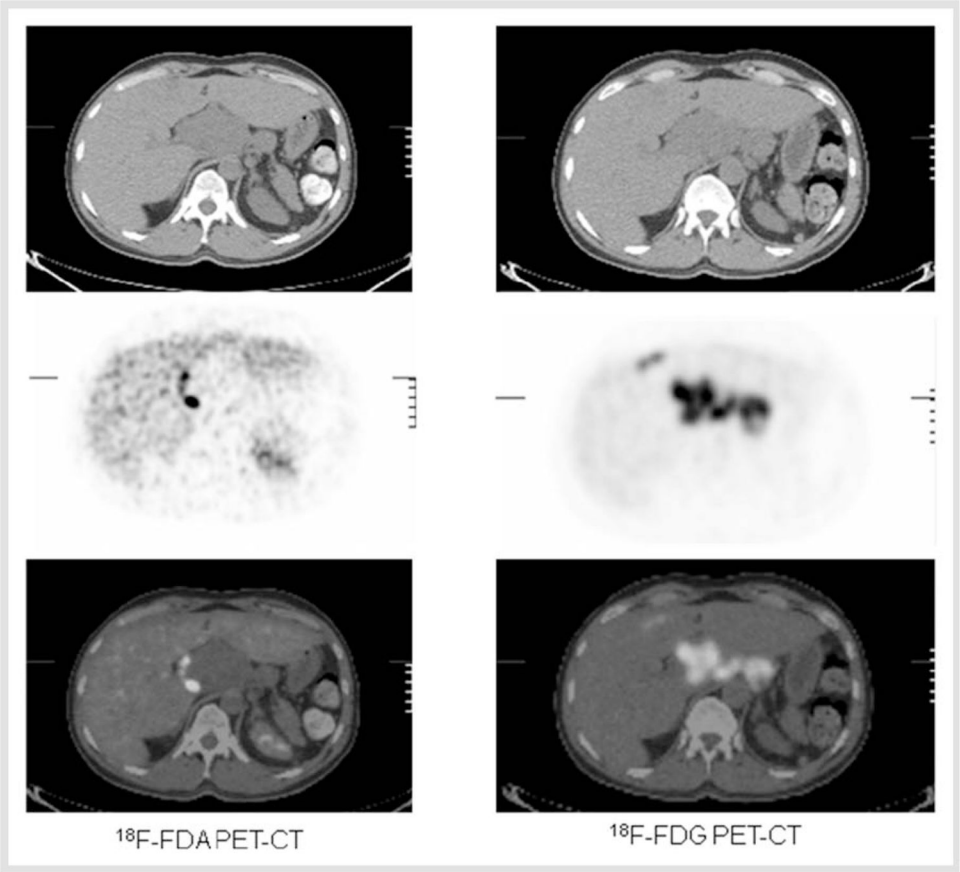

Fig. 1.

^{18}F-FDA PET-CT (left panels) and ^{18}F-FDG PET-CT (right panels) images in a 35-year-old male with retroperitoneal metastases of an SDHB-related PPGL. CT images (upper panels), axial PET images (middle panels), axial PET-CT fused images (lower panels).

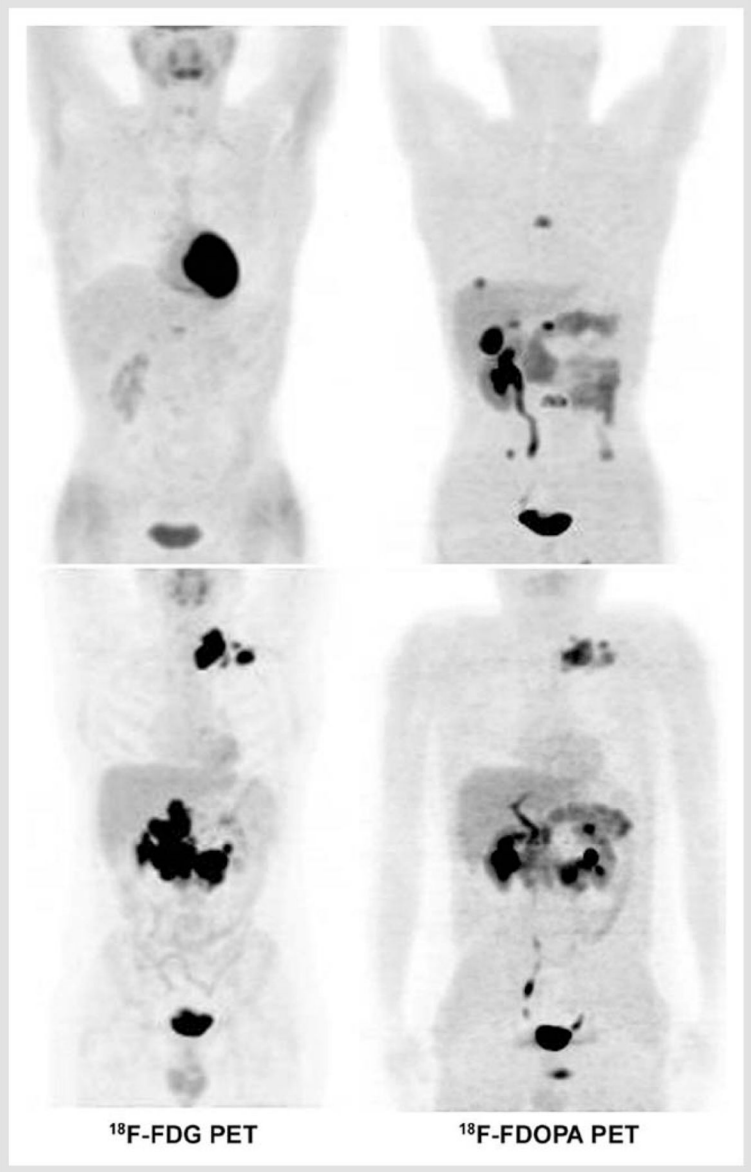

Fig. 2.

Comparison between ^{18}F-FDOPA and ^{18}F-FDG PET in 2 patients with metastatic PPGL (maximal intensity projection images). SDHB-negative patient (upper images). SDHB-positive patient (lower images). ^{18}F-FDOPA was clearly superior to ^{18}F-FDG PET in SDHB-negative PPGL and vice versa in the SDHB-related case.

Table 1

Sensitivity of functional imaging.

Nonmetastatic PPGL (20 patients)					
	CT and/or MRI	**^{18}F-DOPA**	**^{18}F-FDA**	**^{123}I-MIBG**	**^{18}F-FDG**
With ref. to histologically confirmed lesions	100 % (26/26)	81 % (21/26)	77 % (20/26)	77 % (20/26)	88 % (23/26)
Sensitivities are not significantly different between functional imaging modalities					
Metastatic PPGL (28 patients)					
	CT and/or MRI	**^{18}F-DOPA [A]**	**^{18}F-FDA [B]**	**^{123}I-MIBG [C]**	**^{18}F-FDG [D]**
With ref. to lesions on CT and/or MRI	–	45 % (96/211)	76 % (161/211)	57 % (106/187)	74 % (157/211)

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A vs. B, A vs. C, A vs. D, B vs. C, C vs. D: $p < 0.01$. B vs. D: $p = 0.760$