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Detection and treatment of pheochromocytomas and paragangliomas: current standing of MIBG scintigraphy and future role of PET imaging

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Pheochromocytomas are rare tumors arising from chromaffin cells of adrenal medullary or extra-adrenal paraganglionic tissue. These tumors are characterized by synthesis, storage, metabolism and secretion of catecholamines. Similar to the sympathetic nervous system, pheochromocytomas express cellular norepinephrine transporters (NET) through which catecholamines can enter pheochromocytoma cells to be stored in vesicles. Metaiodobenzylguanidine (MIBG) resemblance to norepinephrine and its good affinity and uptake by NET resulted in its use in pheochromocytoma diagnosis from 1981. Both [^{123}I]MIBG and [^{131}I]MIBG (lower sensitivity) scintigraphy are used for localization of these tumors. Recent discoveries of different hereditary syndromes associated with pheochromocytomas led to the identification of several and new distinct genotype-phenotype associations. Importantly, with this distinction of clinical phenotypes, MIBG was found to have a different performance in subsets of pheochromocytoma patients. Reduced sensitivity of MIBG scintigraphy in some familial paraganglioma syndromes, malignant disease and extra-adrenal paragangliomas has been found. Therefore, newer compounds, especially for positron emission tomography (PET), such as [^{11}C]hydroxyephedrine ([^{11}C]HED), [^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG), [^{18}F]fluoro-dihydroxyphenylalanine ([^{18}F]FDOPA) and [^{18}F]fluorodopamine ([^{18}F]FDA) have emerged and were found to be superior to MIBG in the localization of certain types of pheochromocytoma and paragangliomas. Finally, using [^{131}I]MIBG represents an important treatment option in patients with malignant pheochromocytoma, but the development of newer treatment modalities is expected. In this review, we provide the reader with an overview of the current standing of [^{123}I]- and [^{131}I]MIBG in diagnosis and treatment of pheochromocytoma amongst the newer PET imaging agents.

KEY WORDS: Pheochromocytomas - Paragangliomas - Radionuclide imaging - Tomography, emission computed.

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In 2004 the World Health Organization classification of endocrine tumors defined a pheochromocytoma as an intra-adrenal paraganglioma, whereas closely related tumors of extra-adrenal sympathetic or parasympathetic paraganglia are classified as extra-adrenal paragangliomas.[1] In general, approximately 80% of the pheochromocytomas arise from the adrenal medulla.[2] Sympathetic paragangliomas are most frequently found in the abdomen (extra-adrenal),

pelvis and less often in the thorax. These sympathetic paragangliomas almost all produce and most of them secrete catecholamines or their metabolites. On the other hand, head and neck paragangliomas, which were formerly referred to as glomus tumors, are derived from parasympathetic tissue and rarely produce significant amounts of catecholamines. The former estimate that, in general, approximately 10% of paragangliomas and pheochromocytomas are malignant is no longer valid. The prevalence of malignant dedifferentiation depends directly on the underlying genetic mutation.

Metaiodobenzylguanidine (MIBG) is a guanethidine analogue resembling norepinephrine and is, therefore, concentrated by sympatho-adrenergic tissues, especially the chromaffin tissue of the adrenal medulla. The uptake of MIBG in the cells is both driven by passive diffusion and by active uptake.[3] MIBG is an aralkylguanidine that can be labeled with iodine isotopes at the benzoic ring. MIBG is taken up by sympatho-medullary tissues *via* norepinephrine transporters (NET) and deposited in storage granules, which is facilitated by vesicular monoamine transporters (VMAT). MIBG does not bind to postsynaptic adrenergic receptors and, therefore, can be given safely in higher doses. Iodine-131-MIBG has a long half life of approximately 8.2 days, whereas [123I]MIBG has a half life of only 13.2 h. In addition, γ camera efficiency of the 159-keV [123I] isotope is approximately 4 times that of its 364-keV [131I] counterpart and because of the absence of β-emission combined with a shorter half-life, radiation dosimetry is more favorable.[4] To prevent thyroid accumulation it is necessary to block the thyroid gland with potassium iodide. After 24 h and again at either 48 or 72 h after injection of the MIBG the patient will be scanned. MIBG is normally accumulated in myocardium (hence its use in cardiac imaging), liver, spleen, lungs, cerebellum, large intestine and urinary bladder.

In recent years, improvements in diagnosis, genetics, localization, and treatment of pheochromocytomas have changed dramatically the approaches to these tumors. The prevalence of underlying genetic mutations in apparently sporadic pheochromocytomas was found to be much higher than was previously estimated.[5] Hereditary pheochromocytomas occur in multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome (VHL), and neurofibromatosis type 1. The familial paraganglioma syndromes associated with mutations in the succinate dehydrogenase genes (SDHB, C

or D) were more recently discovered as hereditary causes for pheochromocytoma.[6, 7] Several distinct genotype-phenotype associations among SDHB and SDHD mutation carriers have since then been identified.[8-10] For example, patients with a mutation in the SDHB gene have a risk for the development of malignant disease up to 70%, whereas SDHD has been associated with malignant disease in an estimated 2.5-5% of cases.[11, 12] Importantly, the identification of these distinct paraganglioma syndromes prompted a reevaluation of the value of both biochemical tests and radiological imaging in these syndromes separately.

MIBG has been used in pheochromocytoma diagnosis since 1981. However, newer compounds for positron emission tomography (PET) such as [18F]fluorodopamine ([18F]FDA) and [18F]fluoro-dihydroxyphenylalanine ([18F]FDOPA) have been developed in recent years for the diagnosis of pheochromocytomas. This article addresses and reviews three important aspects of MIBG: a) its use as an imaging compound; b) its performance in pheochromocytomas and paragangliomas in comparison to PET compounds; c) its use as a carrier compound for [131I] to treat malignant pheochromocytoma and paraganglioma.

Metaiodobenzylguanidine as an imaging compound in pheochromocytoma and paraganglioma

The radiopharmaceutical agent [131I]MIBG, which was first developed for adrenal scintigraphy and tested on dogs and rhesus monkeys before its use, was reported in a study of 8 pheochromocytoma patients by Wieland *et al.* and Sisson *et al.*[13-15] MIBG was retained for days in tissues where adrenergic vesicles were numerous such as pheochromocytomas, thus offering a means of localization for these tumors. Iodine-131-MIBG scintigraphy was found to have a sensitivity of 77-90% and a specificity of 95-100%.[16-18] Because [123I]MIBG generates a higher dose of γ-rays with a higher specificity, the imaging quality greatly improved. In 1986, Shulkin *et al.* illustrated the superiority of [123I]MIBG over [131I]MIBG in a patient with a primary extra-adrenal pheochromocytoma.[19] Subsequent studies confirmed that the use of the [123I] isotope resulted in a better performance with a sensitivity of 83-100% and a specificity of 95-100%.[18, 20-24] Additional advantages of the [123I] isotope are the possibility to use single photon emission computed

tomography (SPECT) imaging and the fact that a lower half life facilitates the use of higher dosages.

Importantly, the normal adrenal medullary may show physiological uptake of both [131I]- and [123I]MIBG.[25, 26] In [131I]MIBG imaging normal adrenals are visualized in up to 28% of cases (24 and 48 h).[27, 28] Cases studied using [123I]MIBG have been reported to reveal MIBG uptake to a greater extent in normal adrenal medullary tissue than [131I]MIBG.[4] Diffuse adrenal medullary hyperplasia could be responsible for false positive MIBG uptake.[29] However, exemplifying the importance of underlying genetic mutations, this condition appears to be associated with the MEN type 2 syndromes with a well-established risk for pheochromocytoma development. The difficulty is to decide whether or not uptake of [123I]MIBG reflects physiological uptake, adrenal hyperplasia or a pheochromocytoma. In an attempt to improve the accuracy of [123I]MIBG in patients with adrenal or extra-adrenal pheochromocytoma, Cecchin *et al.* assessed the usefulness of a scoring system based on the different uptakes of the radiopharmaceutical between different organs. A scoring system (1: uptake absent or less than liver; 2: uptake equal to the liver; 3: uptake moderately more intense than the liver; 4: uptake intense) was introduced and scintigraphies were classified as positive if there was extra-adrenal focal uptake, adrenal enlargement combined with non-homogeneous uptake or adrenal uptake which was higher than the uptake in the liver (scores 3 and 4).[22] The results were correlated with postoperative histological outcomes and a sensitivity of 91.5% and a specificity of 100% were reported in the localization of adrenal and extra-adrenal pheochromocytomas. Positive and negative predictive values were reported to be 100% and 83%, respectively. According to the authors, using the liver uptake as a reference value resulted in a correct discrimination of physiological adrenal uptake in 18 out of 20 cases.

Suboptimal sensitivity of MIBG might be associated with the relatively low affinity of MIBG to the NET, the lack of storage granules or the loss of NET or VMAT by tumor cell dedifferentiation.[30] Furthermore, several types of medication could interfere with MIBG uptake in patients (Table I) resulting in false-negative results.[31] Several studies have reported the diagnostic value of MIBG scans to be dependent on size and location of the tumor. Reduced sensitivity of MIBG scans in familial paraganglioma syndromes, malignant disease and extra-adrenal paragangliomas has been described.[21, 32-]

TABLE I.—*Interfering pharmaceuticals that may affect imaging with MIBG.*

Interfering pharmaceuticals	Necessary length of cessation before MIBG	Mechanism
Labetalol	72 hours	Inhibition uptake
Reserpine	21 days	Storage depletion
Calcium channel blockers	72 hours	Inhibition uptake
Tricyclic antidepressants	21 days	Storage depletion
Phenylephrine	48 hours	Storage depletion
Pseudoephedrine	48 hours	Storage depletion
Phenylpropanolamine	48 hours	Storage depletion
Ephedrine	48 hours	Storage depletion
Atypical antidepressants Others (e.g. SSRIs)	21 days	Inhibition uptake

MIBG: metaiodobenzylguanidine; SSRI: selective serotonin reuptake inhibitor. [Adapted from: Solanki *et al.*[31]].

[35] Van der Harst *et al.* found MIBG scanning to be less sensitive for familial paraganglioma, malignant disease and extra-adrenal localization.[32] Van der Horst-Schrivers *et al.* reported sensitivity to be 98% for extra-adrenal tumors and 79% in malignant cases.[33] The results in a recent study by Bhatia *et al.*[34] revealed tumor detection in only 58% of the extra-adrenal tumors, whereas 85% of the adrenal pheochromocytomas could be detected. Tumor size correlated with the uptake for adrenal but not for extra-adrenal tumors, which could be a reflection of uptake in small adrenal tumors being obscured by the influence of physiologic adrenal accumulation. Therefore, in general, diagnostic accuracy of MIBG was lower in extra-adrenal and malignant paragangliomas.

With growing knowledge about the genetic background of various pheochromocytoma and paraganglioma syndromes, the evaluation of MIBG scintigraphies focused more on the familial pheochromocytoma and paraganglioma syndromes. Kaji *et al.* reported that 3 out of 7 patients with an adrenal pheochromocytoma associated with VHL had negative results utilizing [123/131I]MIBG.[36] Their results suggested lower sensitivity of MIBG in VHL and they suspected this to be due to the low expression of NET in VHL-related pheochromocytoma cells. The recent discovery of the SDH genes as a hereditary cause for pheochromocytomas and extra-adrenal paragangliomas supported the idea of the existence of different subgroups in familial pheochromocytoma and further addressed the need for proper imaging to detect tumors located outside the adrenals. Several earlier studies, like the

TABLE II.—*Estimated functional imaging performance in separate genotypes.*

	[123/131I]MIBG	specific PET (^{18}F]FDA, [^{18}F]FDOPA)	non-specific PET ([^{18}F]FDG)	Selected references
VHL	+	++	Insufficient data	Kaji *et al.*[36], Hoegerle *et al.*[39]
MEN	+	+	Insufficient data	Greenblatt *et al.*[40], Pacak *et al.*[41]
SDHB	+	++	++/++++*	Timmers *et al.*[10] Timmers *et al.*[38]
SDHC	Insufficient data	Insufficient data	Insufficient data	—
SDHD	+	Insufficient data	Insufficient data	Van Houtum *et al.*[37]
Non-familial**	+**	++**	++**	Hoegerle *et al.*[39], Shulkin *et al.*[42, 43], Mackenzie *et al.*[35]

*Metastatic SDHB-associated disease; **several studies performed before discovery of succinate dehydrogenase gene mutations, SDH associated disease may present as sporadic. MIBG: metaiodobenzylguanidine; PET: positron emission tomography; FDA: fluorodopamine; FDOPA: fluoro-dihydroxyphenylalanine; FDG: fluoro-2-deoxy-D-glucose; VHL: von Hippel Lindau; MEN: multiple endocrine neoplasia; SDH: succinate dehydrogenase type B, C or D; FDG: fluoro-2-deoxy-D-glucose.

paper from van der Harst *et al.*[32] had not specifically addressed MIBG accuracy in SDHD and SDHB mutation carriers separately. It is possible that a considerable number of patients in their large sporadic group were carriers of mutations in the SDH genes, because SDHB-related PGL often present as apparently sporadic tumors, as was described by Timmers *et al.*[10] Only very few studies have investigated the specific value of MIBG scans in SDHD mutation carriers. Based on a study by Van Houtum *et al.*[37] and unpublished data from the Netherlands, we estimate the sensitivity in SDHD patients to be around 80% for detecting pheochromocytomas and extra-adrenal (abdominal and thoracic) paragangliomas combined with an increase in sensitivity to 92% for pheochromocytomas alone. SDHB mutation carriers often display a much more aggressive course of the disease and are prone to developing extra-adrenal malignant disease. Timmers *et al.* reported a sensitivity of only 65% for [123I]MIBG in the evaluation of metastases-positive lesions in SDHB-associated pheochromocytoma and paraganglioma.[38] In conclusion, the different genotype-phenotype associations are most likely also reflected by differences in the performance of imaging with [123/131I]MIBG (Table II).

Some reports have questioned routine use of MIBG imaging in the diagnostic work-up for pheochromocytoma, suggesting that it does not alter the treatment plan in patients with suspected pheochromocytoma in the absence of hereditary disease or a history of pheochromocytoma.[40] In a retrospective study, Miskulin *et al.* concluded that in non-familial cases with a clear biochemical diagnosis and a unilateral adrenal mass on computed tomography (CT) or magnetic resonance imaging (MRI), no additional MIBG imaging is necessary.[44] Although this is a valid recommendation, it needs to be stressed that this is true mainly with regard to epinephrine secreting tumors which are located in the adrenals, whereas the norepinephrine secreting tumors, which are frequently found in familial paraganglioma syndromes, often present recurrent, extra-adrenal, and bilateral disease. Furthermore, especially in older patients, benign adrenal adenomas are often found and can be wrongly considered to be a pheochromocytoma. Another concern with MIBG scintigraphy is that, since MIBG is relatively non-polar, the nonspecific binding is fairly high directly after injection and optimal imaging results are not achieved until 24 h or several days after injection, which is inconvenient for patient care, as is the need to prevent thyroid accumulation with potassium iodide.

Metaiodobenzylguanidine and its performance in pheochromocytomas and paragangliomas in comparison to PET compounds

Because of the above mentioned potential shortfalls of both [123I]- and [131I]MIBG in the imaging of especially extra-adrenal and malignant paragangliomas,
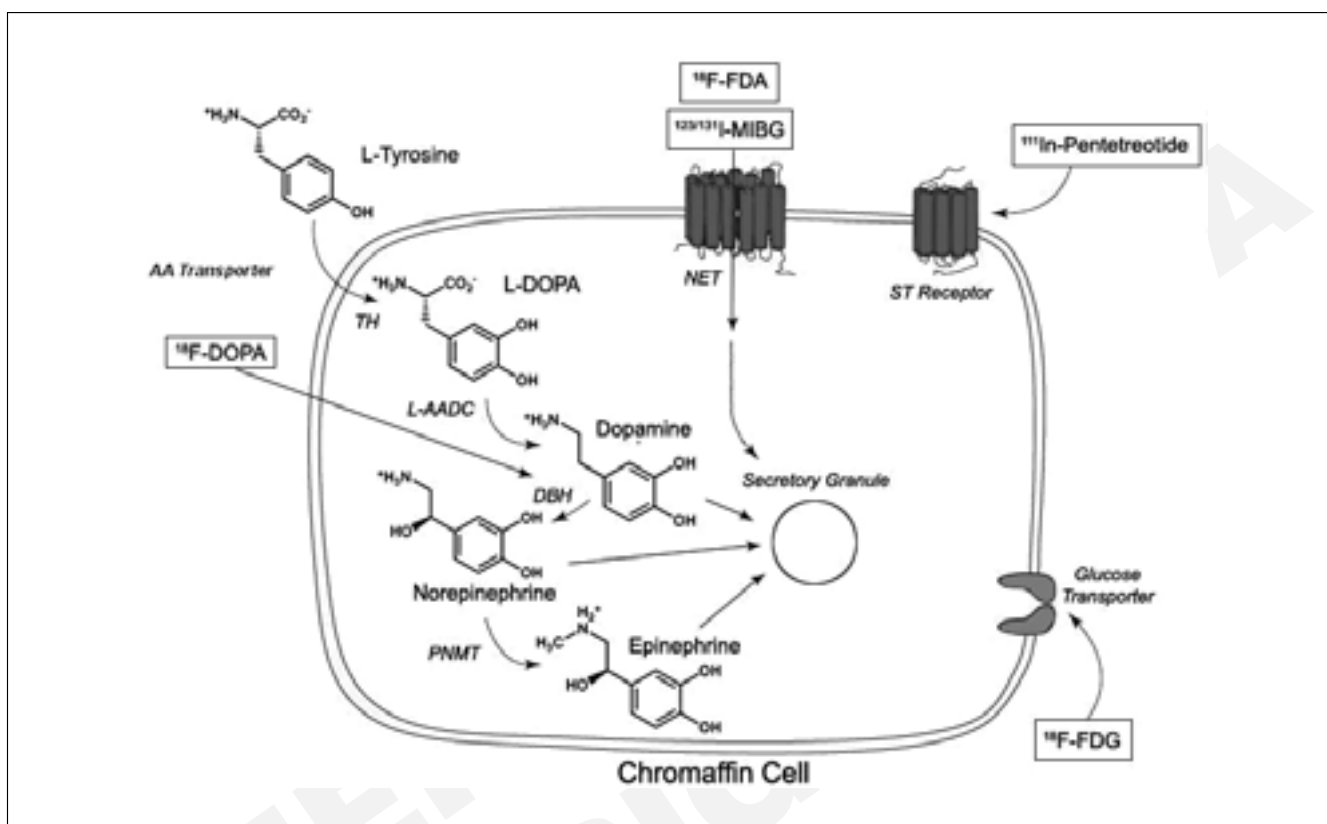
Figure 1.—Chromaffin cell with its specific (left) and less-specific targets (right) for functional imaging. 1: aminoacid uptake; 2: norepinephrine transporter (hNET); 3: somatostatin receptor; 4: GLUT 1 glucose transporter; TH: tyrosine hydroxylase; L-AADC: L-aromatic-aminoacid decarboxylase; DBH: dopamine-β-hydroxylase; PNMT: phenylethanolamine-N-methyltransferase. [Adapted from Ilias *et al.*[45]].

newer means of imaging have been extensively studied. Somatostatin receptors have been demonstrated on paragangliomas (Figure 1) and somatostatin receptor imaging in pheochromocytomas/paragangliomas revealed some favorable results.[46-48] Investigation of [^{111}In]pentetreotide in pheochromocytoma identified most tumors, but appeared to be inferior to the use of MIBG.[49-51] In 2001, van der Harst *et al.* reviewed their experience of preoperative [^{123}I]MIBG and a labeled somatostatin analog in the diagnostic work-up in pheochromocytoma patients and concluded that somatostatin receptor imaging might be considered as a supplement for MIBG in suspected metastatic disease.[32] However, both the expression of NET and the somatostatin receptor may be lost in a dedifferentiated tumor, resulting in false negative imaging in metastatic disease.[32, 51]

PET was developed in the late seventies and has become a more common imaging modality in the imaging of pheochromocytoma in recent years.[52, 53] Compounds used in PET imaging generate positrons that can be detected with high resolution images and their relatively short half-lives compared with other radiopharmaceuticals increases the maximal dose that can be administered safely. PET scanning offers better resolution than SPECT, because signal to noise ratios are increased due to the relatively intense radioactivity and coincidence detection. Furthermore, recent developments enabled to combine conventional imaging methods like CT with PET further improving its diagnostic use.[54] Studies focused on discovery of carriers that could be labeled with positron emitting compounds and still maintain the specificity of MIBG with its selective uptake *via* the NET. Carbon-11-hydroxyephedrine ([^{11}C]HED) is another analogue of norepinephrine and was the first positron-emitting probe of the sympathoadrenal system that was used in humans.[55, 56] In 1992, Shulkin *et al.* reported promis-

ing results of [11C]HED in the localization of pheochromocytoma.[57] Carbon-11-HED is more polar than MIBG, has even greater similarities with norepinephrine and has a very short half-life of only 20 min. Visualization of the [11C] radiotracer was done by the use of PET techniques. The authors reported [11C]HED to accumulate in 9 out of 10 patients, both in benign and malignant pheochromocytoma, only 5 min after injection. However, the synthesis of the [11C]HED compound was very complex and required onsite production for each separate patient because of the very short half-life of the compound. Furthermore, these agents may be subject to interference with the same agents known to interfere with MIBG, because they both use the catecholamine uptake pathway. In conclusion, although [11C]HED had introduced the new field of PET imaging as a promising approach in pheochromocytoma diagnosis, the need for other positron-emitting compounds with a slightly longer half-life, like [18F] (half-life 110 min), was evident.

Fluorine-18-fluorodopamine

Dopamine is a much better substrate for the NET than norepinephrine itself.[30] Therefore, it was hypothesized that a labeled analog of dopamine could be useful for scintigraphy of pheochromocytoma. Fluorine-18-FDA is a sympatho-neuronal imaging agent that was developed at the National Institutes of Health and is a substrate for the transporters in catecholamine synthesizing cells, both those at the membrane and the intracellular vesicular transporters.[30] Fluorine-18 has the advantage that it can usually be incorporated into a molecule with only small effects on the ability of the carrying compound to bind to receptors, or be taken up by their transporters. The result is that the ratio tissue-blood is more than 1 000 which results in a good visualization of cells.[58] Clinical studies have revealed that [18F]FDA is indeed a good imaging agent for pheochromocytoma.[36, 59-61] In 2003, Ilias *et al.* showed the superiority of [18F]FDA imaging over [131I]MIBG scintigraphy, especially in malignant tumors.[62] For PET scanning, patients were studied fasting and caffeine, tobacco and alcohol were avoided for at least 12 h to prevent interference with the imaging, because caffeine is an adrenergic stimulant and the others may influence gastrointestinal motility. However, [18F]FDA is difficult to produce and has limited availability. Like MIBG uptake, uptake of [18F]FDA in normal adrenal glands may lead to false-positive results, because of physiologic uptake. Recently, Timmers *et al.* have reported the usefulness of standardized uptake values for distinguishing adrenal glands with pheochromocytoma from those without.[63] The diagnosis of pheochromocytoma was estimated to be highly unlikely if the SUV was <7.3, whereas a SUV >10.1 confirmed the presence of a pheochromocytoma.

Importantly, the possibility of genotype-specific properties in performance of [18F]FDA imaging must be reemphasized. Its superiority was proven in the detection of pheochromocytoma in a selected cohort of only VHL mutation carriers,[36] however, specific data on [18F]FDA performance in patient cohorts with other genotypes are scarce and will have to be further investigated.

Fluorine-18-dihydroxyphenylalanine

Newer modes of imaging have been developed based on the capabilities of uptake and subsequent decarboxylation of amino acids (like DOPA) in neuroendocrine tumors. DOPA can be decarboxylated to dopamine by L-amino acid decarboxylase (L-AADC), which is shown in Figure 1. This L-AADC enzyme is strongly expressed in neuroendocrine cells and it is evident that cells producing catecholamines may have up regulated amino acid transporters because of the increased demand for precursors. Although, for instance, [11C]methionine and [11C]tyrosine are taken up *via* the same transporter system, they do not accumulate as well in neuroendocrine cells as [18F]FDOPA,[64] suggesting it is only possible for those tracers with a high affinity for L-AADC to remain in the cells. It is suggested that the fact that [18F]FDOPA is converted to [18F]FDA which is subsequently stored in intracellular vesicles may well be the explanation for the ability to localize with these compounds. In 2002, Hoegerle *et al.* described [18F]FDOPA PET imaging to outperform [123I]MIBG scintigraphy in the detection of pheochromocytoma.[39] As was described above, positron emitters tend to have higher spatial resolution and the selective uptake results in imaging within minutes-hours instead of the, at least, 24 h needed in both [123I]- and [131I]MIBG imaging. Furthermore, several studies have noted the lack of uptake in normal adrenal glands,[65, 66] whereas [123I]MIBG reveals some degree of accumulation in normal adrenal glands stressing the importance for evaluation of asymmetric uptake.

Therefore, [18F]FDOPA could be a sensitive and specific tool in the diagnostic strategy of pheochromocytoma and paraganglioma.[64] Timmers *et al.* recently reported that carbidopa enhances the sensitivity of [18F]FDOPA for adrenal pheochromocytomas and extra-adrenal abdominal paragangliomas by increasing the tumor-to-background ratio of tracer uptake. However, the sensitivity of [18F]FDOPA for metastatic paragangliomas was limited.[67]

Fluorine-18-fluoro-2-deoxy-D-glucose

Fluorine-18-fluoro-2-deoxy-D-glucose ([18F]FDG) is the most frequently used PET imaging agent worldwide. Fluorine-18-FDG PET imaging uses the principle of imaging glucose uptake *via* GLUT-1 receptors in tumors with excess uptake of glucose (*e.g.* metabolically active tumor cells). Fluorine-18-FDG is taken into the cells and subsequently trapped by hexokinase-phosphorylation, thus making it resistant to further glycolysis.[68] Fluorine-18-FDG uptake is frequently increased in tumors that are metabolically active and have abundant mitochondria.[69] However, because cancer cells often display high rates of aerobic glycolysis instead of the oxidative phosphorylation pathway *via* the tri-carboxylic-acid cycle (TCA), also termed the Warburg effect, [18F]FDG uptake is not directly proportional to mitochondrial activity alone.[70] However, since [18F]FDG tumor imaging depends primarily on the level of glucose uptake by the tumor cells as a reflection of the level of metabolic activity, it offers little diagnostic specificity. Nonetheless, [18F]FDG localization studies may differentiate between benign and (metabolically more active) malignant tumors. Shulkin *et al.* have reported most pheochromocytomas, both benign and metastasized, to show uptake of [18F]FDG.[42, 43] Fluorine-18-FDG uptake appeared to be unrelated to the secretory status of the tumor. Mann *et al.* reported a study in suspected pheochromocytoma patients where both [11C]HED and [18F]FDG were able to localize more lesions in a more timely fashion than [131I]MIBG.[53] In a recent large study, Timmers *et al.* showed that [18F]FDG is a superior means of visualization in patients with SDHB associated malignant pheochromocytomas.[38] Therefore, we believe [18F]FDG imaging in pheochromocytomas could be reserved for those patients with SDHB metastatic disease or those that had been negative on other functional imaging studies.

Metaiodobenzylguanidine and its role as carrier for ^{131}I to treat malignant pheochromocytoma and paraganglioma

Patients with metastatic paragangliomas have a 5-year-overall survival of approximately 50%.[71] Treatment options in surgically incurable situations are limited. Several studies have reported partial or complete response to have occurred with cyclophosphamide, vincristine and dacarbazine (CVD) chemotherapy.[72] Although chemotherapy may lengthen survival and can be useful for palliative care, the fact that it is associated with significant side effects necessitates an individualized approach. The expression of NET on pheochromocytoma cells does not only provide a method for imaging of these tumors, but could also offer a means for selectively targeting these tumors for treatment.

Iodine-131-MIBG as an experimental treatment for metastasized pheochromocytoma was first reported in 1984.[20, 73] Several studies have since published about the use of [131I]MIBG as a radiotoxic drug to treat pheochromocytomas.[74-78] In 1991, Shapiro *et al.* reported results of a 10 year experience and reported partial tumor response in 8/28 patients with only mild radiotoxicity.[74] A review performed by Loh *et al.* showed tumor response in up to 30% of 116 reported patients.[79] Extended analyses concluded that, in general, a (mostly partial) tumor response was to be expected in 24-45% of the patients, but disease progression after 2 years was common.[80, 81] In line with this finding are the recent results of a retrospective study in 19 patients with a median cumulative dose of 22.2 GBq that revealed tumor response in 47% patient of patients, a biochemical response rate of 67%, whereas no less than 89% of patients mentioned a symptomatic response.[77] Side effects on bone marrow range from mild thrombopenia and leucopenia to overt bone marrow failure, especially in those patients with massive skeletal localizations and higher doses. In addition, although the thyroid had been blocked with potassium iodide, the development of hypothyroidism was possible. Furthermore, higher doses have been reported to result in nausea. However, most studies have been small and had a retrospective design with comparisons made even more difficult because of different doses and treatment intervals.

Usually, patients are treated with multiple medium doses of [131I]MIBG of around 7.4 GBq. Rose *et al.* suggested in 2003 that higher individual doses might

result in increased survival, based upon their study in which 12 patients were treated with a median single treatment dose of 37 GBq leading to 3 patients with a complete and 7 patients with a partial response.[82] Patients had peripheral blood stem cell leukapheresis prior to therapy, unless patients had proven bone marrow metastases. The follow-up study by Fitzgerald *et al.* calculated a 5-year survival of 75% from time of treatment, but stressed the need for newer treatments.[83] Importantly, the level of hematological side effects was much higher; especially grade 3 thrombocytopenia was very frequent (79%). Perhaps repeated intermediate-dosage [131I]MIBG treatment, as was advocated by Lam *et al.* could provide a useful addition in the therapeutic arsenal without the excess of hematological toxicity.[84]

Because malignant pheochromocytomas are rare, no randomized trials have been performed directly comparing the response of CVD chemotherapy with those of [131I]MIBG treatment. In a recent review, Scholz *et al.* concluded that [131I]MIBG therapy and CVD chemotherapy were comparable with regard to both response rate and side effects.[72] As appears to be the case in imaging, treatment results may be expected to vary considerably between patient cohorts with different underlying genetic mutations, which is subject to further prospective and retrospective studies.

Somatostatin receptors have been demonstrated on paragangliomas/pheochromocytomas, and this concept has been used for diagnostic imaging purposes (Figure 1). However, results concerning targeted radionuclide therapy using radiolabeled somatostatin analogues in these tumors are scarcer.[85, 86] Successful use of [177Lu]DOTA0-Tyr3-octreotate in paragangliomas has been reported.[85] Recently, Forrer *et al.* reported that treatment with 90Y- and 117Lu-labeled somatostatin compounds could have long lasting responses with minimal toxicity and could therefore be considered in somatostatin receptor positive surgically incurable paragangliomas.[87] However, most radiolabeled somatostatin analogues target the somatostatin receptor type 2 which may have a low or variable expression, resulting in less efficacy of treatment.[88] Malignant pheochromocytomas may have more expression of type 3 and 5 somatostatin receptors than type 2, so, at least in theory, labeled somatostatin analogues with broader receptor specificity might be more effective in selected cases.[88]

Current treatment options will be further refined in the future. So called 'no-carrier added high specific activity' [131I]MIBG has been reported to improve efficacy of the delivered radiotherapy by increased tumor uptake.[89] Normally, the uptake of [131I]MIBG may be competitively inhibited by the presence of [127I]MIBG, which is formed during the synthesis of [131I]MIBG. Using a 'non-carrier' method of synthesis reduces the amount of 'cold' MIBG with subsequently increased [131I]MIBG uptake and effect of therapy. The development of alternative substrates to MIBG for the NET and storage system will play a role as well. Among these analogues promising results have been suggested for 3-[211At]astatobenzylguanidine ([211At]MABG), which has α-emitting characteristics and a prolonged retention in the targeted tissue.[90, 91]

Local perfusion of affected organs *via* intra-arterial catheters could facilitate the delivery of the radiopharmaceutical compound directly to the tumor in individual patients with metastasized disease located in distinct organs. Brogsitter *et al.* reported patients with carcinoids that had a fourfold increase in local delivery of [131I]MIBG using local perfusion.[92]

Another promising approach is the attempt to increase the expression of key components in the uptake and storage of norepinephrine (and its analogues) to improve the delivery of [131I]MIBG and related radiopharmaceuticals. Recent preliminary developments include increasing tumor accumulation of MIBG by altering NET expression[93, 94] or approaches integrating norepinephrine transporter gene transfer with radionuclide targeting.[95, 96] Some *in vitro* studies suggest MIBG uptake will increase after chemotherapy.[97] Some reports have mentioned doxorubicin and cisplatin increasing the effectiveness of [131I]MIBG as a treatment modality in neuroblastoma.[93, 97, 98]

Conclusions, suggested algorithm and future prospects

In conclusion, the diagnostic and therapeutic strategies in pheochromocytoma have changed dramatically over the last few years. Underlying gene mutations have been identified in a much larger proportion of pheochromocytoma patients than was previously expected. Increased performance of MRI and CT imaging, MIBG, and the emergence of newer means for functional imaging have tremendously increased the diagnostic accuracy in pheochromocytoma diagnosis.

Because of its better accuracy and the fact that they are much more patient friendly, we expect [18F]FDOPA and/or [18F]FDA to (at least partly) replace MIBG in diagnostic imaging for pheochromocytoma and paraganglioma in the future. In metastatic, highly metabolically active SDHB-associated paragangliomas [18F]FDG will certainly be of value, albeit with limited specificity. Future studies will have to take into account the different genotype-phenotype associations with varying imaging performances and provide head-to-head comparisons of imaging methods in these specific subsets of patients. Therapy with [131I]MIBG will remain an essential part of the treatment of malignant pheochromocytomas and paragangliomas, but developments in improving uptake and efficiency can be expected. Currently, clinical trials are being conducted at Duke University with [131I]MIBG preparations synthesized without the unwanted carrier molecules (cold contaminants). Clinical trials comparing high-dose [131I]MIBG *vs* smaller repeated doses *vs* combinations with chemotherapeutic regimens are needed.

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