Radiopharmaceuticals in paraganglioma imaging: too many members on board?

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Since the development of radioiodinated metaiodobenzylguanidine (MIBG) over 30 years ago, nuclear imaging has had a central role in managing patients with paraganglioma (PGL), aiding in the diagnosis and staging of this rare but, for many patients, devastating disease [1]. This role is complemented by anatomical imaging, including computed tomography (CT) and magnetic resonance imaging (MRI). The major advantage of nuclear imaging is in providing high visual contrast between tumor and healthy tissue, which enables the detection of tumors that could potentially be missed by conventional imaging. Beyond its localization value, this imaging modality provides unique opportunities for better characterizing these tumors at molecular levels (e.g., catecholamine synthesis, specific receptor and transporter expression), mirroring *ex vivo* histological classification but on a whole-body, *in vivo*, scale. This opportunity has more recently been augmented by a number of excellent radiopharmaceuticals, which target different functional and molecular pathways that often reflect the diverse

genetic landscape of PGL. Based on these characteristics, nuclear imaging provides a means of linking imaging phenotype to genotype and can be considered a member of the multi-omics approach. For example, an intense 2-fluoro-2-deoxy-D-glucose (¹⁸F-fluorodeoxyglucose, ¹⁸F-FDG) uptake by a PGL is mostly associated with mutations involving one of the genes encoding the succinate dehydrogenase (SDH) complex. Conversely, a low uptake can often rule out a classic SDH deficiency linked to SDH mutations [2]. In addition to genetic mutation, epigenetic mechanisms (histones and methylation modifications) and the tissue of origin may also impact the imaging phenotype. For example, whereas PGLs associated with the sympathetic nervous system often exhibit high ¹⁸F-FDG uptake, parasympathetic PGLs (typically arising in the head and neck region) may have very low uptake values. The ¹⁸F-FDG uptake pattern SDHx-PGLs reflects metabolic reprogramming, a hypermethylation phenotype, and abnormal mitochondrial respiratory function [3] and it is predominantly linked with high succinate and low fumarate metabolomic pattern [4]. Such tumors are classified as exhibiting “pseudohypoxia.” There are further differences based on the site of origin. For example, parasympathetic-associated PGLs almost always have an intense uptake of 6-fluoro-3,4-dihydroxyphenylalanine (¹⁸F-fluorodopa, ¹⁸F-FDOPA) or somatostatin analogs (SSA) labeled with ⁶⁸Ga (e.g., ⁶⁸Ga DOTA analogs), regardless of their genetic background [5].

Advancing understanding of the genetic and metabolic drivers of PGL and their links to specific cell membrane characteristics of these tumors will aid in the selection of the most appropriate staging investigations and also provide the potential for identifying therapeutic targets. In particular, very high expression of somatostatin receptors will identify patients

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suitable for peptide receptor radionuclide therapy (PRRT), for example with ^{177}Lu -DOTA-SSA, in the same way that ^{123}I -MIBG has been used to identify expression of the norepinephrine transporter system and suitability for ^{131}I -MIBG therapy. The high sensitivity of ^{68}Ga -DOTA-SSA in the detection of these tumors as well as its potential “theranostic” application has led to rapid adoption of this technique, where available, for assessing PGL.

While availability of several radiopharmaceuticals offers novel diagnostic approaches for a medical team taking care of a PGL patient, it also presents several challenges. Although utilization of multiple radiotracers for localization, staging, and functional characterization of a PGL in a sequential pattern might improve the sensitivity and specificity of disease detection, this approach poses logistic issues for radiopharmaceutical production and supply, as well as having psychological and financial implications for the patient. Furthermore, despite using modern technology and devices that minimize radiation exposure, the potential radiation hazard of such a paradigm needs to be considered. However, such a paradigm has the potential to identify tumor heterogeneity that may have implications for clinical management.

An alternative approach to minimize radiation exposure could be to administer a “radiotracer cocktail” of different PET tracers with low individual activities to be captured later in one imaging session. Although conceptually attractive, the increase in background noise due to different radiotracers would likely reduce image quality and hence lesion detectability and would negate the possibility of determining which tracer was taken up by the tumor and therefore the potential for choice of radionuclide therapy agent if indicated. Further, the utilization of the radiotracer cocktail approach would negatively impact future studies aiming at establishing links between imaging phenotype, molecular genetic background, and clinical outcomes.

A potential solution to these challenges is to adopt a tailored approach using a diagnostic algorithm based on PGL location, biochemical phenotype, and any known genetic background, which is a strategy that has been recommended in recent guidelines [6, 7]. Selection of the appropriate imaging pathway using such algorithms is, itself, somewhat challenging because it requires information that is not always readily available at the time of investigating a suspected PGL. Firstly, acquiring results of all the required tests may take weeks. Secondly, about 60–70 % of PGL patients have no identifiable germline mutations and therefore, in these patients, imaging phenotype/genotype correlations are not yet fully established. A pragmatic approach would be to assess metastatic risk based on presence or absence of a positive family history and the size of the primary tumor and levels of methoxytyramine. Knowledge about biochemical phenotype is also crucial since PGLs with adrenergic

phenotype are almost always located in the adrenal gland. Catecholamine profiles can usually be obtained within a week of initial work-up. In cases of an adrenergic phenotype, the size of any adrenal lesion on CT or MRI of the adrenal is the most important. If a tumor is more than 5–6 cm, functional imaging should be added. For cases limited to the adrenal on anatomical imaging, ^{123}I -MIBG scintigraphy would generally be the first nuclear imaging option as this is generally widely available and approved for this purpose. ^{18}F -FDOPA PET appears to be the most sensitive imaging tool for these tumors but is not routinely available at most imaging centers worldwide. The role of ^{68}Ga -DOTA-SSA remains to be established in this setting but may replace MIBG as the test of first choice where available. For the noradrenergic biochemical phenotype the choice of imaging becomes more difficult. In this situation, a combination of anatomical or functional imaging is usually required. Based on genotype and anatomical staging, the following first-line strategies could be used based on recent research findings: known SDHB: ^{68}Ga -DOTA-SSA PET/CT [8]; metastatic and sporadic PGL of unknown genotype: ^{18}F -FDOPA or ^{68}Ga -DOTA-SSA PET/CT; head and neck PGL: ^{68}Ga -DOTA-SSA PET/CT [9, 10]; sympathetic PGL: ^{18}F -FDOPA PET/CT [11]. If the chosen imaging techniques is not well matched with the anatomical imaging, another radiopharmaceutical should be considered. Options include, particularly ^{18}F -FDG PET/CT for SDHx, sympathetic PGL or metastatic and sporadic PGL of unknown genotype, ^{18}F -FDOPA for head and neck PGL. The optimal sequencing of tracers in such a step-by-step approach remains to be determined by experienced multidisciplinary centers.

In conclusion, the ability to detect PGLs by molecular imaging goes hand in hand with its ability to characterize the molecular metabolomics and epigenetic features of these tumors [12]. The diversity of available radiopharmaceuticals is an advantage for the current management of patients, no matter which approach is used. It is expected that information provided by novel imaging studies, particularly the application of ^{68}Ga -DOTA-SSA PET/CT to other groups of PHEO/PGL (e.g., sporadic metastatic and various hereditary ones), will offer promising new results that will provide a better understanding of the most efficient use of imaging to determine treatment options for this disease. The development of radiopharmaceuticals against new targets and the combination of PET and MRI (including spectroscopy) [13] will offer new options. Their utilization will, however, require a more expanded understanding of this disease at a molecular level that depends heavily on collaborative research programs between experienced centers that will provide a better understanding of the intimate interaction of imaging phenotype and genotype.

Compliance with ethical standards

Conflicts of interest None.

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