THEMATIC REVIEW

Nuclear medicine in pheochromocytoma and paraganglioma: at a crossroads with precision medicine

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Abstract

Precision medicine (PM) aims to maximize the risk–benefit balance of medical decisions by integrating individual patient and disease characteristics. This approach is gaining increasing recognition from clinicians, healthcare systems, pharmaceutical companies, patients, and governments. Nuclear medicine plays a critical role in PM by its virtue of providing critical information at every step of disease management, digital markers, and companion diagnostics/therapeutics. It is anticipated that technological breakthroughs and new tracers will continue to position nuclear medicine among the significant players in PM.

Key Words

- targeted radionuclide therapy
- precision medicine
- neuroendocrine tumors
- somatostatin receptor

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Nuclear medicine as a component of precision medicine

This article is a summary of a plenary lecture presented at the 6th International Symposium on Pheochromocytoma/Paraganglioma (20 October 2022, Prague, Czech Republic), which explored the current and future roles of diagnostic and therapeutic nuclear medicine in the era of precision medicine (PM), taking into account the accelerating digital revolution in health care.

PM relies on the stratification of management decisions in order to maximize the risk–benefit balance. Molecular imaging is a component of PM by complementing morphologic imaging in the diagnosis and staging of PPGL, providing predictive and prognostic biomarkers, and implementing therapeutic options.

Nuclear medicine is based on the use of radiopharmaceuticals that can contain diagnostic or therapeutic radionuclides. These radiopharmaceuticals can target tumor cells or tumor microenvironments. There are several classes of radiopharmaceuticals (Taieb *et al.* 2016): (i) substrates that reflect metabolic reprogramming (e.g. ^{18}F-FDG); (ii) precursors for cellular products (e.g. ^{18}F-FDOPA); (iii) receptor ligands (e.g. radiolabeled somatostatin analogs), and (iv) antigenic recognition (immuno PET).

Although nuclear medicine is booming, there are still some concerns regarding its routine use in PPGL mainly due to the use of ionizing radiation, practical constraints, and cost burden. Although the Hippocratic oath 'primum non nocere' encourages limitation of radiation as per the ALARA concept (as low as reasonably achievable), the under-use of nuclear imaging should not lead to inaccurate diagnosis or underestimation of the extent of disease. Additionally, technological breakthroughs will drastically decrease exposure in the upcoming years and change current paradigms.

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Technological breakthroughs

Ultra-extended field-of-view PET scanners (total body) have been recently introduced in clinics. They provide an 8- to 10-fold increment in signal-to-noise ratio, permit capture of high resolution whole-body images in a shorter scan time, and allow lower administered activities to be used. This technology provides several advantages: patient comfort, kinetics with delayed images, multi-probe capacity, and reduction of radiation burden from PET to 1 mSv. The need for very small tracer quantities is also important for amortization (Hicks & Van den Abbeele 2022).

An important European initiative called the '10 picosecond TOF-PET challenge' will also lead to important technological improvements in upcoming years. This project aims to stimulate physicists to pass a technological milestone: achieving a 10 picosecond full width at half maximum (FWHM) coincidence resolution time (CRT) (Lecoq *et al.* 2020). It should improve the signal-to-noise ratio and increase PET sensitivity by a factor of more than 16-fold, permitting reduced administrated activities and for late images to be made. The effective dose should be reduced by more than 200-fold (0.03 mSv per PET). Altogether, these improvements will increase the use of PET in oncology including PPGL, and the screening of patients with this hereditary syndrome.

Furthermore, chemputers and robot chemists have also been developed to allow faster and cheaper chemical synthesis (Sanderson 2019), which would further help in the wider acceptance and throughput of PET imaging in various centers.

Diagnostic, staging and disease phenotyping

PPGL can usually be diagnosed by morphologic imaging due to their high vascularization, localization in preferred anatomical sites, and trend toward multifocality, especially for head and neck PGL. There are also some extra-tumoral findings that can orient toward a syndromic disease (e.g. thoracic scoliosis, hemangioblastoma, neurofibroma, GIST, and pituitary adenoma). Nuclear imaging can complement morphologic imaging for diagnosis and staging. The main advantages of nuclear imaging rely on the use of radiopharmaceuticals that can be very specific to PPGL, and associated with an elevated PPGL-background uptake ratio, permitting the detection of very small lesions in the setting of multifocal or metastatic disease.

Radiopharmaceuticals should not be confused with contrast agents because they not only demonstrate the disease but also provide important molecular information and are highly specific (^{123}I-metaiodobenzylguanidine (MIBG), ^{18}F-FDOPA, and somatostatin receptor/SSTR PET). ^{18}F-FDG is not specific but can be considered as a genotypic tracer since high uptake is observed in patients with PPGL related to mutations in one of the genes encoding for succinate dehydrogenase subunits (collectively named *SDH*x-related PPGL), regardless of location (Timmers *et al.* 2007, 2009, Zelinka *et al.* 2008, Taieb *et al.* 2009). *SDHx*-related metastatic PPGL typically exhibit a strong positivity in ^{18}F-FDG and SSTR PET, and a very limited uptake with specific tracers such as ^{18}F-FDOPA and ^{123}I-MIBG. This illustrates that the choice of radiopharmaceutical heavily depends on tumor biology, which is tightly linked with tumor origin (from sympathetic vs parasympathetic paraganglia; adrenal vs extra-adrenal), genetic status, biochemical phenotype, and size, with all being intimately inter-connected (Fig. 1). *SDHx*-related tumors are characterized by succinate accumulation that can be detected by *in vivo* magnetic resonance spectroscopy (MRS) (Varoquaux *et al.* 2015, Lussey-Lepoutre *et al.* 2016, Casey *et al.* 2018). The ^{18}F-FDG uptake pattern is mainly due to the accumulation of succinate at the intracellular level leading to a pseudohypoxia phenotype (i.e. hypoxia-inducible factor (HIF) stabilization despite a normal oxygen supply). Additionally, the enormous amount of succinate cannot be contained in the cells and can act on surrounding stroma cells. In tumor-bearing mice, an intratumoral injection of succinate is sufficient for increasing ^{18}F-FDG uptake (Garrigue *et al.* 2017). In metastatic PPGL, ^{18}F-FDG PET response followed serum succinate levels (Lamy *et al.* 2022).^{18}F-FDG PET imaging can also visualize BAT uptake which is tightly linked to norepinephrine secretion. BAT activity in PPGL patients is associated with higher mortality (Abdul Sater *et al.* 2020). PPGLs are characterized by high SSTR expression regardless of their location and therefore can be imaged by radiolabeled somatostatin analogs (SSA). Despite the absence of theranostic and prognostic information, ^{18}F-FDOPA PET is the ideal tracer of *VHL-, RET-,* and *MAX*-related PPGLs due to high tumor-to-background uptake in the adrenals, which permits the detection of multiple tumors within the same gland or in bilateral cases (Taieb *et al.* 2018, 2019*a*).

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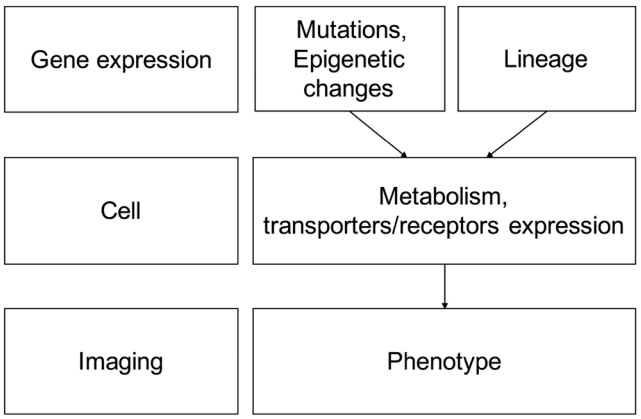

Figure 1
Determinants of molecular imaging phenotypes.

Nutrient tracers

Beyond glucose, there is an expanding metabolic repertoire of agents that are needed to fuel different cancers. Metabolism is influenced by many factors: cell lineage, drivers, and nutrient environment. Understanding how PPGL cells grow may reveal pathways that can be exploited for therapy. In *SDHx*-related tumors, the disrupted tricarboxylic acid (TCA) cycle (also known as the Krebs cycle) leads to a depletion in aspartate (partially compensated by pyruvate carboxylase activity) (Imperiale *et al.* 2015, Lussey-Lepoutre *et al.* 2015). In this situation, glutamine is converted by glutaminase (GLS) to glutamate that fuels TCA in carbons and facilitates aspartate efflux needed to support cellular anabolism. Glutamine metabolism has been shown to be increased in *SDHB KD* Pheo cells (siRNA, itaconic acid, atpenin) (Saxena *et al.* 2016, Sarkadi *et al.* 2020, Kim & Koo 2021). GLS, which is a therapeutic target, was also found to be more frequently expressed in *SDHB* vs non-*SDHB* (30–54% vs 9–22%) (Tabebi *et al.* 2022). It has been shown that high GLS activity results in low intracellular glutamine content (i.e. pool size) on MRS (Zhou *et al.* 2017). Glutamine imaging is not trivial because radiolabeled glutamine is not metabolized by GLS. Therefore, glutamine tracer distribution on PET mainly reflects pool size which is inversely correlated with GLS activity (Zhou *et al.* 2017, 2022, Viswanath *et al.* 2021). The same phenotype can also be observed with ^{18}F-fluciclovine (analog of L-leucine) and needs to be further studied for PPGL. Ultra-extended field-of-view PET scanners have multi-probe capacity and provide the opportunity to perform glutamine imaging followed by ^{18}F-FDG or SSTR PET/CT.

Images are more than pictures, they are data

Improving disease characterization and predicting patient outcome is a main component of PM. In recent years, radiomics has emerged as a potential solution to provide biomarkers from images beyond the capabilities of the human eye. Radiomics is a multistep process that provides more or less sophisticated features through machine (deep) learning that can be integrated into models (Hatt *et al.* 2017). In the setting of PPGL, radiomics has been evaluated for disease characterization (cluster 1 vs others) (Ansquer *et al.* 2020, Noortman *et al.* 2022) and provides promising results. However, there are some challenges due to the lack of standards, resulting in limited reproducibility, the lack of fully automated detection and delineation, and the lack of multicentric validation.

Prospective studies are therefore needed not only for subtyping but also for obtaining biomarkers for risk stratification and prognosis. The development of fully automated segmentation methods will also increase the use of radiomics.

Information obtained from kinetic studies can also provide critical information. It has been shown that glucose phosphorylation rate (i.e. k3), or times required to reach 80% of the metabolized ^{18}F-FDG fraction, could better reflect tumor metabolism than standardized-uptake value-derived indices (Barbolosi *et al.* 2016, van Berkel *et al.* 2019).

Precision radiopharmaceutical therapy

Therapeutic nuclear medicine has gained an increasing role in the management of neuroendocrine tumors, including PPGL. In recent years, newer and older companies have invested in theranostics and revitalized this activity. The concept of theranostics encapsulates the integration of diagnostic and therapeutic functions within the same pharmaceutical platform (a theranostics pair). Therefore, results derived from an imaging study based on a compound labeled with a diagnostic radionuclide can precisely determine whether an individual patient is likely to benefit from a specific treatment using the same related compound labeled with a therapeutic radionuclide. Since PPGL can overexpress SSTR and/or the norepinephrine transporter, they can be treated by radiolabeled SSA or metaiodobenzylguanidine (MIBG). Both radiopharmaceuticals can be considered based on the radionuclide uptake for each tracer, favoring the one that is clearly superior in targeting most or all of the patient's lesions. Using beta emitters, most PPGL

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patients achieve disease stabilization and improvement of hypertension (Taieb *et al.* 2019*b*).

In PPGL, the use of SSTR antagonists that can display higher occupancy and prolonged binding to SSTR may also have >10 times higher uptake compared to agonists, and may represent an interesting alternative approach to agonists (Fani *et al.* 2022).

Beyond the target, alpha emitters that can induce more cytotoxic effects have emerged as an attractive alternative treatment option to beta emitters in peptide receptor radionuclide therapy (PRRT). In a recent study which included nine PPGL patients using actinium-225, partial response was observed in 50% of cases (objective response in 87.5%) (Yadav *et al.* 2022). Seven out of nine have received previous ^{177}Lu-PRRT. A reduction or interruption of antihypertensive drugs was been observed in 3/7 and 2/7, respectively. No high-grade toxicity was observed. More recently, data from phase 1 using Pb212 as *in vivo* generator of alpha particles has shown an OR of 80% in NET (no PPGL) and no serious treatment-emergent adverse events (Delpassand *et al.* 2022). These reassuring results in terms of side effects will probably give a greater impetus toward the use of targeted alpha-particle therapy in PPGL patients.

Based on preclinical studies, other radionuclides also appear promising, notably the combined β- and Auger-emitter terbium-161, especially so when coupled to SSTR antagonists, probably leading to substantial damage to the cell membranes of tumor cells and subsequent apoptosis (Borgna *et al.* 2022).

There is also a lot of exciting work on the combination of targeted radionuclide therapy (TRT) with immunotherapy. The role of TRT would be to allow local control, initiate T cell priming, and turn out 'cold to hot' tumors that together with immune checkpoint blockade could improve outcomes.

In this setting, immuno PET may help to monitor immune response. There are currently two main approaches that have been investigated in humans: CD8-targeted immuno PET (Pandit-Taskar *et al.* 2020, Farwell *et al.* 2022) and anti-PD-L1 adnectins (Huisman *et al.* 2020, Stutvoet *et al.* 2020, Robu *et al.* 2021, Nienhuis *et al.* 2022).

Next-generation medicine

From Hippocrates to the first half of the 20th century, medicine was centered on the treatment of symptoms. Medicine has evolved over time due to major discoveries by the doyens of the field of medicine. In the second half of the 20th century, the means of exploring the body by imaging was enriched and the discovery of cancer-associated genes brought us into the area of causal medicine. Certain major discoveries in biochemistry (Otto Heinrich Warburg, 1931 Nobel Prize) and neurosciences (Louis Sokoloff 1981, Lasker Awar 1986, National Academy of Sciences Award) have been the basis of the emergence of seminal works on PET scanning in oncologic patients. Today, we are able to use these approaches to make PM centered on the patient and their disease. Next-generation medicine will be based on the analysis of big data made possible by artificial intelligence (AI) and mathematical modeling.

For rare diseases, the information obtained from digital twins could be of prime interest. Algorithms provide the opportunity to identify digital twins from databases. This approach, however, requires building a database with reliable electronic health records that can contain critical information such as treatment sequences, responses and toxicities, and follow-up. Nuclear imaging may provide important information on disease (location, extension, phenotype, and quantitative parameters), and could be implemented in this database together with clinical and genetic data. All this information together with modelization will represent the basis of a digital doctor that will, together with the personal experience and knowledge (evidence-based) of a real physician with the support of an MDT, permit a more individualized therapeutic approach (Fig. 2). Many international initiatives led by governments

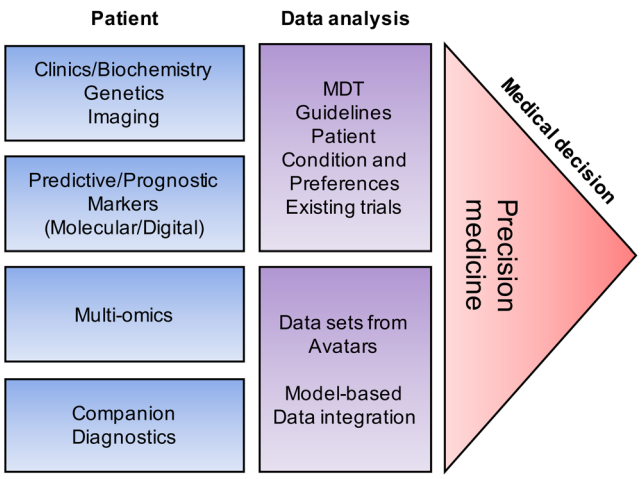

Figure 2
Personalized approach to PPGL patients. MDT, multidisciplinary team.

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or companies with consortium partners have been initiated to support such projects.

At present, even if the use of computer science has increased dramatically, it is not yet fully mature for these sophisticated applications. Only a handful of AI algorithms have been approved by the Food and Drug Administration (FDA); the IBM Watson Health cognitive decision-support system, which is the most clinically advanced tool, has led to disappointing results so far. There are still major concerns regarding the standardization, ergonomics, data management and security of these solutions. Additionally, there are also major challenges regarding ethics, cost-burden, communication for improving acceptance (public, healthcare professionals), and cyber security (attack prevention and detection). It is expected that these aspects will be improved in the coming years and we will see the dawn of a new era in PM.

Conclusion

An accelerating digital revolution in health care will modify various aspects of the medical profession and how we take care of PPGL patients. Technological breakthroughs and new tracers will continue to position nuclear medicine among the significant players in PM.

Declaration of interests

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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