Moving Beyond “Lumpology”: PET/CT Imaging of Pheochromocytoma and Paraganglioma

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Running Title: DOTATATE PET/CT for Imaging Pheochromocytoma/Paraganglioma

Disclosure of Potential Conflicts of Interest

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Summary

High somatostatin receptor expression on the cell membrane of succinate dehydrogenase mutation-related pheochromocytoma (PCC) and paraganglioma (PGL) provides a potential target for imaging and therapy. $^{68}$Ga-DOTATATE positron emission PET/CT may represent a new gold standard for staging PCC/PGL and have future therapeutic implications.
In this issue of *Clinical Cancer Research*, Janssen and colleagues (1) evaluate four different radiotracers with PET/CT in a cohort of patients with pheochromocytoma (PCC) and paraganglioma (PGL) arising on the background of succinate dehydrogenase, subunit B (SDHB) mutation. Compared to a range of conventional imaging approaches, they report a superior lesion detection rate with $^{68}$Ga-DOTATATE PET/CT and propose that this may represent the new ‘gold standard’ for staging these patients. Whilst pathology often serves as the arbiter of truth, in patients with metastatic disease biopsy of multiple sites is neither feasible nor ethical. Therefore, more sensitive tests run the risk of being deemed “false positive” when judged beside conventional comparators, such as CT or MRI. Addressing this potential limitation, the authors adopt an innovative composite of imaging and pathological findings to constitute “truth”.

Cancer staging traditionally uses CT or MRI for detecting suspected malignant lesions and often for guiding biopsy to allow pathological characterization of disease. In this “lumpology” paradigm, the number, size and location of lesions are used to determine prognosis and guide treatment strategies on the assumption that the biopsy result is representative of all sites of disease. Janseen and colleagues demonstrate that molecular imaging also performs well within this conceptual framework. However, more importantly in our opinion, molecular imaging provides powerful disease characterization on a whole body scale and, in particular, in identifying heterogeneity in tumor biology (2).

By leveraging a variety of pathways pertinent to PCC/PGL biology, including glycolytic metabolism with $^{18}$F-fluorodeoxyglucose (FDG), catecholamine synthesis with $^{18}$F-fluorodihydroxyphenylalanine (FDOPA) and $^{18}$F-fluoro-dopamine (FDA), and somatostatin receptor (SSTR) expression with $^{68}$Ga-DOTATATE, the current study demonstrates a variable but generally high PET/CT lesion detection rate with DOTATATE demonstrating the highest
overall accuracy. Accordingly, the current research identifies that SDHB mutation-related PCC/PGL have high SSTR expression in the vast majority of cases. The SSTR was first demonstrated to be a viable imaging target in scintigraphic studies using $^{123}$I-octreotide performed over 25 years ago (3). $^{68}$Ga-DOTATATE PET/CT represents a significant advance owing to the combination of use of superior imaging technology and a peptide that has a higher affinity for the subclass-2 somatostatin receptor, which is known to be overexpressed in SDHB PCC/PGL (4). While these data are useful in guiding the choice of functional imaging agent for staging SDHB PCC/PGL, they cannot necessarily be extrapolated to other genomic subtypes, and nor do they fully address the potential prognostic and therapeutic implications of some lesions being visualized by one tracer but not another.

Pheochromocytoma and paragangliomas have a complex genomic landscape (5). These can be broadly divided into a pseudohypoxic cluster characterized by activation of hypoxia inducible factors (HIF) and a second group characterized by mutations that impact receptor tyrosine kinase signaling. The mutations in the former cluster, including SDHx-associated PCC/PGL, lead to inhibition of oxidative phosphorylation and activation of glycolytic pathway via the Warburg effect, underpinning the high sensitivity of FDG PET/CT in this group (6). One of the consequences of HIF signaling is enhanced angiogenesis, providing a rationale for agents such as sunitinib in such patients (7). On the other hand, catecholamine transport is integral to uptake of FDA while FDOPA is a precursor for catecholamine synthesis. Since the catecholamine secretion profile of PCC/PGL varies significantly, it isn’t surprising that some lesions aren’t visualized by these tracers. Upregulation of the VCAT-1 pathway involved in catecholamine transport is the basis of metaiodobenzylguanidine (MIBG) imaging and therapy, which has been used in PCC/PGL for over 30 years. Nevertheless, FDA, in particular, could be used as a surrogate for MIBG in
order to determine suitability for $^{131}$I MIBG treatment. Alternatively, as the PET radionuclide $^{124}$I becomes more widely available, PET/CT could be used both to select and predict dosimetry for this form of radionuclide therapy.

DOTATATE, or similar peptides, labelled with $^{68}$Ga for diagnostic PET imaging can also be radiolabelled with beta emitters such as $^{177}$Lu or $^{90}$Y enabling targeted delivery of radiation to sites of tumors (Fig. 1). This is called peptide receptor radionuclide therapy (PRRT) and is increasingly utilized to treat gastrointestinal and pancreatic neuroendocrine tumors (NET) with striking results even in patients who have failed all other therapies (8). We have recently described favorable outcomes of combining PRRT with radiosensitizing 5-fluorouracil in patients with more aggressive NET (9). The published evidence base for PRRT in PCC/PGL is small (10) but the high and seemingly ubiquitous expression of SSTR in this disease provides a scientific rationale for this type of therapy. Using the same peptide for both imaging and therapy enables both personalized and precision medicine as patients who are likely to benefit can be determined upfront by imaging with $^{68}$Ga-DOTATATE PET, and post-therapy imaging following delivery of $^{177}$Lu or $^{90}$Y-DOTATATE can measure the actual radiation dose delivered to tumors and normal tissues. Recent evidence of hypermethylation of the MGMT promoter in SHDB PCC/PGL (11) suggests a rationale for combining temozolomide with PRRT as it has been performed in NET (12).

Although there is increasing availability of PET/CT in the broader community, many of these advanced molecular imaging agents and radionuclide therapies are limited to a few academic centers. Furthermore, there are significant regulatory and reimbursement impediments to wider dissemination of these diagnostic and therapeutic techniques. The presence of tumor heterogeneity within an individual (2) provides an additional challenge as more than one type of PET/CT scan may be needed for optimal staging. Despite therapy
being highly efficacious against those elements of the disease that express the therapeutic target, subclones of cells lacking the target may escape and determine the eventual outcome of treatment. The path-length of beta emitters in the order of several millimeters may overcome this to some extent. Nevertheless, in our experience some patients with more poorly differentiated metastatic SDHx PCC/PGL lack uptake on DOTATATE PET/CT and have a rapidly progressive FDG-avid aggressive phenotype. We postulate that this disease is driven by an angiogenic switch mediated by high VEGF levels. We have also observed that within an individual, there can be sites of disease with either DOTATATE or MIBG and, sometimes, both opening the possibility of treatment with combinations of PRRT and $^{131}$I MIBG. Unlike performing single tumor biopsy, which may not be representative of tumors at all sites, we believe integration of the molecular imaging phenotype into patient management is complementary to genetic testing and histopathology and critical to the true realization of personalized medicine. Further, it is likely that complex combinations and sequential treatments will be needed to improve treatment outcomes in individual patients. This will require a paradigm shift from “lumpology” to in vivo, whole-body characterization of tumor biology through advanced molecular imaging with selective targeted biopsy and genomic analysis.

References


Figure 1. Targets in pseudohypoxic cluster metastatic pheochromocytoma and paraganglioma including therapeutic and diagnostic radionuclides, and potential pharmaceuticals. The text in red font and the red bubbles indicate therapeutic radionuclides. The text in green font indicates diagnostic radionuclides. The text in brown font indicates drug targets. MGMT, O(6)-methylguanine-DNA methyltransferase; MTIC, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide; TYMS, thymidylate synthase.
Figure 1:

- **Somatostatin receptor**
- **Nucleus**
- **DNA methylation**
- **Norepinephrine**
- **Secretory granule**
- **GLUT1**
- **Mitochondrion**
- **SDH**
- **VHL**
- **Cytoplasm**
- **VEGFRs**
- **Temozolomide**
- **Capecitabine**
- **MTIC**
- **5FU**
- **Tyrosine kinase inhibitors**
- **Activation of signal-transduction cascades**
- **Upregulation?**
- **HIF-1 inhibitors**
- **HIF-1α**
- **VHL**
- **PARPi**
- **TYMS**
- **PARP**
- **MGMT**
- **MTIC**
- **Temozolomide**
- **Betaparticulate radiation**
  - **177Lu/131I 1mm, 90Y 5mm path length**
- **18F-FDOPA**
- **18F-FDG**
- **GLUT1**
- **Succinate**
- **Fumarate**
- **SDH**
- **Fumarate**
- **HIF-1**
- **PCC/PGL tumor cell**
- **Upregulation**
- **Downregulation**

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