^{68}Ga-DOTATATE PET in Pediatric Paraganglioma / Pheochromocytoma: A Case-series Highlighting the Role of Functional Imaging

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Abstract

Pheochromocytoma and paraganglioma (PPGL) are rare neuroendocrine tumors in childhood. Cancer predisposition syndromes (CPS) are increasingly recognized as the underlying cause for a number of pediatric malignancies and up to 40% of PPGL are currently thought to be associated with a hereditary predisposition1,2. With the increasingly widespread availability of functional molecular imaging techniques, nuclear medicine imaging modalities such as 18F-FDG-PET/CT, 123I-MIBG SPECT/CT, and 68Ga-DOTATATE PET/CT now play an essential role in the staging, response assessment and determination of suitability for targeted radiotherapy in patients with PPGL. Each of these imaging modalities targets a different cellular characteristic, such as glucose metabolism (FDG), norepinephrine transporter expression (MIBG), or somatostatin receptor expression (DOTATATE), and therefore can be complementary to anatomic imaging and to each other. Given the recent FDA approval3 and increasing use of 68Ga-DOTATATE for imaging in children4, the purpose of this article is to use a case-based approach to highlight both the advantages and limitations of DOTATATE imaging as it compares to current radiologic imaging techniques in the staging and response assessment of pediatric PPGL, and to offer a decision algorithm for the use of functional imaging that can be applied to PPGL, as well as other neuroendocrine malignancies.

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Abbreviations: Cancer predisposition syndromes – CPS; Pheochromocytoma Paraganglioma – PPGL; Inflammatory myofibroblastic tumor – IMT; Whole body MRI - wbMRI

Running Title: ^{68}Ga-DOTATATE PET in Pediatric Paragangloma Pheochromocytoma

ABSTRACT

Pheochromocytoma and paraganglioma (PPGL) are rare neuroendocrine tumors in childhood. Cancer predisposition syndromes (CPS) are increasingly recognized as the underlying cause for a number of pediatric malignancies and up to 40% of PPGL are currently thought to be associated with a hereditary predisposition[1,2]. With the increasingly widespread availability of functional molecular imaging techniques, nuclear medicine imaging modalities such as^{18}F-FDG-PET/CT,^{123}I-MIBG SPECT/CT, and^{68}Ga-DOTATATE PET/CT now play an essential role in the staging, response assessment and determination of suitability for targeted radiotherapy in patients with PPGL. Each of these imaging modalities targets a different cellular characteristic, such as glucose metabolism (FDG), norepinephrine transporter expression (MIBG), or somatostatin receptor expression (DOTATATE), and therefore can be complementary to anatomic imaging and to each other. Given the recent FDA approval[3] and increasing use of^{68}Ga-DOTATATE for imaging in children[4], the purpose of this article is to use a case-based approach to highlight both the advantages and limitations of DOTATATE imaging as it compares to current radiologic imaging techniques in the staging and response assessment of pediatric PPGL, and to offer a decision algorithm for the use of functional imaging that can be applied to PPGL, as well as other neuroendocrine malignancies.

INTRODUCTION

Hereditary cancer predisposition syndromes (CPS) have contributed to our growing understanding of pheochromocytoma and paraganglioma (PPGL) biology and clinical behavior. At least 12 different genetic syndromes are known to have a predisposition to developing PPGL and PPGL are associated with at least 15 well-characterized driver genes as well as additional disease-modifying genes [2], underscoring the heterogeneous nature of these tumors. Paragangliomas (PGL) arise from neuroendocrine cells (paraganglia) that extend from the skull base to the pelvis and have variable functional hormone secretion depending on their location and genetic makeup, while pheochromocytoma (PCC) are catecholamine-secreting tumors arising from chromaffin cells of the adrenal medulla. These predominantly well-differentiated tumors can be evaluated anatomically by CT and MRI and with functional imaging techniques such as ^{123}I-MIBG scintigraphy, in which the norepinephrine analog MIBG is taken up by cells expressing the norepinephrine transport receptor, and ^{18}F-FDG PET/CT, in which the glucose analogue ^{18}F-FDG is transported into and trapped in metabolically active cells. Well-differentiated neuroendocrine tumors such as PPGL also express somatostatin receptors and ^{111}In-pentetreotide scintigraphy, using a conjugate of octreotide that binds to

somatostatin receptors, has historically been the functional imaging method of choice for staging neuroendocrine tumors (NETs). With the recent FDA approval of^{68}Ga-DOTATATE for localization of somatostatin receptor positive neuroendocrine tumors in adult and pediatric patients[3], ^{111}In-pentetreotide scintigraphy has largely been replaced by^{68}Ga-DOTATATE PET/CT based on improved diagnostic accuracy, shorter imaging protocol, and lower radiation dose[5-8].

Although most PPGL are not malignant, distinguishing benign from malignant disease is important since operative treatment can be curative for PPGL that are amenable to resection and have not metastasized. Because there are no histopathologic techniques currently available to distinguish primary benign from malignant PPGL[9], both functional and anatomic imaging approaches have been advocated for the detection of metastatic disease. Moreover, these tumors frequently arise in the setting of specific cancer predisposition syndromes with multiple synchronous primary tumors of identical or separate histologies, and functional imaging may help in discriminating between distinct tumor types. In patients with PPGL, the functional imaging techniques most commonly used are ^{68}Ga-DOTATATE PET/CT,^{18}F-FDG PET/CT, and ^{123}I-MIBG scintigraphy, each of which have advantages and limitations. For example, while ^{68}Ga-DOTATATE PET/CT is reported to have higher sensitivity for detection of well-differentiated, less aggressive NETs, there is evidence to suggest that ^{18}F-FDG PET/CT may be preferable for more aggressive, less well-differentiated tumors [10], with other reports suggesting an association between higher ^{18}F-FDG uptake and worse outcome, even in patients with well-differentiated or low-grade tumors[11]. ^{123}I-MIBG scintigraphy has greater specificity for disease characterization than CT and MRI, but much lower sensitivity than somatostatin-receptor directed PET imaging techniques. Despite its lower sensitivity, ^{123}I-MIBG may still be used to establish MIBG avidity in individuals with metastatic disease in whom treatment with ^{131}I-MIBG is a consideration [12,13]. This latter point is critical in pediatrics since ^{131}I-MIBG has US regulatory approval for therapeutic use in children while somatostatin-targeted therapies such as ^{177}Lu-DOTATATE (Lutathera?) are not yet approved in children.

Other pediatric neuroendocrine tumors, including medullary thyroid carcinoma, carcinoid, gastrinoma, insulinoma, VIPoma, glucagonoma also demonstrate increased expression of somatostatin receptors. The approach outlined here, focusing on PPGL as a model for the use of^{68}Ga-DOTATATE to target these receptors, can be applied more generally to patients with other known neuroendocrine tumor types for staging, response-assessment, identifying the primary tumor site(s) in patients with known metastatic disease, and for off-treatment surveillance. This article will highlight both the advantages and limitations of ^{68}Ga-DOTATATE imaging as it compares to other functional and anatomic imaging techniques. With emphasis on the complementary information, as shown in three specific index cases, we propose a diagnostic algorithm to aid in selecting the appropriate functional imaging technique in patients with PPGL.

Methods

For this retrospective case series review, the requirement for patient informed consent was waived by the Boston Children's Hospital Institutional Review Board.

Diagnostic CT and MRI examinations were performed using standard techniques; MRI was performed at 3T.

PET/CT exams were performed using a Siemens Biograph mCT Flow PET/CT scanner equipped with 64 slice CT. Low dose attenuation correction CT images utilized CARE kV dose reduction and CARE Dose 4D tube current modulation. PET images were acquired in 3D mode with dead time correction, decay correction, scatter correction, and time of flight and reconstructed with standard iterative reconstruction parameters at 3 mm increments.

^{18}F-FDG: 5.55 MBq/kg (0.15 mCi/kg, 10 mCi maximum) was administered 60 min prior to imaging.

^{68}Ga-DOTATATE: 2.74 MBq/kg (0.074 mCi/kg; 5.4 mCi maximum) was administered 60 min prior to imaging.

^{123}I-MIBG scintigraphy was performed using a Siemens Intevo SPECT/CT equipped with medium energy

collimators and 16 slice CT. Low dose attenuation correction SPECT/CT images were acquired at 80-100 kVp using CARE Dose 4D tube current modulation. SPECT images were acquired in continuous non-circular mode with 2x360° camera head rotations at 15sec per stop equivalent and reconstructed with FLASH 3D iterative reconstruction per manufacturer recommendations. Static planar images were acquired in anterior/posterior and lateral projections.

^{123}I-MIBG: 5.18 MBq/kg (0.14 mCi/kg, 10 mCi maximum) was administered 24hrs prior to imaging.

CASE SERIES

Case 1: Metastatic paraganglioma without an identified pathogenic germline variant.

A 12-year-old male presented with weight loss of 4.5 pounds over 18 months, loss of appetite, intermittent vomiting, constipation, and fatigue. CT of the chest, abdomen and pelvis showed a heterogeneous left paraspinous/retroperitoneal mass with multiple pulmonary nodules that were suspicious for metastases; both adrenals were normal. A right ileo-ileal intussusception was also present and initial differential considerations included inflammatory myofibroblastic tumor (IMT), sarcoma, lymphoma, and neuroblastoma. Biopsy yielded a broad differential, with low-grade spindle-cell sarcoma and extra-intestinal GIST variant among the considerations. Staging^{18}F-FDG-PET/CT (Fig. 1A-D) showed low-level uptake in the abdominal mass and the pulmonary nodules, but no other sites of FDG-avid disease were detected. Upon surgical resection, the mass appeared to be paraspinous in orgin, extending into the retroperitoneum. Pathology was consistent with paraganglioma, with cells positive for chromogranin, synaptophysin, INSM1, CH56, GATA3, and S100, with evidence of multifocal vascular invasion and positive resection margins. Germline pathogenic variants in genes typically associated with hereditary paraganglioma were not identified. ^{68}Ga-DOTATATE PET was performed to evaluate for metastatic disease and revealed widespread somatostatin receptor-expressing disease throughout the axial and appendicular skeleton, lungs, and right hepatic lobe (Fig 1E). The hepatic lesions were seen by MRI, but were not initially evident by CT. Based on the extensive burden of systemic disease,^{131}I-MIBG therapy was a consideration. Staging^{123}I-MIBG scintigraphy (Fig. 1F) demonstrated a similar distribution of disease compared to the^{68}Ga-DOTATATE PET, with numerous axial and appendicular lesions, although there were far fewer MIBG-avid lesions (no MIBG uptake seen in the ribs, humeri, left scapula, and tibiae) in comparison with the ^{68}Ga-DOTATATE PET/CT. Known liver lesions detected by DOTATATE PET were also not well visualized on the^{123}I-MIBG study, due to background physiologic hepatic MIBG uptake. These studies were all performed within 21 days of each other, and ^{68}Ga-DOTATATE PET showed both increased sensitivity and specificity for detecting disease.

Case 2: Cancer predisposition with germline pathogenic variant in *SDHC* and co-existing GIST and paraganglioma.

A 17-year-old male with known germline pathogenic variant in *SDHC*and metastatic GIST with lesions in the liver, peritoneum, and lungs was being treated with the tyrosine kinase inhibitor regorafenib. Biochemical monitoring showed progressive elevation in chromogranin A over a 12-month period, from 46 ng/mL to 505 ng/dL.^{68}Ga-DOTATATE PET revealed an intensely avid lesion in the porta hepatis (Fig. 2), histologically confirmed to represent paraganglioma. This DOTATATE-avid paraganglioma was also FDG avid, but there were multiple FDG-avid metastatic GIST lesions remarkably negative by ^{68}Ga-DOTATATE PET, indicating two functionally distinct tumor types co-existing in the same patient. The co-existence of two tumor types in the same patient would be unusual in most circumstances, but not in patients with underlying CPS. Complicating the discovery of a new paraganglioma was the heterogeneous pattern of^{18}F-FDG uptake in the GIST lesions, resulting both from prior RF ablations and ongoing treatment with tyrosine kinase inhibitors, which are known to alter the pattern of FDG-uptake in GIST lesions [14,15].

Case 3: Cancer predisposition associated with polycythemia and multiple functional paragangliomas (Pacak-Zhuang syndrome).

A 16-year-old female with somatic mosaicism for an activating mutation in the *EPAS1* (*HIF2A*) gene leading to polycythemia and paraganglioma (Pacak-Zhuang syndrome) was found to have a right suprarenal

mass and 3 additional retroperitoneal masses. These were resected and identified as paragangliomas[16]. Surveillance whole-body MRI (wbMRI) obtained almost 2 years later identified a 1.5 cm left suprarenal mass. Plasma normetanephrine levels were slowly rising, and re-staging ^{18}F-FDG PET demonstrated an FDG-avid suprarenal mass, as well as additional small FDG-avid retroperitoneal nodules concerning for paragangliomas which had not been identified on the earlier MRI exams (Fig. 3A-D).^{18}F-FDG PET/CT obtained 6 months later for continued clinical progression (worsening hypertension along with progressive elevations in normetanephrine and chromogranin A levels) was limited secondary to a marked increase in hypermetabolic brown fat activity that presumably resulted from the elevated serum catecholamines (Fig. 3E), a phenomenon that has been described in adult PGL patients with elevated catecholamines[17]. This degree of intense brown fat uptake, in addition to obscuring primary tumor sites along the sympathetic chain, has a "sink effect", with the marked increase in FDG uptake in brown fat FDG uptake limiting availability of tracer for detecting disease elsewhere. Tracers targeting somatostatin receptors are unaffected by elevated catecholamines and a subsequent^{68}Ga-DOTATATE PET, performed 2 weeks after the patient started systemic targeted therapy[16], clearly demonstrated the left suprarenal lesion and the para-aortic paraganglioma (Fig. 3F-K), with no other sites of disease seen.

DISCUSSION

Nuclear medicine studies have become essential when evaluating pediatric neuroendocrine tumors. They provide relatively specific anatomic localization of both primary and metastatic lesions, insight into tumor function, and inform treatment decisions. These examinations are particularly useful in cancer predisposition syndromes where neuroendocrine tumors, such as PPGL are component tumors[18]. These conditions are driven by germline pathogenic variants in a number of different genes, including the genes encoding succinate dehydrogenase subunits (*SDHx* genes), and others such as*SDHAF2* , *FH* , *MAX* , *NF1* , *RET* ,*TMEM127* , *MEN2* , and *VHL* . Other tumor predisposition syndromes exist, such as the case presented here in which an*EPAS1* activating mutation resulted in development of multiple paragangliomas. Depending on the underlying genotype patients may also be predisposed to other tumors. For individuals with pathogenic variants in the *SDH genes* , these include gastrointestinal stromal tumors, renal cell carcinoma, and others[19]. Patients with*EPAS1* mutations (encoding for the transcriptional regulator HIF2-alpha) are not only at risk for pheochromocytoma and paraganglioma, but can also develop somatostatinomas, vascular malformations, and ocular abnormalities[18,19]. Patients with pathogenic variants in the von Hippel Lindau (*VHL*) tumor suppressor gene are predisposed not only to paragangliomas, but also to central nervous system hemangioblastoma, clear cell renal cell carcinoma and others[15]. In these settings, it is especially important to detect new lesions early and to be able to differentiate between possible tumor types in a patient at risk for synchronous or metachronous co-existing malignancies.

Functional imaging options to evaluate pheochromocytoma and paraganglioma include ^{18}F-FDG PET/CT,^{68}Ga-DOTATATE PET/CT, and ^{123}I-MIBG scintigraphy, and each exam is best suited for evaluation of certain types of disease. ^{18}F-FDG PET/CT is very sensitive and well suited to detecting small, hypermetabolic lesions, especially when structural imaging findings are subtle and/or non-specific.^{123}I-MIBG scintigraphy is very specific in its targeting of tumors expressing the norepinephrine transport receptor, however, in patients with PPGL, ^{68}Ga-DOTATATE PET has been shown to be more sensitive in disease detection[20-22]. This is partially attributable to inherently better spatial resolution of PET/CT compared to SPECT/CT, which was shown here in Figure 1, and potentially to differences in norepinephrine transporter expression as compared to somatostatin receptor expression. ^{68}Ga-DOTATATE binds to somatostatin receptor type 2 which has a high level of expression in well-differentiated paragangliomas and pheochromocytomas and most SDHB-deficient tumors [17,23,24], while decreased^{123}I-MIBG uptake may be related to an underlying genetic mutation, usually associated with SDHB [23]. In one study, up to 50% of patients with metastatic PPGL, especially those with pathogenic variants in *SDHB* , reportedly lacked norepinephrine transporter expression and derived no benefit from^{131}I-MIBG therapy[25], emphasizing the importance of establishing tumor MIBG avidity when considering^{131}I-MIBG therapy. It is also important to note that non-MIBG-avid PPGL are more aggressive than their^{123}I-MIBG avid counterparts, and are associated with increased malignancy rates and increased rates of metastasis[17,23-28].

Despite the inherently lower sensitivity of MIBG scintigraphy, along with physiologic uptake of MIBG in liver and adrenal glands potentially obscuring detection of small adrenal lesions and hepatic metastases,^{131}I-MIBG is the only targeted radiotherapy option currently approved for treating metastatic pediatric neuroendocrine tumors. ^{177}Lu-DOTATATE (Lutathera, theranostic partner to ^{68}Ga-DOTATATE) is not yet approved for pediatric use despite success in treating metastatic neuroendocrine tumors in adults[29]. Current recommendations for PPGL are^{68}Ga-DOTATATE PET/CT for staging and follow-up, with^{123}I-MIBG reserved for evaluating patients prior to potential ^{131}I-MIBG therapy[30].

^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT have similar rates of detection for paragangliomas and pheochromocytomas with reported sensitivities of ˜72-100% and ˜66-78%, respectively, although ^{68}Ga-DOTATATE has greater specificity and comparatively better contrast between lesions and background tissues[17,22]. However, as presented here, these two imaging techniques may be complementary to one another, particularly among patients with CPS in whom histologically and functionally distinct tumors are present (Case 2). As shown in Case 2, the identification of a new neuroendocrine tumor that was separate and distinct from known metastatic GIST disease was essential and led to surgical resection. This treatment course may not have been considered for a new GIST lesion in a patient with known metastatic disease, emphasizing how distinct tumor phenotypes, based on differences in tumor glucose metabolism and expression of somatostatin receptors, could be exploited by functional imaging and ultimately impact treatment.

PPGL also differ from other neuroendocrine tumors in that well-differentiated tumors are not necessarily hypometabolic, and in fact, even benign tumors may show marked FDG avidity[22,28,31]. Several authors have noted that^{18}F-FDG SUV values were higher in PGLs harboring mutations in SDHx and VHL when compared to the PGL associated with NF-1 and MEN-2A[28,32,33], and have speculated that this may be the result of a genetically driven Warburg effect (aerobic glycolysis) in which SDHx or VHL inactivation results in a pseudohypoxic state, leading to increased glucose utilization (and FDG uptake) in this subset of PPGL. The pathways leading to enhanced glucose utilization (and FDG uptake) in PPGL are like to involve other mediators, such as HIF1A[2,34], emphasizing the importance of considering a patient's genetic background when choosing a particular radiotracer and interpreting the functional imaging results.

Historically, ^{18}F-FDG PET had been the imaging modality of choice for evaluation of pheochromocytomas and paragangliomas in adults, with multiple studies supporting this imaging method's effectiveness over other imaging techniques. As shown in Case 3 (Figure 3), the increased sensitivity of ^{18}F-FDG PET allowed identification of sub-cm FDG-avid lesions that were not evident by MRI. However, this same case highlighted the limitations of FDG PET imaging for patients in whom elevated levels of catecholamine secretion from metabolically active paragangliomas may lead to non-specific FDG uptake at sites of hypermetabolic brown fat activity, decreasing both the sensitivity for detecting other sites of disease and the specificity for characterizing known sites of tumor. Interestingly, not all patients with elevated catecholamine levels show increased brown fat uptake[17], suggesting that PPGL tumor heterogeneity may be the result of an evolving molecular taxonomy tumor with PPGL disease clusters defined by unique molecular/imaging/clinical/biochemical/imaging phenotypes[2,35], which could include the degree to which hypermetabolic brown adipose tissue responds to catecholamine excess and accumulates FDG.

More recently, studies have shown superiority of^{68}Ga-DOTATATE PET over ^{18}F-FDG PET in detecting *SDHB* -related metastatic paragangliomas/pheochromocytomas [17,23,24,28]. In fact, Janssen et al. showed that ^{68}Ga-DOTATATE PET was more effective in detecting *SHDB* -related paragangliomas than^{18}F-FDG, ^{18}F-fluorodopamine (^{18}F-FDA), ^{18}F- fluorodihydroxyphenylalanine (^{18}F-FDOPA), and anatomic imaging with either CT or MRI[23]. Advantages to^{68}Ga-DOTATATE PET imaging also include a relatively short uptake time of 60 minutes, which is similar to^{18}F-FDG PET but shorter than^{123}I-MIBG (18-24 hour delay between injection and imaging). ^{68}Ga-DOTATATE PET/CT requires 20-45 minutes of imaging, which is similar to FDG PET/CT but dramatically shorter than typical MIBG imaging protocols which include both static planar and SPECT imaging. In addition to the shorter exam times which allow younger patients to be imaged without sedation, the effective radiation dose from ^{68}Ga-DOTATATE PET is also less than both^{123}I-MIBG and ^{18}F-FDG, which remains an important consideration in a pediatric population often with cancer

predisposition syndromes and protracted disease courses necessitating multiple serial evaluations[32,36].

For these reasons, our imaging algorithm (Figure 4) includes^{68}Ga-DOTATATE PET as the initial functional imaging technique of choice for evaluation of most subtypes of pheochromocytoma and paraganglioma, with ^{18}F-FDG PET and^{123}I-MIBG SPECT/CT reserved for characterizing DOTATATE-negative lesions and for evaluating patients for possible^{131}I-MIBG therapy. If ^{68}Ga-DOTATATE PET is not readily available, ^{18}F-FDG PET is the functional imaging study of choice.

CONCLUSION

We present here three unique clinical cases, each of which highlights both advantages and limitations to the use of^{68}Ga-DOTATATE PET, ^{18}F-FDG PET, and^{123}I-MIBG SPECT/CT in the evaluation of patients with PPGL. In these patients, who frequently have complex clinical manifestations of their disease, no single imaging technique can be forwarded as the single "best test". Rather, as the cases shown here emphasize, different clinical considerations necessitate a customized choice of functional imaging techniques. The proposed algorithm may serve as a guideline for physicians when determining which of the available imaging selections is best suited to an individual patient's care.

REFERENCES

1. Lenders JW, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2014;99(6):1915-1942.

2. Crona J, Taieb D, Pacak K. New Perspectives on Pheochromocytoma and Paraganglioma: Toward a Molecular Classification. *Endocr Rev.*2017;38(6):489-515.

3. NETSPOT (kit for the preparation of gallium Ga 68 dotatate injection), for intravenous use Initial U.S. Approval: 2016. United States Food and Drug Administration. Online Document. Published June, 2016. Accessed July 24, 2021. . https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208547s000lbl.pdf

4. McElroy KM, Binkovitz LA, Trout AT, et al. Pediatric applications of Dotatate: early diagnostic and therapeutic experience. *Pediatr Radiol.* 2020;50(7):882-897.

5. Haug AR, Cindea-Drimus R, Auernhammer CJ, et al. Neuroendocrine tumor recurrence: diagnosis with 68Ga-DOTATATE PET/CT. *Radiology.*2014;270(2):517-525.

6. Hofman MS, Kong G, Neels OC, Eu P, Hong E, Hicks RJ. High management impact of Ga-68 DOTATATE (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours. *J Med Imaging Radiat Oncol.* 2012;56(1):40-47.

7. Srirajaskanthan R, Kayani I, Quigley AM, Soh J, Caplin ME, Bomanji J. The role of 68Ga-DOTATATE PET in patients with neuroendocrine tumors and negative or equivocal findings on 111In-DTPA-octreotide scintigraphy.*J Nucl Med.* 2010;51(6):875-882.

8. Win Z, Al-Nahhas A, Towey D, et al. 68Ga-DOTATATE PET in neuroectodermal tumours: first experience. *Nucl Med Commun.*2007;28(5):359-363.

9. Else T, Greenberg S, Fishbein L. Hereditary Paraganglioma-Pheochromocytoma Syndromes. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews((R)).* Seattle (WA)1993.

10. Panagiotidis E, Alshammari A, Michopoulou S, et al. Comparison of the Impact of 68Ga-DOTATATE and 18F-FDG PET/CT on Clinical Management in Patients with Neuroendocrine Tumors. *J Nucl Med.*2017;58(1):91-96.

11. Garin E, Le Jeune F, Devillers A, et al. Predictive value of 18F-FDG PET and somatostatin receptor scintigraphy in patients with metastatic endocrine tumors. *J Nucl Med.* 2009;50(6):858-864.

12. Gonias S, Goldsby R, Matthay KK, et al. Phase II study of high-dose [131I]metaiodobenzylguanidine

therapy for patients with metastatic pheochromocytoma and paraganglioma. *J Clin Oncol.*2009;27(25):4162-4168.

13. Pryma DA, Chin BB, Noto RB, et al. Efficacy and Safety of High-Specific-Activity (131)I-MIBG Therapy in Patients with Advanced Pheochromocytoma or Paraganglioma. *J Nucl Med.*2019;60(5):623-630.

14. Hong X, Choi H, Loyer EM, Benjamin RS, Trent JC, Charnsangavej C. Gastrointestinal stromal tumor: role of CT in diagnosis and in response evaluation and surveillance after treatment with imatinib.*Radiographics.* 2006;26(2):481-495.

15. Levy AD, Quiles AM, Miettinen M, Sobin LH. Gastrointestinal schwannomas: CT features with clinicopathologic correlation. *AJR Am J Roentgenol.* 2005;184(3):797-802.

16. Kamihara J, Hamilton KV, Pollard JA, et al. Use of belzutifan, a potent HIF2a inhibitor, in a pediatric patient with Pacak-Zhuang syndrome. *NEJM.* 2021;in press.

17. Chang CA, Pattison DA, Tothill RW, et al. (68)Ga-DOTATATE and (18)F-FDG PET/CT in Paraganglioma and Pheochromocytoma: utility, patterns and heterogeneity. *Cancer Imaging.* 2016;16(1):22.

18. Erlic Z, Rybicki L, Peczkowska M, et al. Clinical predictors and algorithm for the genetic diagnosis of pheochromocytoma patients.*Clin Cancer Res.* 2009;15(20):6378-6385.

19. Bardella C, Pollard PJ, Tomlinson I. SDH mutations in cancer.*Biochim Biophys Acta.* 2011;1807(11):1432-1443.

20. Kroiss A, Shulkin BL, Uprimny C, et al. (68)Ga-DOTATOC PET/CT provides accurate tumour extent in patients with extraadrenal paraganglioma compared to (123)I-MIBG SPECT/CT. *Eur J Nucl Med Mol Imaging.* 2015;42(1):33-41.

21. Maurice JB, Troke R, Win Z, et al. A comparison of the performance of (6)(8)Ga-DOTATATE PET/CT and (1)(2)(3)I-MIBG SPECT in the diagnosis and follow-up of phaeochromocytoma and paraganglioma. *Eur J Nucl Med Mol Imaging.* 2012;39(8):1266-1270.

22. Mojtahedi A, Thamake S, Tworowska I, Ranganathan D, Delpassand ES. The value of (68)Ga-DOTATATE PET/CT in diagnosis and management of neuroendocrine tumors compared to current FDA approved imaging modalities: a review of literature. *Am J Nucl Med Mol Imaging.*2014;4(5):426-434.

23. Janssen I, Blanchet EM, Adams K, et al. Superiority of [68Ga]-DOTATATE PET/CT to Other Functional Imaging Modalities in the Localization of SDHB-Associated Metastatic Pheochromocytoma and Paraganglioma. *Clin Cancer Res.* 2015;21(17):3888-3895.

24. Janssen I, Chen CC, Millo CM, et al. PET/CT comparing (68)Ga-DOTATATE and other radiopharmaceuticals and in comparison with CT/MRI for the localization of sporadic metastatic pheochromocytoma and paraganglioma. *Eur J Nucl Med Mol Imaging.* 2016;43(10):1784-1791.

25. Fonte JS, Robles JF, Chen CC, et al. False-negative (1)(2)(3)I-MIBG SPECT is most commonly found in SDHB-related pheochromocytoma or paraganglioma with high frequency to develop metastatic disease.*Endocr Relat Cancer.* 2012;19(1):83-93.

26. Milardovic R, Corssmit EP, Stokkel M. Value of 123I-MIBG Scintigraphy in Paraganglioma. *Neuroendocrinology.*2010;91(1):94-100.

27. Swensen SJ, Brown ML, Sheps SG, et al. Use of 131I-MIBG scintigraphy in the evaluation of suspected pheochromocytoma. *Mayo Clin Proc.*1985;60(5):299-304.

28. Taieb D, Neumann H, Rubello D, Al-Nahhas A, Guillet B, Hindie E. Modern nuclear imaging for paragangliomas: beyond SPECT. *J Nucl Med.* 2012;53(2):264-274.

29. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of (177)Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med.*2017;376(2):125-135.

30. Ambrosini V, Kunikowska J, Baudin E, et al. Consensus on molecular imaging and theranostics in neuroendocrine neoplasms. *Eur J Cancer.* 2021;146:56-73.

31. Subramaniam RM, Bradshaw ML, Lewis K, Pinho D, Shah C, Walker RC. ACR Practice Parameter for the Performance of Gallium-68 DOTATATE PET/CT for Neuroendocrine Tumors. *Clin Nucl Med.* 2018;43(12):899-908.

32. Swami M. Hypoxia: The HIF2alpha puzzle. *Nat Rev Cancer.*2010;10(9):603.

33. Tarade D, Robinson CM, Lee JE, Ohh M. HIF-2alpha-pVHL complex reveals broad genotype-phenotype correlations in HIF-2alpha-driven disease. *Nat Commun.* 2018;9(1):3359.

34. Hayashi Y, Yokota A, Harada H, Huang G. Hypoxia/pseudohypoxia-mediated activation of hypoxia-inducible factor-1alpha in cancer. *Cancer Sci.* 2019;110(5):1510-1517.

35. Fishbein L, Leshchiner I, Walter V, et al. Comprehensive Molecular Characterization of Pheochromocytoma and Paraganglioma. *Cancer Cell.* 2017;31(2):181-193.

36. Walker RC, Smith GT, Liu E, Moore B, Clanton J, Stabin M. Measured human dosimetry of 68Ga-DOTATATE. *J Nucl Med.* 2013;54(6):855-860.

FIGURE LEGENDS

Figure 1 : **Metastatic paraganglioma.** Fused axial PET and CT images from ^{18}F-FDG PET/CT at diagnosis (A) demonstrate a large heterogeneous retroperitoneal mass (circle) with central photopenia and hypoattenuation suggestive of necrosis (*). Multiple lung nodules were seen by CT (B, white arrow), the largest of which were FDG avid (C, black arrow), consistent with metastatic disease. Coronal MIP image shows no FDG avid disease elsewhere (D). Coronal MIP image from ^{68}Ga-DOTATATE PET/CT (E) shows widespread skeletal metastatic disease (red arrows), none of which was present on the ^{18}F-FDG PET/CT (D). Coronal static planar image from ^{123}I-MIBG scan (F) revealed MIBG-avid metastatic disease in the calvarium, axial, and appendicular skeleton, although the image quality is inferior to the DOTATATE PET/CT and the overall disease burden is underestimated by^{123}I-MIBG. Although some lesions not seen by planar imaging were discernable by SPECT/CT, many lesions seen by^{68}Ga-DOTATATE PET, for example in the liver, ribs, humeral shafts, femoral shafts, and tibiae (arrows) were not evident by^{123}I-MIBG scintigraphy.

Figure 2: Cancer predisposition with SDHC germline mutation and co-existing GIST and paraganglioma.^{18}F-FDG PET MIP images (A) demonstrates diffuse metastatic disease from the patient's known gastrointestinal stromal tumor. Axial contrast-enhanced CT and ^{18}F-FDG PET images (B, C) highlight numerous hepatic masses with varying degrees of^{18}F-FDG avidity (red arrows), complicating the detection of new lesions with a different histology. Axial non-contrast CT and ^{68}Ga-DOTATATE PET images (E, F) reveal an intensely avid mass in the porta hepatis (circle), consistent with paraganglioma. The adjacent lesions that had been FDG-avid on the earlier ^{18}F-FDG PET/CT (white arrow) showed no DOTATATE uptake, indicating co-existing GIST and paraganglioma in the same patient. The paraganglioma was resected surgically; the patient continues on medical therapy for his metastatic GIST.

The low attenuation region near the periphery that has neither FDG nor DOTATATE uptake (*) represents a site of prior RF ablation.

Figure 3: Cancer predisposition associated with polycythemia and multiple functional paragangliomas (Pacak-Zhuang syndrome).^{18}F-FDG PET/CT was obtained for restaging after surveillance wbMRI revealed new sites of disease. Coronal^{18}F-FDG PET MIP image (A) and axial fused PET/CT images (D) from ^{18}F-FDG PET/CT, demonstrate increased^{18}F-FDG uptake in the left suprarenal mass (B, arrow) seen by MRI. Multiple additional foci of FDG uptake, for example in an aortocaval lesion (A, D: circle), were also concerning for paraganglioma, and even in retrospect were difficult to convincingly see by MRI (C).

^{18}F-FDG PET/CT obtained six months later when serum catecholamine and chromogranin A levels were continuing to rise, was markedly limited for evaluation of metastatic lesions, secondary to intensely FDG-

avid hypermetabolic brown adipose tissue uptake, best illustrated on the coronal MIP image (E) from the FDG PET/CT.

Given the patient's hyper-catecholamine secreting state resulting from her underlying *HIF2A* activating mutation, she was started on molecularly targeted therapy. ^{68}Ga-DOTATATE PET/CT, obtained just 17 days after drug initiation (F), showed no background brown fat uptake and demonstrated the suprarenal lesion (arrow) and aorto-caval lesion (circle), with the suprarenal lesion having already decreased slightly in size in response to targeted therapy. She continues on treatment and has been monitored by surveillance MRI and ^{68}Ga-DOTATATE PET/CT.

Figure 4: Proposed algorithm for^{68}Ga-DOTATATE imaging children with known PPGL or PPGL predisposition syndrome.