Original Article

The Utility of ^{68}Ga-DOTATATE PET/CT in Localizing Primary/Metastatic Pheochromocytoma and Paraganglioma: Asian Indian Experience

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Abstract

Purpose: Pheochromocytoma and paraganglioma (PGL), together called PPGL, are rare tumors with a limited number of studies on the diagnostic performance of ^{68}Ga-DOTA (0)-Tyr (3)-octreotate positron emission tomography-computed tomography (^{68}Ga-DOTATATE PET/CT) from the Asian-Indian subcontinent. **Materials and Methods:** In this retrospective study, PPGL suspects ($n = 87$) who had undergone at least contrast-enhanced computed tomography (CECT) and ^{68}Ga-DOTATATE PET/CT, were included. Lesion-wise, patient-wise, and region-wise sensitivities of ^{68}Ga-DOTATATE PET/CT, ^{18}F fluorodeoxyglucose positron emission tomography CT (^{18}F-FDG PET/CT, $n = 53$), ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG, $n = 37$), and CECT were compared, and diagnostic performance of ^{68}Ga-DOTATATE PET/CT in the detection of PPGL was calculated. **Results:** ^{68}Ga-DOTATATE PET/CT had significantly higher lesion-wise sensitivity than ^{131}I-MIBG for both primary (94% vs 75%, $P = 0.004$) and metastatic disease (85% vs 59%, $P = 0.001$) and higher sensitivity than CECT for metastatic lesions (83% vs 43%, $P = 0.0001$). The lesion-wise sensitivity of ^{68}Ga-DOTATATE PET/CT was similar to ^{18}F-FDG PET/CT for both primary tumors (94% vs 85%, $P = 0.08$) and metastatic lesions (82% vs 84%, $P = 0.76$) in the whole cohort but tended to be inferior in the head to head comparison. **Conclusion:** ^{68}Ga-DOTATATE PET/CT had higher sensitivity for detection of PPGL than ^{131}I-MIBG (primary and metastatic) and CECT (metastatic) but similar to ^{18}F-FDG PET/CT (primary and metastatic).

Keywords: 18F-FDG PET/CT, 68Ga-DOTATATE PET/CT, pheochromocytoma and paraganglioma, sensitivity

Introduction

Pheochromocytomas (PCCs) and paragangliomas (PGL), also known as PPGL together, are rare tumors arising from chromaffin cells in the adrenal medulla and extra-adrenal paraganglia. PCC and sympathetic paraganglioma (sPGL) usually secrete catecholamines, whereas the parasympathetic head and neck paraganglioma (HNPGL) are usually nonsecretory.[1] Mutations (germline or somatic) in more than 20 susceptible genes (divided into three clusters) are associated with PPGL. Cluster 1-related PPGLs (pseudohypoxia pathway) are characterized by upregulation of hypoxia-inducible factor type 2 alpha (HIF-2α), whereas those associated with cluster 2-related PPGLs are associated with the upregulation of kinase pathway.

After biochemical confirmation, localization with anatomical imaging [contrast-enhanced computed tomography (CECT)/magnetic resonance imaging] is the next step in the evaluation of suspected PPGL. Functional imaging is required in patients with high suspicion for PPGL but negative or inconclusive anatomical imaging or to rule out multifocal/metastatic disease. Recently published European society guidelines (2019) have expanded the indications of functional/molecular imaging in PPGL, which include larger tumors (>5 cm), extra-adrenal PGL, normetanephrine- and/or methoxytyramine PPGL, or

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mutations in succinate dehydrogenase subunit B (*SDHB)* or alpha-thalassemia/mental retardation syndrome X-linked mutations (*ATRX* gene).[2] Although the Endocrine Society recommends ^{131}I-meta-iodo-benzyl-guanidine (^{131}I-MIBG) and ^{18}F-fluorodeoxyglucose PET/CT (^{18}F-FDG PET/CT), recent studies have demonstrated better sensitivity of somatostatin receptor (SSTR)-based PET/CT.[2-8]

68Ga-DOTA (0)-Tyr (3)-octreotate positron emission tomography-computed tomography (^{68}Ga-DOTATATE PET/CT) has a high affinity for SSTR2, which is overexpressed in most PPGL.[2] A few studies in the adult population have shown the superiority of ^{68}Ga-DOTATATE PET/CT over other functional and anatomical imaging modalities, especially in sporadic and *SDHB*-related metastatic PPGL.[5,6,8-14]

We aim to describe the sensitivity of ^{68}Ga-DOTATATE PET/CT in the evaluation of adults with suspected PPGL. In addition, we have compared the sensitivity of ^{68}Ga-DOTATATE PET/CT with other functional (^{18}F-FDG PET/CT and ^{131}I-MIBG scintigraphy) and anatomical (CECT) imaging modalities.

Materials and Methods

Retrospective evaluation of consecutive patients of PPGL suspects (n = 87) registered at tertiary care hospital, Mumbai, India, between January 2005 and March 2020, who had at least undergone ^{68}Ga-DOTATATE PET/CT and CECT. The study was approved by the institutional independent ethics committee (IEC-II# EC/OA: 174/2018) with a waiver of consent. Besides ^{68}Ga-DOTATATE PET/CT, other functional imaging modalities [^{18}F-FDG-PET/CT (n = 53), ^{131}I-MIBG (n = 37)] were also done due to diagnostic uncertainty, suspected/known metastasis, and planning further management (with predicted change in management with imaging). A total of 31 patients had undergone all four imaging modalities (^{68}Ga-DOTATATE PET/CT, ^{18}F–FDG-PET/CT, ^{131}I-MIBG, and CECT) and were included in the head to head comparison. All the imaging modalities in a given patient were performed within 50 days. The median (range) time gaps of ^{68}Ga-DOTATATE PET/CT from CECT, ^{18}F-FDG PET/CT, and ^{131}I-MIBG were 32 (8–47), 6 (1–9), and 10 (1–28) days, respectively. None of our patients had received octreotide therapy before or during ^{68}Ga-DOTATATE PET/CT scan, and blood glucose was appropriately controlled in diabetic patients undergoing ^{18}F-FDG PET/CT. None of our patients had received any other interfering drugs (tricyclic antidepressants, labetalol, diltiazem) before (14 days) and/or during the ^{131}I-MIBG scintigraphy.

The study population was classified into two cohorts: cohort 1 comprising true positive cases, that is, PPGL and cohort 2 consisting of true negative (TN) cases. The diagnosis of TN lesions was based on histopathology (n = 10), and/or multiple imaging modalities and/or clinical follow-up (n = 07). True negative lesions for comparison of PCC were adrenal tumors, namely, adrenal adenoma (n = 11), adrenocortical carcinoma (n = 1), adrenal lymphoma (n = 1), and metastasis (n = 1) and for PGL, retroperitoneal schwannomas (n = 2) and sarcoma (n = 1). Cohort 2 thus included patients in whom DOTATATE-PET scan was done for non PPGL indication or patients who were referred to rule out PPGL in view of CT characteristics.

The diagnosis of PPGL (primary tumor) was confirmed by histopathology in 61 patients. In patients in whom histopathology was not available (n = 09), the diagnosis of PPGL was based on biochemistry[elevated plasma-free normetanephrine (PFNMN) and plasma-free metanephrine (PFMN)], clinical follow-up, and imaging (anatomical with functional) findings. Demographic details, family history, PPGL characteristics (location, size, secretory status, and metastasis), management details, and genotype (wherever available) were retrieved from the medical records. The secretory phenotype was based on the measurement of PFNMN (cluster 1) and PFMN (cluster 2) as described previously.[15-17] Metastasis was defined as the presence of tumor cells at sites that normally lack chromaffin tissue,[15-17] and was further classified based on the diagnosis of metastasis at or within 3 months (synchronous) or after 3 months (metachronous) of the diagnosis and resection of the primary tumor.[18] CECT was done using the protocol as described in previous study,[18,19] ^{68}Ga-DOTATATE PET/CT, ^{18}F-FDG PET/CT, and ^{131}I-MIBG scintigraphy were done as described in these studies.[20,21]

Previous CECT images were reviewed independently by two experienced radiologists, who were blinded for patient details (biochemistry, genetics, prior imaging, and outcome) except for age and gender. In CECT, the characteristic contrast enhancement pattern was used to detect primary and/or metastasis. Similarly, all functional imaging were reviewed independently by two experienced nuclear medicine physicians, who were blinded (except for the age and gender) for the clinical, biochemical, genetic, and prior imaging findings and outcome. Any discrepant results were resolved by mutual consensus. Patient-wise, lesion-wise, and region-wise analyses were performed. In the patient-wise analysis, each patient with at least one lesion was counted as one regardless of the number of lesions, whereas in lesion-wise analysis, all lesions in a given patient were counted. Per-lesion analysis was done for both primary and metastatic lesions. The sites of metastases were classified based on the region and if the number of lesions in any region exceeded 15, it was truncated to 15 to avoid the bias toward that patient.[13] All the scans were stored on a mass storage device (Seagate, Cupertino, CA, USA) and retrieved whenever required for analysis by connecting the mass storage device to a picture archiving and communication system.

The composite of anatomical and/or all the performed functional imaging tests were considered as the Image comparator (IC). A positive result in any functional and/or anatomical imaging was considered as "true positive" for the evidence of disease as it was neither possible nor ethical to

obtain histopathological proof of every metastasis as described in the previous study.[13]

Statistical analysis

Categorical variables were expressed in actual numbers and percentages. Continuous variables were expressed as mean ± standard deviation or median and range as appropriate. Sensitivity was calculated using the mathematical formula, that is, total lesions detected by an imaging modality/total lesions detected by IC. A comparison of sensitivities among various functional imaging modalities was done through the Chi-square test and Fischer's exact test as appropriate. In head to head comparison, sensitivities among different imaging modalities were compared using the McNemar's test, whereas the SUVmax was compared using the Wilcoxon sign test. *P* value <0.05 was considered as statistically significant. All analyses were done using MedCalc lnk (Version 19.1.6), an online calculator, and SPSS (version 25 IBM).

Results

A total of 87 patients with PPGL suspects were included in the study. Cohort 1:70 patients (males: 39) with a mean age at diagnosis of 42.7 ± 12.4 years were included. There were a total of 77 primary tumors (65: isolated primary; 12 primary tumor from 11 patients with synchronous metastasis) including 24 (31%) sPGL, 44 (57%) PCC, and 09 (12%) HNPGL. Twenty-four had metastatic disease, and of these, metachronous metastasis was seen in 13 (54%) after a median follow-up of 12 (range: 6–36) months. Eight (11%) patients had bilateral PCC, two each had multifocal disease (PCC+PGL), and multiple PGL, whereas five (16%) had a familial syndromic presentation. Genetics were available for 14 (20%) patients; six had mutations in *RET* (MEN2A: 4, MEN2B: 2), whereas two each had mutations in *VHL*, *SDHB*, and *SDHD*; no pathogenic variants were detected in two patients.

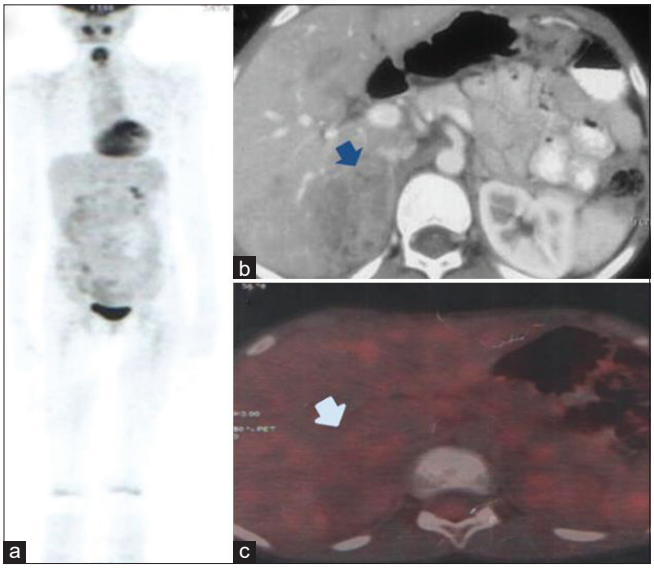

Figure 1: Maximum intensity projection image of ^{18}F-FDG PET (a), cross-sectional early arterial phase image of CECT (b) and fused image (c) of ^{18}F-FDG PET/CT of patient 31 with isolated right-sided pheochromocytoma (PCC). ^{18}F-FDG PET/CT was done to rule out multifocal/ metastatic disease in this 19 years old; however, primary lesion itself was missed by ^{18}F-FDG PET/CT

Cohort 2 included 17 patients (males: 08) having 23 lesions which were further classified as PCC-mimics (*n* = 14) and PGL-mimics (*n* = 3). PCC-mimics were adrenal adenomas (*n* = 12 in 11 patients), adrenocortical carcinoma (*n* = 2 in one patient), adrenal lymphoma (*n* = 2 in one patient), and adrenal metastasis (*n* = 1), whereas the PGL-mimics were retroperitoneal sarcoma (four lesions in a patient) and schwannoma (*n* = 2). The mean age at diagnosis was 37.1 ± 12.0 years and the median tumor size was 2.83 (1.5–4.8) cm. All of the lesions were diagnosed based on histopathology except 11 adrenal adenomas which were diagnosed based on noncontrast CT attenuation <10 HU and follow-up. ^{68}Ga-DOTATATE PET/CT was done during the evaluation of multiple endocrine neoplasia 1 (MEN1) syndrome (*n* = 5, 29%), Cushing syndrome (*n* = 4, 24%), and PCC-mimic (*n* = 2, 12%) in cases of adenoma.

Overall, in the lesion-wise analysis [Table 1], sensitivities of ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT were similar (85% vs. 84%, *P* = 0.9) and was significantly higher than that of ^{131}I-MIBG (59%, *n* < 0.0001) and CECT (61%, *n* < 0.0001).

In the subgroup analysis for primary and metastatic lesions, lesion-wise sensitivities of ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT were similar for both primary (94% vs 85%, *P* = 0.08) and metastatic lesions (82% vs 84%, *P* = 0.56) [Figure 1]. ^{68}Ga-DOTATATE PET/CT had significantly higher sensitivity than ^{131}I-MIBG in the detection of both primary (94% vs 75%, *P* = 0.005) and metastatic disease (82% vs 52%, *P* < 0.0001) with the exception in one patient where lesion was missed by ^{68}Ga-DOTATATE PET/CT but seen in ^{131}I-MIBG [Figure 2]. ^{68}Ga-DOTATATE PET/CT and CECT had the same (94%) sensitivities for the detection of primary PPGL, but the former had higher sensitivity (82% vs 48%, *P* < 0.0001) for metastatic lesions than the latter.

SUVmax of ^{68}Ga-DOTATATE PET/CT was significantly higher than that of ^{18}F-FDG PET/CT (28.5 ± 20.6 vs 10.0 ± 10.1, *P* = 0.001) in primary PPGL but were similar for metastatic lesions (17.3 ± 13.71vs 14.7 ± 8.9, *P* = 0.53).

In the cluster-based subgroup analysis, lesion-wise sensitivities of ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT were similar for both primary and metastatic lesions in cluster 1-related (NMN-secreting) as well as cluster 2-related PPGLs [Table 2]. ^{68}Ga-DOTATATE PET/CT had higher sensitivity than ^{131}I-MIBG for cluster 1-related primary tumors and higher sensitivity than both ^{131}I-MIBG and CECT for metastatic lesions but had a comparable sensitivity to other imaging modalities for cluster 2-related primary and metastatic lesions.

Table 1: Lesion -wise sensitivities of ^{18}F-FDG PET/CT, ^{68}Ga-DOTATATE PET/CT, ^{131}I-MIBG, and CECT to detect total, primarya, and metastatic pheochromocytoma and paraganglioma (PPGLs)

Imaging modalities	Primary tumors (P[a])		Metastatic lesions (M[b])		Total	
	Detection rate (*n*/*N*)[c]	95% CI	Detection rate (*n*/*N*)[c]	95% CI	Detection rate (*n*/*N*)[c]	95% CI
^{68}Ga-DOTATATE PET/CT P (57) + M (24)	94% (73/77)	87.2-98.5%	82% (156/192)	75.0-86.5%	85% (229/269)	80.31-89.16%
^{18}F-FDG PET/CT P (41) + M (21)	85% (50/59)	73.0-92.7%	84% (122/145)	77.1-89.6%	84% (172/204)	78.58-89.02%
^{131}I-MIBG P (25) +M (21)	75% (24/32)	56.6-88.5%	52% (96/186)	48.3-63.7%	59% (120/203)	52.0-65.94%
CECT P (57) + M (24)	94% (73/77)	87.2-98.5%	48% (92/192)	40.6-55.2%	61% (165/269)	55.2-67.1%
P	1 vs 2: 0.08, 1 vs 3: 0.005, 4 vs 3: 0.005,		1 vs 2: 0.56, 1 vs 3: < 0.0001, 1 vs 4: < 0.0001, 2 vs 3: < 0.0001, 2 vs 4: < 0001		1 vs 2: 1, 1 vs 3: < 0.0001, 1 vs 4: < 0.0001, 2 vs 3: < 0.0001, 2 vs 4: < 0.0001	

[a]Include isolated primary tumors and primary tumors in synchronous metastatic PPGLs, [b]Includes metastatic lesions [synchronous (SM)/metachronous metastasis (MM)], *c*Detection rate (*n*/*N*): Total lesions detected by modality (*n*)/total lesions detected by composite image comparator (*N*)

Table 2: Lesion-wise sensitivities of ^{18}F-FDG PET/CT, ^{68}Ga-DOTATATE PET/CT, ^{131}I-MIBG, and CECT to detect cluster 1- and cluster 2-related pheochromocytoma and paraganglioma (PPGLs)

	Cluster 1		Cluster 2	
	Primary[a]	Metastasis[b]	Primary[a]	Metastasis[b]
^{68}Ga-DOTATATE PET/CT (1)				
Detection rate[c] (%)	96 (43/45)	82 (147/180)	92 (22/24)	75 (9/12)
95% CI	84.8-99.4	75.23-87.0	73.0-98.9	42.8-94.5
^{18}F-FDG PET/CT (2)				
Detection rate[c] (%)	90 (35/39)	83 (110/133)	67 (10/15)	100 (12/12)
95% CI	75.7-97.1	75.1-88.7	38.38-88.1	73.5-100
^{131}I-MIBG (3)				
Detection ratec (%)[c]	79 (19/24)	52 (91/174)	67 (4/6)	42 (5/12)
95% CI	57.8-92.8	44.6-59.9	22.2-95.6	15.1-73.3
CECT (4)				
Detection rate[c] (%)	91 (41/45)	47 (85/180)	96 (23/24)	75 (9/12)
95% CI	78.7-97.5	39.75-54.7	78.8-99.8	42.8-94.5
P	1 vs 2: 0.32, 1 vs 3: 0.045, 1 vs 4: 0.67	1 vs 2: 0.81, 1 vs 3: < 0.0001, 1 vs 4: < 0.0001	1 vs 2: 0.08, 1 vs 3: 0.10, 1 vs 4: 1	1 vs 2: 0.21, 1 vs 3: 0.21, 2 vs 3: 0.005

[a]Include isolated primary tumors and primary tumors in synchronous metastatic PPGLs, [b]Includes metastatic lesions (synchronous/metachronous metastasis), [c]Detection rate (*n*/*N*): Total lesions detected by modality/total lesions detected by composite image comparator

In the tumor location-wise subgroup analysis [Table 3], lesion-wise sensitivities of ^{68}Ga-DOTATATE PET/CT (92% and 95%), ^{18}F-FDG PET/CT (77% and 100%), ^{131}I-MIBG (75% and 79%), and CECT (100% and 100%), for PCC and PGL, respectively, were similar. In patients with multiple/multifocal disease, ^{68}Ga-DOTATATE PET/CT (17/17, 100%) had numerically higher sensitivity, though statistically insignificant, than ^{18}F-FDG PET/CT (12/15, 80%), CECT (13/17, 76%), and ^{131}I-MIBG (4/6, 67%).

In the region-wise analysis for metastatic lesions, ^{68}Ga-DOTATATE PET/CT had significantly lower sensitivity than ^{18F}-FDG PET/CT (73% vs 100%, $P = 0.03$) for liver lesions (6/15, 40%, $P = 0.0004$) as shown in Figure 3. There were no significant differences among the sensitivities of other imaging modalities for any other region as described in Table 4.

In the patient-wise analysis, for both primary and metastatic lesions, ^{68}Ga-DOTATATE PET/CT (93%, 88%), ^{18}F-FDG PET/CT (88%, 95%), ^{131}I-MIBG (80%, 81%), and CECT (100%, 100%) had similar sensitivities.

Thirty-one out of 70 patients had undergone all the four imaging modalities (^{68}Ga-DOTATATE PET/CT, ^{18}F-FDG PET/CT, ^{131}I-MIBG, and CECT) available for head to head comparison [Table 5]. ^{68}Ga-DOTATATE PET/CT (77%) and ^{18}F-FDG PET/CT (83%) had similar overall lesion-wise sensitivities but both had higher overall lesion-wise sensitivities than ^{131}I-MIBG (61%) and CECT (58%)(2). There were no differences among the sensitivities of all the four imaging modalities for primary tumors. For metastatic lesions, ^{68}Ga-DOTATATE PET/CT had similar sensitivity as ^{18}F-FDG PET/CT (74% vs 84%, $P = 0.08$) but higher than

Table 3: Lesion -wise sensitivities of ^{18}F-FDG PET/CT, ^{68}Ga-DOTATATE PET/CT, ^{131}I-MIBG, and CECT to detect primary [a]pheochromocytoma and paraganglioma (PPGLs) based on tumor number and location

	Pheochromocytoma	Paraganglioma	Multifocal/multiple PPGL
^{68}Ga-DOTATATE PET/CT (1)			
Detection rate (%)[b]	92 (36/39)	95 (20/21)	100 (17/17)
95% CI	79.1-98.3	76.1-99.8	80.4-100
^{18}F-FDG-PET/CT (2)			
Detection rate (%)[b]	77 (20/26)	100 (18/18)	80 (12/15)
95% CI	56.3-91.03	81.4-100	51.9-95.6
^{131}I-MIBG (3)			
Detection rate (%)[b]	75 (9/12)	79 (11/14)	67 (4/6)
95% CI	42.8-94.5	49.2-95.3	22.2-95.6
CECT (4)			
Detection rate (%)[b]	100 (39/39)	100 (21/21)	76 (13/17)
95% CI	90.9-100	83.8-100	50.1-93.1
P	1 vs 2: 0.13, 1 vs 3: 0.13, 1 vs 4: 0.24	1 vs 2: 0.1, 1 vs 3: 0.14	1 vs 2: 0.09, 1 vs 3: 0.059, 1 vs 4: 0.1

PPGL: pheochromocytoma and paraganglioma, [a]Include isolated primary tumors and primary tumors in synchronous metastatic PPGLs, [b]detection rate (*n/N*): Total lesions detected by modality/total lesions detected by a composite image comparator

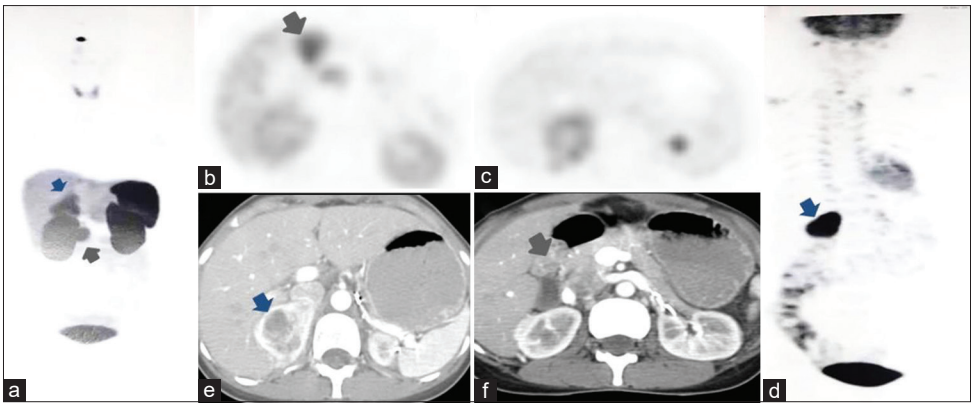

Figure 2: ^{131}I-MIBG scintigraphy (a), fused image of ^{68}Ga-DOTATATE PET/CT (b) and fused image of ^{18}F-FDG PET/CT, (c) image of nor-metanephrine secreting isolated left-sided pheochromocytoma (case no. 45), which was nonavid in both ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT, similarly maximum intensity projection image (e) and fused ^{68}Ga-DOTATATE PET/CT (d) and cross sectional image (f) (case no. 63) of right- sided pheochromocytoma which was nonavid on ^{68}Ga-DOTATATE PET/CT

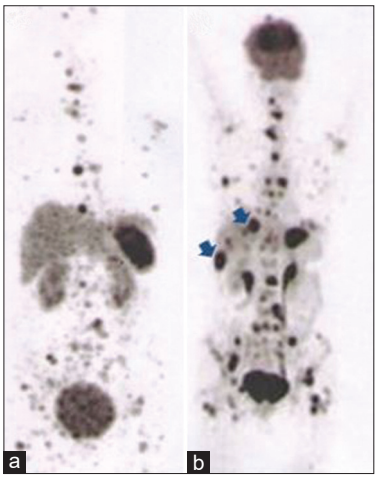

Figure 3: Maximum intensity projection image of 68Ga-DOTATATE PET/CT (a) and 18F-FDG PET/CT (b) of a patient with synchronous metastasis liver lesions (blue arrow) were missed by 68Ga-DOTATATE PET/CT

^{131}I-MIBG (80/141, 57%, $P = 0.002$) and CECT (78/141, 55%, $P = 0.001$).

^{68}Ga-DOTATATE PET/CT missed (false negative) three PCC (36/39) and one PGL (20/21) in cohort 1 and detected three false-positive (FP) lesions in PCC-mimics but none in PGL-mimics. So, overall ^{68}Ga-DOTATATE PET/CT had lesion-wise sensitivity of 95% for PPGL. On subgroup analysis, ^{68}Ga-DOTATATE PET/CT had lesion-wise sensitivities, of 93% for PCC, and for PGL, respectively, Among the FP lesions, two had adrenal adenoma and one had adrenal metastatic lesion from renal cell carcinoma (RCC) . The mean SUVmax of adrenal adenomas yielding FP uptake was 20.5 ± 10.5.

Discussion

The study including a large number of patients from the Indian subcontinent demonstrates high sensitivity of ^{68}Ga-DOTATATE

Table 4: Lesion-wise sensitivities of ^{18}F-FDG-PET/CT, ^{68}Ga-DOTATATE PET/CT, ^{131}I-MIBG, and CECT to detect metastatica pheochromocytom[a] and paraganglioma lesions in different regions

	^{68}Ga-DOTATATE PET/CT (1)		^{18}F-FDG-PET/CT (2)		^{131}I-MIBG (3)		CECT (4)	
	Detection rate (%)[b]	95% CI	Detection rate (%)[b]	95% CI	Detection rate (%)[b]	95% CI	Detection rate (%)[b]	95% CI
All compartments	82 (156/192)	75.0-86.5	84 (122/145)	77.1-89.6	52 (96/186)	44.1-58.9	48 (92/192)	40.6-55.4
Neck	89 (8/9)	51.7-99.7	88 (7/8)	47.3-99.6	38 (3/8)	8.5-75.51	33 (3/9)	7.4-70
Mediastinum	67 (2/3)	9.4-99.1	100 (3/3)	29-100	33 (1/3)	0.84-90.5	33 (1/3)	0.84-90.5
Lungs	77 (23/30)	57.7-90.0	87 (13/15)	59.5-98.3	10 (3/30)	2.1-26.53	27 (8/30)	12.2-45.8
Liver	73 (11/15)	44.9-92.2	100 (15/15)	78-100	20 (3/15)	4.3-48.09	53 (8/15)	26.5-78.7
Abdomen	90 (27/30)	73.4-97.8	100 (14/14)	77-100	35 (9/26)	17.2-55.6	23 (7/30)	9.9-42.2
Bone	86 (90/105)	77.5-91.7	78 (70/90)	67.7-85.8	74 (77/104)	64.5-82.1	62 (65/105)	51.9-71.2

[a]Includes metastatic lesions (synchronous/metachronous metastasis). [b]Detection rate (*n/N*): Total lesions detected by modality/total lesions detected by composite image comparator, Liver - 1 vs 2: 0.033

Table 5: Lesion-wise sensitivity analysis in head to head comparison (*n*=31) of ^{18}F-FDG-PET/CT, ^{68}Ga-DOTATATE PET/CT, ^{131}I-MIBG, and CECT to detect pheochromocytoma and paraganglioma

	Primary tumor (*n*=20, P: 12, SM: 08)	Metastasesa (*n*=19)	Total
^{68}Ga-DOTATATE PET/CT (1)			
Detection rate (%)[b]	89 (24/27)	78 (110/141)	77 (129/168)
95% CI	70.8-97.6	70.2-84.5	69.6-82.9
^{18}F-FDG PET/CT (2)			
Detection rate (%)[b]	78 (21/27)	84 (118/141)	83 (139/168)
95% CI	57.7-91.3	76.5-89.3	76.1-88.1
^{131}I-MIBG (3)			
Detection rate (%)[b]	81 (22/27)	57 (80/141)	61 (102/168)
95% CI	61.9-93.7	48.1-65.0	52.9-68.1
CECT (4)			
Detection rate (%)[b]	85 (23/27)	55 (78/141)	60 (101/168)
95% CI	66.2-95.8	46.7-63.6	52.2-67.5
P	1 vs 2: 0.3	1 vs 2: 0.078	1 vs 2: 0.178
	1 vs 3: 0.7	1 vs 3: 0.002	1 vs 3: 0.002
	1 vs 4: 1	1 vs 4: 0.001	1 vs 4: 0.001

[a]^{68}Ga-DOTATATE PET/CT detected significantly lesser number of metastatic lesion than the ^{18}F-FDG PET/CT in liver (73% vs 100% *P*=0.033). [b]Detection rate: Total lesions detected by modality/total lesions detected by composite image comparator (IC)

PET/CT in the diagnosis of PPGL. The study also clearly demonstrates the superiority of ^{68}Ga-DOTATATE PET/CT over ^{131}I-MIBG for the detection of primary lesions and both ^{131}I-MIBG and CECT for the detection of metastatic lesions but similar sensitivity as ^{18}F-FDG PET/CT for the detection of both primary and metastatic PPGL. However, it had a lower sensitivity to detect metastatic lesions in the liver and lung with a tendency for lower sensitivity for overall metastatic lesions in the head to head comparison.

Overall lesion-wise sensitivity of ^{68}Ga-DOTATATE PET/CT was 85% in our study, similar to that (85%) reported in a recently published prospective study from India for ^{68}Ga-DOTA PET/CT.[22] The pooled overall lesion-wise sensitivities of ^{68}Ga-DOTATATE PET/CT in a recent meta-analysis was 93%, which was significantly higher than ^{18}F–FDG (74%).[14] Another recent meta-analysis by Kan *et al.*[14] (96% vs 83%, $P < 0.0001$) reported significantly higher lesion-wise sensitivity of ^{68}Ga-DOTA peptide PET/CT than ^{18}F-FDG PET/CT in detecting metastatic PPGL.[6] In contrast, the lesion-wise sensitivities of ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT for overall lesions and metastatic lesions were similar in our cohort, probably due to the lower sensitivity of ^{68}Ga-DOTATATE PET/CT for liver lesions in our study. This may be due to higher background activity in the liver. However, such a finding was not observed in the previous studies.[5,8] This observation is in contrast to most of the previous studies which may be due to aggressive PPGL with diffuse metastasis with lower SSTR but higher GLUT2 expression Despite the tendency for the lower sensitivity of ^{68}Ga-DOTATATE PET/CT than ^{18}F-FDG PET/CT for metastatic PPGL in the head to head comparison, the former offers an advantage of exploring PRRT as a therapeutic option for metastatic PPGL making it a more suitable option for imaging of suspected or proven metastatic PPGL. The lower sensitivity of $^{123/131}$I-MIBG, another scintigraphy with therapeutic potential, than ^{68}Ga-DOTATATE PET/CT to detect metastatic lesions has been consistently reported in several studies including our study.[23,24]

The sensitivity of ^{68}Ga-DOTATATE PET/CT for primary PPGL tended to be higher than that of ^{18}F-FDG PET/CT. Notably, the SUVmax of ^{68}Ga-DOTATATE PET/CT was higher in primary tumors than that of ^{18}F–FDG PET/CT (28.5 ± 20.6 vs 10.0 ± 10.1, P = 0.001) in our study. A similar observation has also been reported in a previous study.[5] Higher SUVmax makes lesions more conspicuous compared to the background in ^{68}Ga-DOTATATE PET/CT and may account for the trend toward higher sensitivity of ^{68}Ga-DOTATATE PET/CT for primary PPGL than ^{18}F–FDG PET/CT. Higher mean SUV max in the primary tumors could be due to a higher expression of SSTR. However, sensitivities to detect metastatic lesions and SUVmax in metastatic lesions were similar in ^{68}Ga-DOTATATE PET/CT and ^{18}F–FDG PET/CT. This can be due to decreased SSTR expression and increased GLUT2 receptor expression because of metabolic reprogramming in malignant PPGL.

The sensitivities to detect primary PCC (92%) and PGL (95%) in our study were comparable, which is similar to a previous large report in adult PPGL (88% for PCC, and 100% for PGL).[9] Similarly, Chang *et al*.[5] (16/18 vs 13/18, P = 0.4) and Jing *et al*.[12] (9/9 vs 8/9, P = 0.31) did not find significant differences in the sensitivities of ^{68}Ga-DOTATATE PET/CT and ^{18}F–FDG PET/CT for the detection of primary PCC and sPGL. This suggests a similar expression of SSTR in the benign forms of PCC and PGL. In cluster 1 (pseudo-hypoxia pathway), both ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT were comparable in the detection of both primary tumor and metastases, whereas in cluster 2 (kinase pathway), ^{68}Ga-DOTATATE PET/CT tended to be superior to ^{18}F-FDG PET/CT in the detection of primary tumors but equivalent in the detection of metastases. This represents poor sensitivity of ^{18}F-FDG PET/CT in cluster 2-related benign PPGL due to lack of pseudohypoxia pathway involvement, unlike cluster 1-related PPGL.[21] However, as CECT also had 100% sensitivity for cluster 2-related primary PPGL most of which are adrenal, this advantage of ^{68}Ga-DOTATATE PET/CT may not have much clinical relevance. Interestingly, ^{68}Ga-DOTATATE PET/CT (100%) tended to have better sensitivity than ^{18}F-FDG PET/CT (80%), in the detection of multifocal/multiple diseases. This was most probably due to the better sensitivity of ^{68}Ga-DOTATATE PET/CT for cluster 2-related bilateral PCC and HNPGL. A higher sensitivity of ^{68}Ga-DOTATATE PET/CT (99%) than ^{18}F-FDG PET/CT (62%) for HNPGL and cluster 2-related PPGL has been demonstrated in previous studies.[13] Hence, ^{68}Ga-DOTATATE PET/CT may be preferred in the evaluation of patients with suspected multifocal disease.

To the best of our knowledge, the present study is the largest head-to-head comparison of the four imaging modalities (^{68}Ga-DOTATATE PET/CT, ^{18}F-FDG PET/CT, ^{131}I-MIBG, and CECT) in the detection of primary and/or metastatic PPGL, which is the major strength of the study. Another major strength of our study is the evaluation of ^{68}Ga-DOTATATE PET/CT in suspected PPGL patients, which makes our study one of the few such studies. In our cohort, FP results were seen with adrenal adenomas (n = 2) and metastasis from RCC (n = 1). A study by Gild *et al*.,[9] in which PPGL, PCC suspects (TN, n = 4), and PGL suspects (TN, n = 1) were included reported 100% specificity of ^{68}Ga-DOTATATE PET/CT for PCC. Another study by Singh *et al*. including 106 patients with PPGL suspects (histopathology proven in 35) found specificity and accuracy of 92 and 86% respectively for ^{68}Ga-DOTA peptide PET/CT.[22] Gild *et al*.[9] had excluded adrenal adenoma for calculation of specificity, which probably provided 100% specificity. The SUV max of ^{68}Ga-DOTATATE PET/CT in adrenal adenomas with FP uptake was similar to that of PCC (20.3 ± 3 vs 28.5 ± 20.6 P = 0.49) in our cohort. Moreover, adrenal adenomas, especially those with poor washout, may closely mimic cluster 2-related PCC on CECT.[19] These imaging pitfalls may rarely pose an important diagnostic challenge.

The study also had a few limitations. First, the genetic testing results were not available in the majority of patients which limited the genotype-wise comparisons. Second, ^{131}I-MIBG scintigraphy was performed rather than ^{123}I-MIBG SPECT/CT because of non-vailability, which might have slightly underestimated the sensitivity of MIBG scintigraphy. Third, the retrospective nature of the study with its inherent limitations. Fourth, the number of patients in cohort 2 especially of PGL-mimics was small; hence, specificity could not be accurately calculated. However, considering the rare occurrence of PPGL and limited available data in this regard, observations from this study are a significant addition to the literature.

Conclusion

^{68}Ga-DOTATATE PET/CT had higher sensitivity for detection of PPGL than ^{131}I-MIBG (primary and metastatic) and CECT (metastatic), but similar to ^{18}F-FDG PET/CT (primary and metastatic). ^{68}Ga-DOTATATE PET/CT tended to have a higher sensitivity to detect cluster 2-related and multiple/multifocal primary PPGL.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Patient characteristics of cohort 1

S. NO	Sex	Age at diagnosis (yrs.)	Max. diameter on CT (cm Primary tumor	Hpersecrtion	Treatment for primary/ metastasis	Lesions	Lesions detected by IC	Total lesions CECT	Total lesions ^{18}F-FDG	Total lesions ^{68}Ga-DOTATATE	Total lesions ^{131}I-MIBG
Case 1	F	39	Mediastinal PGL (5.6)	NMN	^{177}Lu-PRRT	SM	5	1	5	4	1
					-	SMP	1	1	1	1	1
Case 2	M	48	sPGL: OOZ (3.2)	NMN	Sx	SM	17	17	17	15	15
					^{225}AC PRRT	SMP	1	1	1	1	0
case3	F	62	sPGL (6.7)	NMN	Sx	SM	1	1	1	0	0
					^{131}I-MIBG therapy	SMP	1	1	1	1	1
Case 4	F	28	2HNPGL(8.2)	NMN	Sx	SM	15	2	ND	15	0
					^{177}Lu-PRRT planned	SMP	2	2	ND	2	ND
Case 5	M	42	Testicular PGL (3.2)	NMN	Sx	SM	1	1	1	1	ND
					^{177}Lu-PRRT	SMP	1	1	1	1	ND
Case 6	M	43	Rt.PCC (8.5)	NMN	^{131}I-MIBG therapy	SM	5	1	5	4	2
					Sx	SMP	1	1	1	1	1
Case 7	M	41	Hilar PGL (10.5)	NMN	^{177}Lu-PRRT	SM	2	2	ND	2	ND
					Sx	SMP	1	1	ND	1	ND
Case 8	M	49	Bladder PGL (3.2)	NMN	^{177}Lu-PRRT	SM	8	4	8	7	1
					Sx	SMP	1	1	1	1	1
Case 9	M	41	OOZ PGL (8.2)	NMN	^{131}I-MIBG therapy	SM	3	2	2	3	2
					Sx	SMP	1	1	1	1	1
Case 10	M	53	OOZ PGL (3.7)	NMN	^{131}I-MIBG therapy	SM	10	1	9	5	7
					-	SMP	1	1	1	1	1
Case 11	M	53	Left PCC (5.7)	NMN	^{131}I-MIBG therapy	SM	12	6	12	8	7
					-	SMP	1	1	1	1	1
Case 12	M	52	Rt PCC (5.2)	NMN	^{131}I-MIBG therapy	MM	3	1	2	2	2
Case 13	M	40	Rt PCC (7.2)	NMN	Loss to follow up	MM	2	1	2	0	2
Case 14	F	35	OOZ PGL (9.7)	NMN	^{177}Lu-PRRT	MM	14	4	14	5	0
Case 15	M	18	Left PCC (3.7)	MN	^{131}I-MIBG therapy	MM	6	4	6	6	3
Case 16	M	43	Left PCC (10.8)	MN	^{131}I-MIBG therapy	MM	3	3	3	1	1
Case 17	F	38	OOZ, sPGL (4.2)	NMN	^{177}Lu-PRRT	MM	3	1	3	3	ND
Case 18	F	40	Rt PCC (5.3)	NMN	Follow up	MM	3	2	3	0	0
Case 19	F	54	Hilar sPGL (12.5)	MN	^{177}Lu-PRRT	MM	3	2	3	2	1
Case 20	M	51	Left PCC (11.4)	NMN	^{131}I-MIBG therapy	MM	4	1	3	2	3
Case 21	M	14	Left PCC (4.5)	NMN	^{131}I-MIBG therapy	MM	16	16	16	16	16
Case 22	F	40	Rt.PCC (4)	NMN	Dead	MM	10	1	7	10	1
Case 23	F	60	OOZ, Spgl (9.8)	NMN	^{131}I-MIBG therapy	MM	16	10	0	15	16
Case 24	F	31	Hilar sPGL (13.6)	NMN	^{131}I-MIBG therapy	MM	30	10	ND	30	16
Case 25	M	61	Rt PCC (15)	MN	Sx	NO	1	1	ND	1	1
Case 26	F	54	B/L PCC, 4cm (R), 3cm (L)	MN	Sx	NO	2	1	2	2	1
Case 27	F	32	Hilar, SPGL	NMN	Sx	NO	1	1	1	1	1
Case	M	45	Rt, PCC (6.3)	NMN	Sx	NO	1	1	1	1	ND
Case 29	M	21	Rt PCC (4.3)	NMN	Sx	NO	1	1	1	1	ND
Case 30	0	45	B/L PCC	MN	Sx	NO	2	2	ND	2	ND
Case 31	F	75	sPGL (4.1)+HNPGL (4.6)	NS	Sx	NO	2	2	2	2	ND
Case 32	M	56	Left PCC (5.2)	MN	Sx	NO	1	1	ND	1	ND
Case 33	M	40	Rt PCC (4.6)	MN	Sx	NO	1	1	1	1	ND
Case 34	M	51	Left PCC (3.3)	MN	Sx	NO	1	1	ND	1	ND
Case 35	M	45	Hila sPGL	NS	Sx	NO	1	1	ND	1	1
Case 36	F	30	B/L PCC Rt (5.2), left 1.2)	NMN	Sx	NO	2	2	2	2	ND
Case 37	M	41	Rt PCC (4.7)	NMN	Sx	NO	1	1	ND	1	ND
Case	F	48	Left PCC (3.7)	NS	Sx	NO	1	1	ND	1	ND
Case 39	M	26	Hilar sPGL (4.8)	NMN	Sx	NO	1	1	1	1	ND
Case 40	F	45	Rt PCC (4.7)	MN	Sx	NO	1	1	ND	1	ND
Case 41	F	65	RtPCC (5.6)	MN	Sx	NO	1	1	ND	1	ND

Contd...

Supplementary Table 1: Contd...

S. NO	Sex	Age at diagnosis (yrs.)	Max. diameter on CT (cm Primary tumor	Hpersecrtion	Treatment for primary/ metastasis	Lesions	Lesions detected by IC	Total lesions CECT	Total lesions ^{18}F-FDG	Total lesions ^{68}Ga-DOTATATE	Total lesions ^{131}I-MIBG
Case 42	M	38	5.3 (RT),6 (LEFT)	NMN	Sx	NO	2	2	2	2	2
Case 43	M	28	B/L PCC, (Rt) 9.9, Lt (1.2)	MN	Sx	NO	2	2	0	2	ND
Case 44	F	36	Left PCC (3.3)	MN	Sx	NO	1	1	ND	1	ND
Case 45	F	62	Left PCC (4)	NMN	Sx	NO	1	1	0	0	1
Case 46	F	30	OOZ sPGL (6)	NMN	Sx	NO	1	1	1	1	1
Case 47	F	34	OOZ sPGL (4)	NMN	Sx	NO	1	1	1	1	1
Case 48	F	55	Left PCC (11)	NS	Dead	NO	1	1	1	1	ND
Case 49	M	47	OOZ sPGL (2.1)	NMN	Sx	NO	1	1	ND	1	0
Case 50	M	26	Left PCC (1.3)	NS	Sx	NO	1	1	ND	1	0
Case 51	F	53	OOZ sPGL (12.6)	NMN	Sx	NO	1	1	1	0	1
Case 52	M	40	B/L PCC	MN	Sx	NO	2	2	2	2	ND
Case 53	F	24	Left PCC (8.1)	NMN	Sx	NO	1	1	ND	1	ND
Case 54	M	32	B/L PCC+Spgl	NMN	^{177}Lu-PRRT	NO	6	3	3	6	4
Case 55	M	37	Mediastinal sPGL (4.9)	NMN	^{177}Lu-PRRT	NO	1	1	1	1	0
Case 56	M	43	Rt PCC (9.5)	MN	Sx	NO	1	1	1	1	ND
Case 57	M	32	Hilar sPGL (6.8)	NS	Sx	NO	1	1	1	1	ND
Case 58	M	28	RT (4CM) LEFT (6)	MN	Sx	NO	2	2	2	2	ND
Case 59	M	35	Rt PCC (2.7)	MN	Sx	NO	1	1	1	1	ND
Case 60	M	64	Left PCC (4.4)	MN	Sx	NO	1	1	1	1	ND
Case 61	F	35	OOZ sPGL (6)	NMN	Sx	NO	1	1	1	1	ND
Case 62	F	54	Hilar sPGL (2.2)	NMN	Sx	NO	1	1	1	1	ND
Case 63	F	37	Rt PCC (7)	MN	Sx	NO	1	1	ND	0	0
Case 64	F	57	Rt PCC (4.2)	MN	Sx	NO	1	1	0	0	1
Case 65	F	30	Rt PCC (8.3)	MN	Sx	NO	1	1	0	1	ND
Case 66	F	55	Lt PCC (11)	MN	Sx	NO	1	1	0	1	1
Case 67	F	38	Hilar sPGL (6)	NS	Sx	NO	1	1	1	1	ND
Case 68	M	43	B/L PCC+Spgl+HNPGL	NMN	^{177}Lu-PRRT therapy	NO	7	6	7	7	ND
Case 69	M	68	Lt PCC (3.9)	NMN	Sx	NO	1	1	1	1	ND
Case 70	M	36	OOZ sPGL (9.3)	NMN	^{131}I-MIBG therapy	NO	1	1	1	1	1

PCC: Pheochromocytoma, sPGL: sympathetic paraganglioma, HNPGL: Head and neck paraganglioma, NMN: normetanephrine, MN: metanephrine, NS: nonsecretory, PNET: pancreatic neuroendocrine tumor, NA: not available, ND: not done, CLVHL: clinical VHL, ^{177}Lu-PRRT: Lutetium-177-based peptide receptor based radionuclide therapy, ^{131}I-MIBG: metaiodobenzylguanidine, Rt: right, Lt: left, OOZ: organ of Zukerkandl, P; paravertebral, UB: urinary bladder, Sx: Surgery, Mets: Metastasis, and IC: Image comparator

Supplementary Table 2: Baseline characteristics of cohort 2

Case no	Age (Yrs)	Sex	Primary lesion	Laterality	No of lesion (on CT)	Max. size of lesion (cm)	Plain HU	No of lesions in ^{68}Ga-DOTATATE PET/CT	SUV MAX (mean)	Gene	Therapy
Case 1	22	M	Adenoma	Unilateral	1	2.1	-2.1	0	0	MEN1	Observation
Case 2	21	F	Adenoma	Unilateral	1	3.2	11	0	0	CS	Sx
Case 3	43	F	Adenoma	Unilateral	1	3.16	44	1	31	CD	Observation
Case 4	54	F	Adenoma	Unilateral	1	1.1	20	1	10	CD	Observation
Case 5	54	M	Metastasis	Unilateral	1	1.7	18	1	14	ND	Sx
Case 6	41	M	Adenoma	Unilateral	1	2.5	16	0	0	ND	Observation
Case 7	61	F	lymphoma	Bilateral	2	8 (rt), 8.4 (left)	ND	0	0	ND	Chemotherapy
Case 8	27	M	Adenoma	Unilateral	1	1.3	-18	0	0	MEN1	Observation
Case 9	39	F	Adenoma	Bilateral	2	3.3 (rt),1.8 (Lt)	-11	0	0	MEN1	Observation
Case 10	27	M	Adenoma	Unilateral	1	1.4	-5	0	0	MEN1	Observation
Case 11	25	F	Adenoma	Unilateral	1	1.2	43	0	0	MEN1	Observation
Case 12	35	F	Adenoma	Unilateral	1	2	12	0	0	CD	Observation
Case 13	46	M	ACC	Bilateral	2	13 (Rt) 8.8 (Lt)	35, 32	0	0	ND	SX
Case 14	28	F	Schwanoma	Unilateral	1	3.7	40	0	0	ND	SX
Case 15	38	M	Adenoma	Unilateral	1	1.5	-10	0	0	ND	Observation
Case 16	27	F	Retroperitoneal sarcoma	multiple	4	5.1	ND	0	0	ND	SX
Case 17	43	M	Schwanoma	Unilateral	1	4	25	0	0	ND	Sx

M: male, F: Female, ACC: Adrenocortical carcinoma, CD: Cushing disease, CS: Cushing syndrome, MEN1: Multiple endocrine neoplasia type 1, NA: not available, ND: not done, Rt: right, Lt: left, Sx: Sugery, and HU: Hounsfield units