Comparison of the Sensitivity of ^{68}Ga-DOTATATE PET/CT with Other Imaging Modalities in Detecting Head and Neck Paraganglioma: Experience from Western India

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Abstract

Background   This study aimed to compare the sensitivity of ^{68}Ga-DOTATATE positron emission tomography/computed tomography (PET/CT) with other imaging modalities in the detection of head and neck paraganglioma (HNPGL).

Methods   The data of consecutive HNPGL patients ($n = 34$) who had undergone at least ^{68}Ga-DOTATATE PET/CT and anatomical imaging (contrast-enhanced computed tomography/magnetic resonance imaging [CECT/MRI]) were retrospectively reviewed. The diagnosis of HNPGL (the primary tumor) was confirmed either by histopathology ($n = 10$) or was based on clinical follow-up and correlation of anatomical with functional imaging in whom histopathology was not available ($n = 24$). The sensitivities of ^{68}Ga DOTATATE PET/CT, 18F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT), ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy, and CECT/MRI for primary HNPGL, associated primary pheochromocytoma + sympathetic paraganglioma (PCC + sPGL), and metastatic lesions were analyzed.

Keywords
► head and neck paraganglioma
► ^{68}Ga-DOTATATE PET/CT
► ^{18}F-FDG-PET/CT

Results   Thirty-four patients (males: 15) [isolated HNPGL: 26, HNPGL + PCC: 04, HNPGL+ sPGL: 03, HNPGL + PCC + sPGL: 01] harboring 50 primary lesions were included. For total lesions, ^{68}Ga-DOTATATE PET/CT (99.3%) had significantly higher

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lesion-wise sensitivity than ^{18}F-FDG PET/CT (81.6%, $p = 0.0164$), ^{131}I-MIBG (15.2%, $p \leq 0.0001$), CECT (46.3%, $p \leq 0.0001$) but similar sensitivity as MRI neck (97%, $p = 0.79$). On head-to-head comparison (21 primary HNPGL and 39 metastatic lesions), ^{68}Ga DOTATATE PET/CT had significantly higher lesion-wise sensitivities for the detection of metastatic (100 vs. 71.9%, $p = 0.04$) and total lesions (100 vs. 77.2%, $p \leq 0.0001$).

Conclusion ^{68}Ga-DOTATATE PET/CT was the most sensitive imaging modality for the detection of HNPGL and related lesions with significantly higher lesion-wise sensitivities than those of ^{18}F-FDG PET/CT, ^{131}I-MIBG, and CECT.

Introduction

Pheochromocytomas (PCC) and paragangliomas (PGL), collectively called PPGL, are rare tumors arising from sympathetic lineage derived cells in the adrenal medulla (PCC), extra-adrenal thoracic, and abdominal paraganglia known as sympathetic paraganglioma (sPGL) or the parasympathetic ganglia known as head and neck paraganglioma (HNPGL). HNPGLs are further classified according to the site of origin as carotid body tumor (CBT), vagal paraganglioma (VP), jugular paraganglioma (JP), and tympanic paraganglioma (TP). HNPGLs account for 0.6% of head and neck tumors.[1] Although less than 5% of HNPGL are catecholamine secretory, a recent study has shown a significantly higher proportion of HNPGL secrete 3-methoxytyramine (3-MT) (28%).[2] The metastatic disease is also less prevalent in HNPGL (3.5%) than PCC (10%) and sPGL (25%).[3]

Anatomical imaging (contrast-enhanced computed tomography [CECT]/magnetic resonance imaging [MRI]) is the initial imaging modality for the localization of PPGL in biochemically confirmed cases. Endocrine Society guidelines recommend additional functional imaging in patients with high suspicion of metastatic and/or multifocal disease. Besides, ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) and ^{68}Ga-DOTATATE-PET/CT have role in patient selection for ^{131}I-MIBG therapy and peptide receptor radionuclide therapy (PRRT), respectively. HNPGLs predominantly express the somatostatin receptor type 2 (SSTR2) that acts as target sites for ^{68}Ga-DOTATATE PET/CT and ^{177}Lutetium, offering the potential for their utility in the diagnosis and therapy of HNPGL, respectively.

This study aimed to describe our experience of ^{68}Ga-DOTATATE PET/CT and also compared its sensitivity with those of ^{18}F-FDG PET/CT, ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy, and CECT/MRI in the diagnosis of HNPGL.

Materials and Methods

Patients

Retrospective evaluation of consecutive patients of HNPGL ($n = 34$) registered at KEM Hospital, Mumbai, India, between January 2010 and March 2020, was performed after approval by the Institutional Ethics Committee II (IEC II) of Seth GS Medical College (IEC-II# EC/OA:95–2020) with a waiver of consent. Patients who had undergone at least ^{68}Ga-DOTATATE PET/CT and anatomical imaging (CECT/MRI) were included. The diagnosis of HNPGL (the primary tumor) was confirmed either by histopathology ($n = 10$) or based on clinical follow-up, and correlation of anatomical with functional imaging in whom histopathology was not available ($n = 24$).

All other details including demographics, symptomatology, biochemistry, and imaging (CECT/MRI, ^{68}Ga-DOTATATE PET/CT, ^{18}F-FDG PET/CT, and ^{131}I-MIBG scintigraphy) were reviewed from the medical records. The measurement and interpretation of plasma free metanephrines (metanephrine [PFMN]; normetanephrine [PFNMN]) have been described previously.[4]

In our institute, HNPGL patients are routinely evaluated with PFNMN to rule out coexisting secretory PCC and sPGL as part of the multifocal disease (PCC + PGL) and/or multiple PGL (HNPGL + sPGL). Besides, anatomical imaging (CECT/MRI) is routinely followed by one or more functional imaging (^{68}Ga-DOTATATE PET/CT, and ^{18}F-FDG PET/CT or ^{131}I-MIBG scintigraphy) to better characterize the primary tumor and rule out multifocal disease or multiple PPGL. Once the diagnosis is confirmed, cases are discussed in the tumor board meeting, and further management is tailored, based on the symptomatology, size, and number of PPGL, and life expectancy of the patient. Various treatments are offered that include active observation, surgery, external beam radiotherapy, and ^{177}Lu-PRRT.

All functional imaging modalities were performed at the Radiation Medicine Center, Mumbai, Maharashtra, India, at a subsidized cost or free of cost. ^{18}F-FDG PET/CT was performed as described in a previous study.[5] For ^{68}Ga-DOTATATE PET/CT, ^{68}Ga was obtained from the in-house ^{68}Ge–^{68}Ga generator. The 1850 MBq ITG ^{68}Ge–^{68}Ga generator (GMP) was obtained from Isotope Technologies Garching, GmbH (ITG GmbH), Oberding, Bayern, Germany. ^{68}Ga labeling was performed using Eckert and Zeigler automated labeling module, Eurotope, GmbH, Germany. To 40 µL of the peptide dissolved in water (1 µg/µL), 2 mL sodium acetate buffer (1 M, pH 4.0), and 0.5 mL of the preclean solution (acidified 5M NaCl) eluted ^{68}Ga activity from the Strata SCX (Phenomenex, India) were added. After heating for 6 minutes at 90°C, the solution was passed to a Light tC18 cartridge (Sep-Pak, Waters, Milford, Massachusetts, United States). The labeled peptide was eluted

with 0.7 mL 50% ethanol and reconstituted with 8 to 10 mL physiological saline. The whole-body contrast-enhanced PET/CT images with a slice thickness of 5 mm were obtained on a Philips Gemini TF PET/CT (Philips Health Care, United States) after administering 0.11–0.185 GBq (3–5 mCi) of ^{68}Ga-DOTATATE intravenously. Attenuation correction in PET/CT was done using the low-dose protocol (120 kV, 80 mAs). The overall imaging time was approximately 10 to 15 minutes. A list-mode time-of-flight algorithm and line-of-response row-action maximum likelihood algorithm methods were used for image reconstruction. Maximum standardized uptake value (SUVmax) for both (^{18}F-FDG PET/CT and ^{68}Ga-DOTATATE PET/CT) the scans were determined by the software incorporated in the PET workstation. It was defined as a focal area of abnormal uptake in a region of interest compared with the surrounding.

MRI neck ($n = 25$) was done by 1.5 T MR system (Sonata Vision: Siemens, Erlangen, Germany) using an 8-channel circularly polarized head coil. CECT of the neck ($n = 24$) or CECT of neck to pelvis ($n = 8$) was performed in a similar way as described in our previous studies.[3] While calculating the sensitivity of CECT or MRI, metastatic lesions outside head and neck, sPGL and PCC detected by other modalities (image comparator) were excluded from the denominator for patients in whom anatomical imaging of neck to pelvis was not performed.

Analysis of Data

All the functional and anatomical imaging were retrospectively reviewed and reported by an experienced nuclear physician and a radiologist respectively, who were blinded for the patient details (except for the age and sex). Both patient-wise and lesion-wise analyses were performed. In the patient-wise analysis, a patient was considered as positive if at least one lesion was detected and negative if no lesion was detected. In the case of metastatic disease, if the number of lesions in any region exceeded 15, it was truncated to 15 to avoid the bias toward that patient as done in a previous study.[6]

Composite Image comparator

The composite of anatomical and/or all performed functional imaging tests was considered as the imaging comparator. Unless proven otherwise, a lesion detected in any imaging study was considered as a "true positive" lesion.

Statistical Analysis

Normal distribution was determined by the Shapiro–Wilk test. Categorical variables were represented with actual numbers and percentages. Continuous variables were represented as mean with standard deviation and categorical variables as absolute numbers and percentages. The differences between categorical variables were calculated by the chi-squared test or Fischer's exact t-test as appropriate. A p-value of less than 0.05 was considered statistically significant. All the statistical analysis was conducted by using the IBM SPSS software version 25.

Results

Baseline Characteristics

Thirty-four patients (males:15) of HNPGL (Isolated HNPGL:26, HNPGL + PCC:04, HNPGL + sPGL:03, HNPGL + PCC + sPGL:01) harboring 50 primary lesions (HNPGL)

Table 1 Lesion-based analysis including HNPGL, sPGL + PCC, and metastatic lesions

Imaging modalities	Primary HNPGL	Primary PCC + sPGL	Metastatic lesions	Total lesions
	Detection rate (%), 95% CI	Detection rate (%), 95% CI	Detection rate (%), 95% CI	Detection rate (%) 95% CI
^{68}Ga-DOTA-TATE PET/CT[1] ($n = 34$)	98 (49/50), 87.8–99.8 87.8–99.8	100 (14/14), 73.2–100	100 (96/96), 95.2–100	99.3 (159/160), 95.1–99.7
18F-FDG PET/CT[2] ($n = 20$)	84.3 (27/32), 66.4–94.1	87.5 (⅞), 46.6–99.3	78.7 (37/47), 63.9–88.8	81.6 (71/87), 73.1–89.8
^{131}I-MIBG[3] ($n = 12$)	35.2 (6/17), 15.2–61.3	42.8 (3/7), 11.8–79.6	0 (0/26), –	15.2 (9/59), 7.6–27.4
CECT[4] ($n = 24$)[a]	91.6 (33/36), 76.4–97.8	100 (7/7), 62.8–100	4 (2/50), 0.6–14.8	46.3 (44/95), 36.1–56.8
MRI neck[5] ($n = 25$)	96.9 (32/33), 82.4–99.8 –	– –	– –	– –
p-Values	1 vs. 2: 0.03, 1 vs. 3: < 0.0001, 1 vs. 4: 0.255, 1 vs. 5: 0.79, 2 vs. 3: 0.0042	1 vs. 2: 0.36, 1 vs. 3: 0.0002, 1 vs. 4: 0.297, 2 vs. 3: 0.0072	1 vs. 2: 0.0054, 1 vs. 3: < 0.0001, 1 vs. 4: < 0.0001, 2 vs. 3: < 0.0001	1 vs. 2: 0.0164, 1 vs. 4: < 0.0001, 2 vs. 3: 0.0002

Abbreviations: CECT, contrast-enhanced computed tomography; CI, confidence interval; ^{18}F-FDG PET/CT, 8F-fluorodeoxyglucose positron emission tomography/computed tomography; HNPGL, head and neck paraganglioma; ^{131}I-MIBG, ^{131}I-metaiodobenzylguanidine; MRI, magnetic resonance imaging; PCC, pheochromocytoma; sPGL, sympathetic paraganglioma.
[a]Only eight patients had CECT neck to pelvis.

were included. Eight (24%) patients had bilateral HNPGL. The mean age at diagnosis was 38 ± 12.8 years and the mean tumor size was 4.6 ± 2.48 cm. The 50 primary HNPGL were localized to CBT (32, 64%), VP (04, 8%), JP (06, 12%), and TP (08, 16%). The most common presentation was neck mass (23, 67%). Nine (22%) had elevated PFNMN of whom four had coexisting PCC/sPGL, and the median PFNMN was 73.4 (45–128) pg/mL. Two (5.88%) patients had a familial presentation.

Comparison of the Sensitivity of ⁶⁸Ga DOTATATE PET/CT with ¹⁸F-FDG PET/CT, ¹³¹I-MIBG, and Anatomical Imaging (CECT/MRI) in the Total Cohort

⁶⁸Ga DOTATATE PET/CT, ¹⁸F-FDG PET/CT, ¹³¹I-MIBG, and anatomical imaging (CECT/MRI) were available in 34, 20, 12, and 34 (CECT: 24; MRI: 25) patients, respectively.

Per-Patient Analysis

⁶⁸Ga-DOTATATE PET/CT and CECT/MRI detected HNPGL in all (34/34, 100%), whereas ¹⁸F-FDG PET/CT missed HNPGL in one patient (19/20, 95%, $p = 0.19$) and ¹³¹I-MIBG missed HNPGL in five patients (7/12, 58.33%, $p = 0.0001$).

Per-Lesion Analysis

For total lesions, ⁶⁸Ga-DOTATATE PET/CT (99.3%) had higher lesion-wise sensitivity than ¹⁸F-FDG PET/CT (81.6%, $p = 0.0164$), ¹³¹I-MIBG (15.2%, $p \leq 0.0001$), and CECT (46.3%, $p \leq 0.0001$) as described in ►Table 1.

For primary HNPGL, ⁶⁸Ga DOTATATE PET/CT (49/50, 98%) had similar sensitivity as CECT (33/36, 92%; $p = 0.255$), MRI (32/33,97%; $p = 0.79$) but higher sensitivity than ¹⁸F-FDG PET/CT (27/32, 84.3%; $p = 0.03$) and ¹³¹I-MIBG (6/17, 35.2%; $p \leq 0.0001$). For metastatic lesions, ⁶⁸Ga DOTATATE PET/CT

Table 2 Head-to-head comparison between ⁶⁸Ga-DOTATATE-PET/CT scan and ¹⁸F-FDG PET/CT

Imaging modalities	Primary HNPGL		Primary PCC+ sPGL		Metastatic lesions		Total
	Per-patient analysis (%)	Per- lesion detection rate (%), 95% CI	Per-patient analysis (%)	Per-lesion detection rate (%), 95%CI	Per-patient analysis (%)	Per-lesion detection rate (%), 95% CI	Per-lesion detection rate (%), 95% CI
⁶⁸Ga-DOTATATE[1] (n = 13)	100 (13/13)	100(21/21), 80.7–100	100 (4/4)	100 (6/6), 51.6–100	100 (5/5)	100 (39/39), 88–100	100 (66/66), 93.1–100
¹⁸F-FDG PT/CT[2] (n = 13)	92.3 (12/13)	80.9(17/21), 57.4–93	100 (4/4)	100 (6/6), 51.6–100	80 (⅘)	71.4 (28/39), 54.8–84.4	77.2 (51/66), 65–86.3
p-Value	1	0.1	1	1	1	0.0004	< 0.0001

Abbreviations: CI, confidence interval; ¹⁸F-FDG PET/CT, 8F-fluorodeoxyglucose positron emission tomography/computed tomography; HNPGL, head and neck paraganglioma; PCC, pheochromocytoma; sPGL, sympathetic paraganglioma.
Detection rate: Total lesions detected by imaging modality/total lesions detected by imaging comparator.
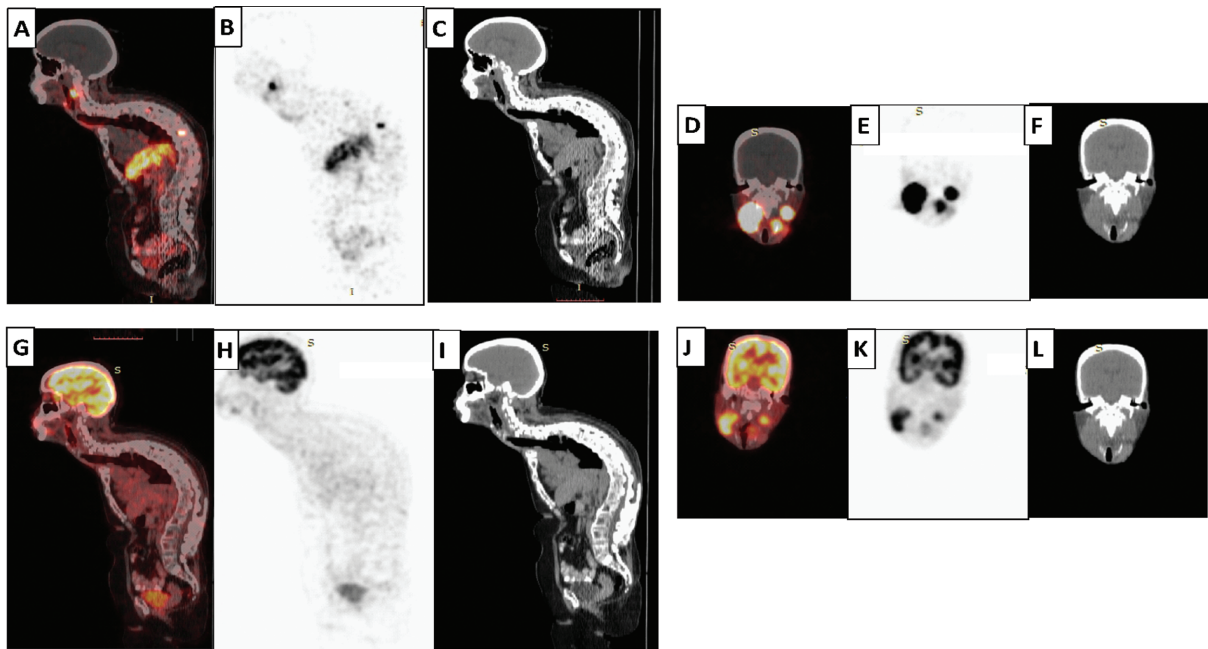

Fig. 1 Nuclear imaging in patient 8. **(A–F)** show DOTA-PET/CT, whereas **(G–L)** show FDG-PET/CT. **A, D, G,** and **J** are fused images. **B, E, H,** and **K** are MIP images. **C, F, I,** and **L** are CT images. **(A–C)** and **(G–I)** show sagittal section with uptake in vertebral metastases in DOTA but not in FDG. **(D–F)** and **(J–L)** are coronal images with uptake in primary lesion in both DOTA and FDG, but lesser avidity on FDG. FDG, fluorodeoxyglucose; MIP, maximum-intensity projection; PET/CT, positron emission tomography/computed tomography.
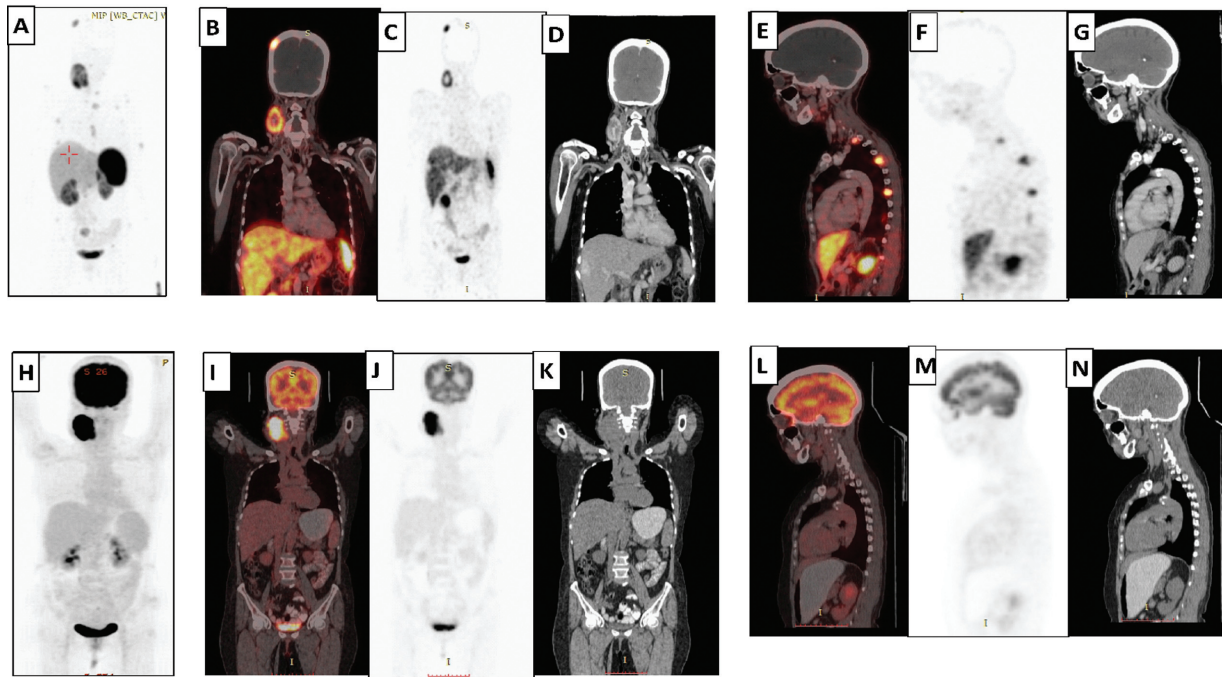
Fig. 2 Imaging of patient 22. (**A–G**) show DOTA-PET/CT, whereas (**H–N**) show FDG-PET/CT. **B, E, I,** and **L** are fused images. **A, C, F, H, J,** and **M** are MIP images. **D, G, K,** and **N** are CT images. **A** and **H** show MIP projection with uptake at multiple sites on DOTA, whereas FDG showing avidity in only primary lesion. (**B–D**) and (**I–K**) show coronal section with uptake in skull metastases in DOTA but not in FDG. Primary lesion is showing avidity in both imaging modalities. (**E–G**) and (**L–N**) are sagittal images showing multiple vertebral metastases that are DOTA avid and not FDG avid. FDG, fluorodeoxyglucose; MIP, maximum-intensity projection; PET/CT, positron emission tomography/computed tomography.

(96/96,100%) had significantly higher sensitivity than ^{18}F-FDG PET/CT (37/47, 78.7% $p = 0.0054$), ^{131}I-MIBG (0/26, $p \leq 0.0001$), and CECT (2/50, 4%; $p \leq 0.0001$). In multifocal disease,^{68}Ga-DOTATATE PET/CT (14/14, 100%) had similar sensitivity as CECT (9/9, 100%) and^{18}F-FDG PET/CT (7/8, 87.5%; $p = 0.36$) but higher than ^{131}I-MIBG(3/7, 42.8%; $p = 0.0058$).

Head-to-Head Comparison

A head-to-head comparison was performed to negotiate bias due to the different number of patients with each scan in our study. However, we did not include CECT and ^{131}I-MIBG in the head-to-head comparison as all the imaging modalities were performed only in two patients (►**Supplementary Table S1** [available online only]). Hence, the head-to-head comparison was performed between ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT, in which a total of 21 primary HNPGL and 39 metastatic lesions (in 13 patients) (►**Table 2**) were assessed. ^{68}Ga-DOTATATE PET/CT detected a higher number of primary HNPGL than ^{18}F-FDG PET/CT (100 vs. 80.9%, $p = 0.1$), although statistically insignificant, whereas the sensitivity of the former was significantly higher for the detection of metastatic lesions than the latter (100 vs. 71.9%, $p = 0.04$ ►**Figs. 1** and **2**). In four patients with multifocal disease, both the imaging modalities detected all six non-HNPGL (PCC + sPGL) lesions. In five patients with metastatic disease (per-patient analysis), ^{68}Ga DOTATATE PET/CT detected the metastatic disease in all, whereas ^{18}F-FDG PET/CT failed to do so in one.

On ^{68}Ga DOTATATE PET/CT, HNPGL had a significantly higher mean SUVmax than that of sPGL/PCC (79 ± 67.41 vs.
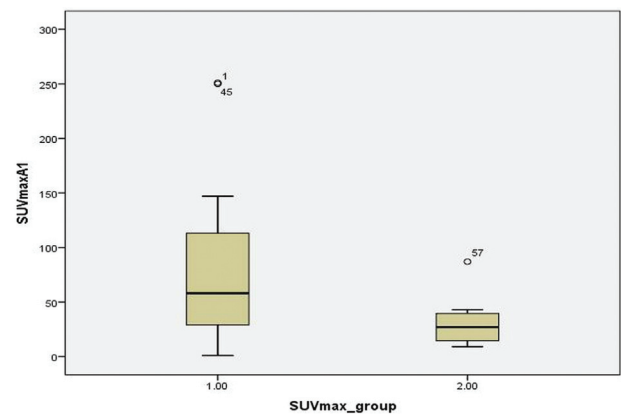

Fig. 3 Boxplot showing higher maximum standardized uptake value (SUVmax) associated with head and neck paraganglioma (HNPGL). Group 1.0 represents HNPGL primary lesions and group 2 represents non-HNPGL group (sympathetic paragangliomas and pheochromocytomas). Datapoints located outside the whiskers of the boxplot are outliers, that is, SUVmax 250 in HNPGL and SUVmax 80 in non-HNPGL group.

31 ± 21, $p = 0.029$, ►**Fig. 3**). There was no significant positive correlation between the maximum tumor size and SUVmax among HNPGL ($r = 0.132$, $p = 0.549$).

Discussion

In this largest monocentric study, ^{68}Ga-DOTATATE PET/CT had significantly higher sensitivity for the detection of HNPGL, particularly for metastatic lesions, than ^{18}F-FDG PET/CT, ^{131}I-MIBG, and anatomical imaging (CECT/MRI).

Table 3 Comparison of ^{68}Ga DOTA-based PET/CT with other imaging modalities in the evaluation of the HNPGL

Authors, year, country	Type of study	Gold standard	Number of HNPGL patients	[68]Ga DOTA-based PET/CT		MIBG (planar/SPECT/CT)		^{18}F-FDG PET/CT		^{18}F-FDOPA PET/CT		CT/MRI	
				Per patient	Per lesion	Per patient	Per lesion	Per patient	Per lesion	Per patient	Per lesion	Per patient	Per lesion
Janssen et al[7] 2016/USA[a] (DOTATATE)	Prospective single center	^{18}F-FDOPA or CT/MRI	20	NA	38/38 (100%) n=20	NA	NA	NA	27/38 (71.1%) n=20	NA	37/38 (97.4%) n=20	NA	23/38 (60.5%) n=20
Sharma et al[13] 2013/INDIA (DOTATOC)	Retrospective single center	Histopathology, digital subtraction angiography, CT/MRI	26	26/26 (100%)	78/78 (100%) n=26	14/26 (85.7%)	30/78 (38.4%) n=26	NA	NA	NA	NA	NA	42/49 (85.7%) n=NA
Kroiss et al[9] 2013/AUS-TRIA[b] (DOTATOC)	Retrospective single center	CT/MRI	19	20/20 (100%)	43/43 (100%) n=20	NA	NA	NA	NA	20/20 (100%)	32/43 (71.1%) n=20	20/20 (100%)	43/43 (100%) n=20
Kroiss et al[10] 2014/Austria[c] (DOTATOC)	Retrospective single center	CT scan	10	10/10 (100%)	27/27 (100%) n=10	1/10 (10%)	1/27 (3.7%) n=10	NA	NA	NA	NA	NA	NA
Archier et al[12] 2015/France (DOTATATE)	Retrospective single center	Histopathology, composite of anatomical and functional scans	Not mentioned	100%	30/30 (100%)	–	–	–	–	NA	26/30 (87%)	–	–
Jha et al[6] 2018 /USA[d] (DOTATATE)	Prospective single center	Composite of anatomical and functional scans	21	23/23 (100%)	105/106 (99.1%) n=23	NA	NA	22/23 (95.7%)	66/106 (62.3%) n=23	19/19 (100%)	84/97 (86.6%) n=19	23/23 (100%)	91/106 (85.8%) n=23
Kroiss 2019 et al[11]/AUS-TRIA[e] (DOTATOC)	Retrospective single center	CT Scan	10	10/10 (100%)	27/27 (100%) n=10	1/10 (10%)	1/27 (3.7%)	–	–	10/10 (100%)	18/27 (66.6%)	10/10 (100%)	27/27 (100%) n=10
Present study (DOTATATE)	Retrospective single center	Histopathology (n=10) Composite of anatomical and functional scans	34	34/34 (100%)	159/160 (99.3%) n=34	7/12 (58.3)	9/59 (15.2%) n=12	19/20 (95%)	72/87 (82.7%) n=21	NA	NA	33/34 (97%.)	43/92 (46.3%) n=34

Abbreviations: ^{18}F-FDG PET/CT, 8F-fluorodeoxyglucose positron emission tomography/computed tomography, HNPGL, head and neck paraganglioma; NA, not available; PCC, pheochromocytoma; SPECT/CT, single-photon emission computed tomography; sPGL, sympathetic paraganglioma. ^{131}I-MIBG, ^{131}I-metaiodobenzylguanidine; MRI, magnetic resonance imaging; NA, not available; PCC, pheochromocytoma; SPECT/CT, single-photon emission computed tomography; sPGL, sympathetic paraganglioma.

[a][18]F-fluorodopamine (18F-FDA) PET/CT-per-patient analysis-6/14 (42.85%), per-lesion analysis-8/27 (29.62%, n=20).

[b]Study had a total of 20 patients among which 19 were head and neck paraganglioma patients and ^{68}Ga-DOTATATE scan detected two additional lesions in head and neck area but these were not considered for total lesions as CT/MRI scans were considered as the gold standard in this study.

[c123]I MIBG SPECT/CT detected two lesions (2/27, 7.4%), ^{68}Ga-DOTATOC PET CT scan detected two additional MIBG negative lesions in the head and neck region which were not detected by CT scan.

[d]Among a total of 21 patients, 19 were HNPGL patients.

[e]This study includes the same patients which were previously included in Kroiss et al study (2014).

Similar to our study, several studies have consistently demonstrated high (99–100%) sensitivity of ^{68}Ga-DOTATATE PET/CT in the diagnosis of HNPGL.[7–13] In our study, ^{68}Ga-DOTATATE PET/CT had significantly higher overall lesion-wise sensitivities than ^{18}F-FDG PET/CT both in the total cohort and in the head-to-head comparison. Similarly, significantly higher overall sensitivities of ^{68}Ga-DOTATATE PET/CT than ^{18}F-FDG PET/CT have been reported in an unselected HNPGL cohort (100 vs. 71%, $p < 0.01$)[7] and an succinate dehydrogenase D (SDHD)-associated, mostly HNPGL comprising, PPGL cohort (99 vs. 62%, $p < 0.001$).[6] In our study, ^{68}Ga-DOTATATE PET/CT had significantly higher sensitivities than ^{18}F-FDG PET/CT for both primary and metastatic lesions. Similar observations were also reported in an unselected HNPGL cohort.[6] Robust expression of SSTR2 in HNPGL may be the reason for the highest sensitivity of ^{68}Ga-DOTATATE PET/CT.

Similar to our study, the superiority of ^{68}Ga-DOTATATE PET/CT over ^{123}I-MIBG planar (3.7%) and ^{123}I-MIBG SPECT/CT (7.4%) for the detection of primary HNPGL as well as the associated metastatic lesions has consistently been demonstrated in several studies (►Table 3).[10,11,13] The much lower sensitivity of ^{131}I-MIBG in HNPGL (parasympathetic) can be explained by the nonchromaffin origin of HNPGL.

Several studies have also demonstrated the superiority of ^{68}Ga-DOTATATE PET/CT over anatomical imaging (CT/MRI) for the overall and metastatic lesions which was also noted in our study. Notably, the sensitivities of CT and MRI to detect primary HNPGL were comparable to ^{68}Ga-DOTATATE PET/CT in our study. In contrast, a few studies have demonstrated significantly lower sensitivity of anatomical imaging, especially of CT, than ^{68}Ga-DOTATATE PET/CT.[7]

HNPGL in our cohort had a higher SUVmax compared with sPGL and PCC. Similarly, Sharma et al have also demonstrated a higher SUVmax in HNPGL (42.2 ± 53.8) than in non-HNPGL (14.1 ± 23.1). These differences in SUVmax can be attributed to quantitatively higher expression of SSTR on the tumor surface.[13] Besides, a less dedifferentiated nature of HNPGL may also contribute to higher SUVmax in them. This offers a higher sensitivity to detect HNPGL than other PPGL with ^{68}Ga-DOTATATE PET/CT.[14] However, there was no difference in the sensitivities of ^{68}Ga-DOTATATE PET/CT to detect HNPGL and other associated PPGL in this study, probably due to a small number of non-HNPGL. Notably, the difference was also not significant when compared with our whole PCC + sPGL (94%, 64/68) cohort (under review for publication elsewhere).

We recognized a few limitations in our study. First, the retrospective design with small sample size. Second, genetic details were not available in most of our patients; hence, genotype-based sensitivity analysis could not be performed. Third, 3-MT, the most sensitive marker of the secretory status of HNPGL, was not measured. Lastly, the diagnostic specificity of the imaging modalities was not evaluated in our study. Unless proven otherwise, lesions detected in any functional and/or anatomical imaging were considered as PPGL-related lesions. Although it is ideal to have a histopathological diagnosis to define diagnostic accuracy, it was neither possible nor ethical to obtain the histopathological proof of every suspected metastatic lesion as discussed in a previous study.[6]

Conclusion

^{68}Ga-DOTATATE PET/CT had the highest lesion-wise sensitivities to detect overall, primary, and metastatic HNPGL that were significantly higher than those of ^{18}F-FDG PET/CT and ^{131}I-MIBG. Hence, we recommend that ^{68}Ga-DOTATATE PET/CT should be the preferred functional imaging modality in HNPGL patients.

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