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Original Article

Comparison of ^{68}Ga-DOTA-Nal^{3}-Octreotide/tyr^{3}-octreotate positron emission tomography/computed tomography and contrast-enhanced computed tomography in localization of tumors in multiple endocrine neoplasia 1 syndrome

ABSTRACT

The optimum imaging modality for the screening of multiple endocrine neoplasia type 1 (MEN1)-associated tumors is not well established. Here, we compare the performance of contrast-enhanced CT (CECT) versus ^{68}Ga DOTA-NOC/TATE PET/CT in MEN1 patients. The retrospective case record study is conducted at a tertiary health-care center. Thirty-four patients, who have undergone both CECT and ^{68}Ga DOTA-NOC/TATE PET, were included in the analysis. CECT had higher per-lesion sensitivity than ^{68}Ga DOTA-NOC/TATE PET/CT for the detection of parathyroid lesions, (82.6% vs. 24.6%, $P < 0.001$). ^{68}Ga DOTA-NOC/TATE PET/CT had higher per-lesion sensitivity than CECT for the detection of metastases (85% vs. 47.5%, $P < 0.001$) and gastrinomas (90% vs. 10%, $P = 0.003$). When combined use of the two imaging modalities is compared to CECT alone (63.7% vs. 93.1%, $P = 0.00012$) and ^{68}Ga-DOTA-NOC/TATE PET/CT alone (74.1% vs. 93.1%, $P = 0.0057$), it provided significantly higher per-lesion sensitivity for the detection of gastroenteropancreatic neuroendocrine tumors (GEP-NETs). ^{68}Ga-DOTA-NOC/TATE PET was more sensitive for the detection of gastrinomas and metastases than CECT, whereas it was less sensitive for the detection of parathyroid lesions than CECT. The combined use of both the imaging modalities significantly increases the sensitivity for detection of GEP-NETs.

Keywords: ^{68}Ga-DOTA-Nai^{3}-octreotide/tyr^{3}-octreotate positron emission tomography/computed tomography, contrast enhanced computed tomography, gastrointestinal-pancreatic neuroendocrine tumor, multiple endocrine neoplasia type 1 imaging, multiple endocrine neoplasia type 1 syndrome

INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant disorder involving multiple endocrine glands with an estimated incidence of 1 in 10,000 in general population.[1] The most common MEN1-associated endocrine tumors are primary hyperparathyroidism (PHPT, 95%) gastrointestinal-pancreatic neuroendocrine tumor (GEP-NET, 40%–70%) and pituitary tumors (30%–40%).[2] Other endocrine tumors include adrenal lesions (5%–40%) and thymic carcinoids (4%–9%).[2] However, the main cause of morbidity and mortality is due to malignant pancreatic and thymic NET.[3] There is no consensus on optimum imaging modality for GEP-NET in MEN1. The latest guidelines on MEN1 recommended minimal imaging with annual computed

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tomography (CT)/magnetic resonance imaging/endoscopic ultrasound.[2]

Somatostatin receptor (SSTR)-based imaging has been proven to be superior in the detection of sporadic NET. In recent meta-analysis of SSTR positron emission tomography (PET) or PET/CT in detecting sporadic NET, pooled sensitivity and specificity on per-patient analysis were 93% (95% confidence interval [CI]: 91%–95%) and 91% (95% CI: 82%–97%), respectively.[4] Most of the MEN1-associated tumors are characterized by overexpression of cell surface SSTRs.[4] However, data on SSTR-based imaging in MEN1 patients are limited.[5-8] In this study, we compare the performance of contrast enhanced CT (CECT) versus ^{68}Ga DOTA-Nal^{3}-Octreotide (NOC)/tyr^{3}-Octreotate (TATE) PET/CT in MEN1 patients.

METHODS

It is a retrospective case record review (January 2008–December 2016) of consecutive MEN1 patients managed at our center. The study was approved by Institutional Ethics Committee (IEC-I) of Seth GSMC and KEM Hospital in letter dated 16 August 2017 (Letter number IEC-I/OUT/1854/17). The patient consent waiver was granted by IEC, considering the retrospective nature of the study.

Patients

MEN1 diagnosis was based on the demonstration of pathogenic MEN1 gene mutations and/or occurrence of two or more primary MEN1-associated endocrine tumors in the index case. In first degree relatives of a patient with a clinical diagnosis of MEN1, the occurrence of one or more of the MEN1-associated primary endocrine tumors was considered diagnostic of MEN1. All patients underwent screening and surveillance tests for manifestations of MEN1, as per the published guidelines.[2] Forty patients with MEN1 have been registered at our center during the study. Only those patients who had undergone both ^{68}Ga DOTA-NOC/TATE PET/CT and CECT were included in the analysis. Previously published 11 patients are included.[9] Six patients having suspected MEN1-associated lesions but lacking confirmation on histology and/or clinical/imaging follow-up were excluded from the analysis. Of 34 patients in the study, 29 have a pathogenic mutation in the MENIN gene. Two were first-degree relative of genetically confirmed MEN1 patients and had MEN1-associated endocrine tumors. Three patients were diagnosed based on clinical diagnosis.

Computed tomography imaging

Imaging was performed with 64-slice multidetector CT system (Brilliance 64, Philips Healthcare, Best, and The Netherlands) using standardized protocol. Patients were placed in supine position, with arms pulled caudally. The scanning protocol consisted of four identical helical scans obtained in automated, predetermined, and timed sequence. The scanning range was from hard palate to pelvis, and a small field of view (168 mm × 168 mm) was used. Scanning parameters were 120 kVp, with automatic exposure control (range, 140–220 mA), rotation time of 0.75 s, pitch of 0.797, and a 0.625-mm detector configuration, with beam width of 40 mm. The first phase included baseline imaging before the administration of contrast material (unenhanced). After the first phase imaging, 100 ml of iodinated contrast material (Omnipaque 300, GE healthcare, Phoenix, United States) was injected in cubital vein (preplaced 18–22-gauge cannula) at the rate of 4 ml/s and was followed by a saline flush. Second phase (early arterial) imaging was obtained at 20 s after the start of contrast injection. Third (early venous phase) and fourth phases imaging was obtained at 45 and 90 s, respectively. Images were stored on mass storage device (Seagate, Cupertino, California, United States) and retrieved by attaching mass storage to picture archiving and communication system. After archiving, standardized postprocessing was performed at workstation yielding multiplanar reconstructions, including a "true axial" plane parallel to vocal cords and coronal/sagittal planes orthogonal to "true axial" plane.

68Ga DOTA-Nal3-octreotide/tyr3-octreotate positron emission tomography/computed tomography imaging

^{68}Ga-DOTA-NOC/TATE PET/CT scan was done in 34 patients (DOTA-NOC $n = 12$, DOTATATE $n = 22$). ^{68}Ga was obtained from in-house ^{68}Ge–^{68}Ga generator. It was labeled with DOTA-conjugated peptide (DOTA-NOC/DOTATATE), a somatostatin analog. Whole-body (head to toe) scans were obtained after 1–1.5 h of intravenous injection of 3–5 mCiof ^{68}Ga-DOTA-NOC/TATE. PET scan was performed after CT scan acquisition. Scans were acquired on dedicated PET/CT scanner (STE-16, BGO crystal, 16-slice CT scanner, GE Healthcare). Vertex-to-mid-thigh acquisitions were obtained with hands being placed above the head position. PET scan was acquired in 7–8 min of overlapped body position with 3 min acquisition per body position. CT data were used for attenuation correction and fusion imaging. Images were reconstructed in standard display consisting of transaxial, sagittal, and coronal projections.

Imaging analysis

All CECT images were reported by an experienced radiologist (experience of 20 years) whereas two experienced nuclear medicine physicians with experience of 10 years and 6 years reviewed ^{68}Ga-DOTA-NOC/TATE PET/CT images. Radiologist and both nuclear physicians were blinded for

imaging results, intraoperative findings, and histology but were aware of the MEN1 diagnosis in these patients. They were asked to look for the MEN1-associated lesions such as parathyroid lesions, thyroid nodules, thymic carcinoid, bronchial carcinoid, GEP-NET, and adrenal nodules. Lesions in the pancreas which showed maximum enhancement at 20 s or 45 s were diagnosed as NETs. The maximum diameter in axial images was used to describe the tumor size.[10] Criteria for image interpretation of ^{68}Ga-DOTA-NOC/TATE PET/CT were based on the visual analysis where a focally increased uptake compared to that of the surrounding tissues was read as positive. Diffuse uptake over the uncinate process was considered physiological.

Reference standard

A lesion was confirmed to be MEN1-associated when there was histological evidence, or the diagnosis was confirmed by clinical and radiologic follow-up with either CECT or ^{68}Ga DOTA-NOC/TATE PET/CT scan in the next 6 months.

Statistical analysis

Continuous data are expressed as mean ± standard deviation or median and range as appropriate whereas categorical data are expressed in number and percentage. Kolmogorov–Smirnov test is used to check the normality of the data. Per-lesion sensitivity and positive predictive value (PPV) is calculated for CECT and ^{68}Ga DOTA-NOC/TATE PET/CT. $P < 0.05$ is considered as statistically significant.

RESULTS

Study cohort and imaging results

The study cohort demographics and clinical characteristics are summarized in Table 1. A total of 34 patients with a known diagnosis of MEN1were enrolled, with a mean age of 33.3 ± 12.4 years. All patients had undergone ^{68}Ga-DOTA-NOC/TATE PET/CT and CECT within a span of 15 days as a part of the evaluation.

Parathyroid

At the time of diagnosis of MEN1 syndrome, 23 patients had symptomatic PHPT, and 7 patients had asymptomatic PHPT. For the detection of parathyroid lesions, per-patient sensitivity of CECT was 96.6% and that of ^{68}Ga-DOTA-NOC/TATE PET/CT was 43.3%. Both imaging was done before parathyroid surgery. A total of 69 lesions were identified as true positive lesions. CECT had significantly higher sensitivity than ^{68}Ga-DOTA-NOC/TATE PET/CT (82.6% vs. 24.6%, $P < 0.0001$) with 100% PPV for both the modalities. Per-lesion sensitivity with the combined use of two imaging modalities was not significantly better compared to CECT. Twenty-three patients had multiglandular (more than one gland) parathyroid disease which was identified in 21 by CECT and in four by ^{68}Ga-DOTA-NOC/TATE PET/CT (91.3% vs. 21.7%, $P < 0.00001$). ^{68}Ga DOTA-NOC/TATE PET/CT-negative parathyroid lesions were 12 ± 9.5 mm. They were detected on CECT based on contrast enhancement on arterial phase CT.[11] Sensitivity of ^{68}Ga-DOTA-NOC PET/CT (9/29) and ^{68}Ga-DOTA TATE PET/CT (8/40) was comparable for the detection of metastasis. ($P = 0.29$) Tc99m-sestamibi scan was not done.

Gastroenteropancreatic neuroendocrine tumors

Twenty-eight patients had GEP-NET at the time of analysis (15 histologically proven and 13 confirmed on imaging follow-up). In per-patient analysis, CECT and ^{68}Ga-DOTA-NOC/TATE PET/CT had sensitivity of 71.4% (20/28) and 89.2% (25/28), respectively ($P = 0.09$). A total of 58 lesions were identified as true-positive lesions with a mean diameter of 19.2 ± 14.2 mm. In per-lesion analysis, CECT and ^{68}Ga-DOTA-NOC/TATE PET/CT had sensitivity of 63.7% (37/58) and 74.1% (43/58), respectively ($P = 0.23$). In per-lesion analysis, sensitivity for ^{68}Ga-DOTA-NOC (12 patients) was 78.2% (18/23) and for ^{68}Ga-DOTATATE (22 patients) was 71.4% (25/35) ($P = 0.56$). Both the imaging modalities have 100% PPV [Table 2].

Standardized uptake value maximum (SUVmax) for true-positive lesions was 28.3 ± 39 (median: 11.6, range: 2.6-108). Combined use of two imaging modalities provided significantly higher per-lesion sensitivity when compared to CECT alone (63.7% vs. 93.1%, $P = 0.00012$) and ^{68}Ga-DOTA-NOC/TATE PET/CT alone (74.1% vs. 93.1%, $P = 0.0057$).

Among 17 patients with multifocal GEP-NETs (two or more), all existing lesions were detected by CECT in eight patients, whereas only one lesion was detected in other patients. ^{68}Ga-DOTA-NOC/TATE PET/CT detected all existing lesions in eight patients and at least one lesion in other

Table 1: Demographics and distribution of multiple endocrine neoplasia 1 tumors

Characteristic	Number
Age	33.3±12.4 years
Sex (male/female)	22/12
PHPT (n=30)	
Symptomatic	23
Asymptomatic	7
GEP-NET (n=28)*	
Insulinoma	10
Gastrinoma	7
Nonfunctioning	12
Thymic carcinoid	6
Adrenal nonfunctioning tumors	16 (4 B/L)

*One patient had both insulinoma (n=3) and gastrinoma (n=3). B/L: Bilateral; GEP-NET: Gastroenteropancreatic neuroendocrine tumors; PHPT: Primary hyperparathyroidism

eight patients but missed all lesions in one patient [Figure 1a]. This patient had two insulinoma lesions which were identified by CECT [Figure 1b]. Surprisingly, only in two patients, both the modalities identified all the existing multifocal GEP-NETs simultaneously. Hence, performing the second imaging modality was beneficial in 15 patients with multifocal GEP-NETs (^{68}Ga-DOTA-NOC/TATE PET/CT in 8 patients and CECT in 7 patients) to detect GEP-NETs that were missed by the first imaging modality. Figure 2 shows GEP-NET missed on CT [Figure 2b] but identified on ^{68}Ga-DOTA-NOC PET/CT [Figure 2a].

Depending on the secretory pattern, GEP-NETs were divided into insulinoma, gastrinoma, and nonfunctional NET (NF-NET). Ten patients had insulinoma (24 true-positive lesions). CECT has numerically higher, but statistically insignificant, per-lesion sensitivity than ^{68}Ga-DOTA-NOC/TATE PET/CT (83.3% vs. 66.6%, $P = 0.18$) for the detection of insulinomas. Seven patients had gastrinoma (10 lesions). One patient was having both gastrinoma and insulinoma simultaneously (3 lesions each). Nine of 10 (90%) lesions were identified by ^{68}Ga-DOTA-NOC/TATE PET/CT, whereas one was detected by upper gastrointestinal endoscopy. CECT could identify only one gastrinoma lesion. ($P = 0.0003$). Thirteen patients had NF-NETs (24 lesions). For NF-NET, ^{68}Ga-DOTA-NOC/TATE PET/CT had numerically higher, but statistically insignificant, sensitivity than CECT in per-lesion analysis (75% vs. 66.6%, $P = 0.52$). Both imaging modalities had similar per patient sensitivity (76.9%) for NF-NET detection.

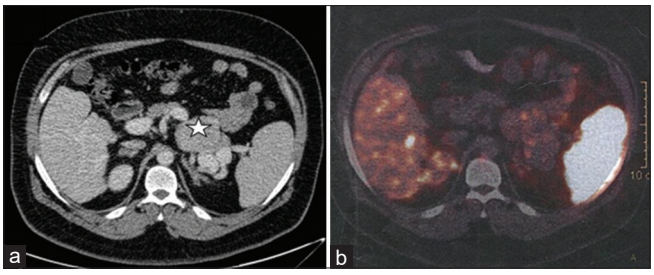

Figure 1: (a) Insulinoma lesion (*) identified on contrast-enhanced computed tomography (b) but not showing somatostatin receptor uptake

Thymic carcinoids

Six patients had thymic carcinoids at the time of analysis. CECT-detected all six thymic carcinoids whereas ^{68}Ga-DOTA-NOC/TATE PET/CT showed SSTR uptake in five carcinoids. Mean size of the ^{68}Ga-DOTA-NOC/TATE PET/CT-positive thymic carcinoids were 4.1 ± 1.6 cm, whereas that of the negative one was 1.6 cm. This lesion was seen on CT component of ^{68}Ga-DOTA-NOC/TATE PET/CT but not showing any SSTR uptake. Mib1 labeling index of this lesion was 15%. The grade of thymic carcinoid had a correlation with SSTR uptake. Grade1 thymic carcinoid had SUV_{max} of 54.4 whereas Grade 2 carcinoids had SUVmax of 1.23, 8.5, and 7.8 and while Grade 3 carcinoid had SUV of 4.1.

Metastasis

A total of 40 metastatic lesions were identified in 15 patients. These metastases were from GEP-NET in 11 patients and thymic carcinoids in 4 patients. Of these, 25 were in lymph nodes, 11 in bones and 4 in the liver. ^{68}Ga-DOTA-NOC/TATE PET/CT had significantly higher per-patient sensitivity for detection of metastases than CECT (100% vs. 40%, $P = 0.0003$). In per-lesion analysis also, ^{68}Ga-DOTA-NOC/TATE PET/CT had significantly higher sensitivity than CECT (85% vs. 47.5%, $P < 0.00001$). However, ^{68}Ga-DOTA-NOC PET/CT also showed two false-positive metastatic lesions in a patient in the form of two retroperitoneal nodes [Figure 3a] which were not detected in followup scan after 8 months [Figure 3b]. Most of the metastatic lesions missed on CT were peripancreatic lymph nodal metastasis, in one patient liver lesion and one patient vertebral metastasis. The size of metastatic lesions

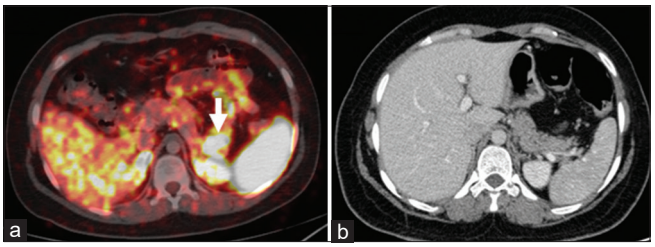

Figure 2: (a) Pancreatic tail nonfunctional - neuroendocrine tumor (arrow) identified in ^{68}Ga-DOTA-NaI3-octreotide positron emission tomography/computed tomography (b) but missed on contrast-enhanced computed tomography

Table 2: Lesion-wise sensitivity and positive predictive value

	True positive by histology	True positive by follow-up imaging	^{68}Ga-DOTANOC/TATE PET/CT		CECT		Combined imaging	
			Sensitivity (%)	PPV (%)	Sensitivity (%)	PPV (%)	Sensitivity (%)	PPV (%)
Parathyroid (n=69)	37	32	24.6	100	82.6	100	84.05	100
GEP-NET (n=58)	35	23	74.1	100	63.7	100	93.1	100
Thymic carcinoids (n=6)	4	2	85.7	100	100	100	100	100
Metastasis (n=40)	3	37	85	94.4	47.5	100	95	95

GEP-NET: Gastroenteropancreatic neuroendocrine tumors; CECT: Contrast-enhanced computed tomography; PPV: Positive predictive value; ^{68}Ga-DOTANOC/TATE PET/CT: ^{68}Ga DOTA-NaI3-Octreotide/tyr3-octreotate positron emission tomography/computed tomography

missed on CT scan was 10.1 ± 3.7 mm (range 7–21 mm). The sensitivity of ^{68}Ga-DOTA-NOC PET/CT (19/40) and ^{68}Ga-DOTA TATE PET/CT (15/40) was comparable for the detection of metastasis ($P = 0.36$).

Pituitary Tumors

Sixteen patients had pituitary tumors (11 prolactinoma, 2 patients with Cushing's disease, and 3 patients had nonfunctioning pituitary tumor). ^{68}Ga-DOTA-NOC/TATE PET/CT showed physiological SSTR uptake even in patients not having pituitary tumors.

Twelve patients had concomitant pituitary, parathyroid, and pancreatic NETs.

Adrenal nodules

Sixteen patients had adrenal nodules (4 bilateral and 12 unilateral). All nodules were detected by CECT whereas four of them were showing SSTR uptake on ^{68}Ga-DOTA-NOC/TATE PET/CT though all adrenal nodules were seen on CT component of it. We have not found any patient having pheochromocytoma or Cushing's syndrome. We did not evaluate patients for hyperaldosteronism.

DISCUSSION

Preoperative imaging in MEN1 can be obtained by several different methods, which vary from institute to institute depending on the availability. ENETS guidelines mention that ^{68}Ga-PET/CT is more sensitive than any of the other modalities in MEN1 patients for GEP-NET.[12] In our cohort of MEN1 patients, we assessed the performance of CECT and ^{68}Ga-DOTA-NOC/TATE PET/CT for the detection of MEN1-associated tumors. For the detection of gastrinomas and metastases, ^{68}Ga-DOTA-NOC/TATE PET/CT performed better than CECT. In identification multiglandular PHPT, CECT showed higher sensitivity than ^{68}Ga-DOTA-NOC/TATE PET/CT.

PHPT in MEN1 is a multi-glandular disease. In our series, CECT showed good sensitivity (82.6%) as compared to

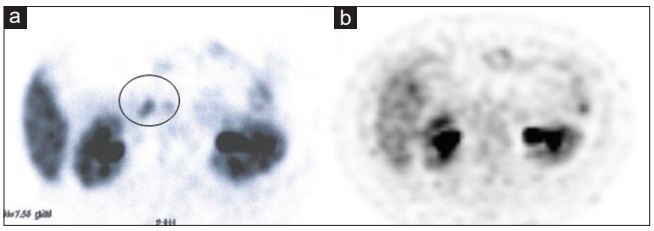

Figure 3: (a) False-positive retroperitoneal nodes (circled) (b) showing standardized uptake value maximum 4.9 identified on 68Ga-DOTA-Nal3-octreotide PET/CT which were absent on follow-up scan after 8 months

^{68}Ga-DOTA-NOC/TATE PET/CT (24.6%) for the detection of parathyroid lesions. Unlike in sporadic PHPT patients in whom the role of preoperative imaging is clear, preoperative parathyroid imaging is not routinely recommended in MEN1 patients, as an exploration of all four glands irrespective of imaging findings is standard of care in them. However, in recent years, unilateral neck exploration and removal of both ipsilateral glands is also gaining popularity,[13] which requires the accurate identification of diseased glands. CECT has been shown to be more sensitive than Tc-99m-sesta-methoxyisobutylisonitrile (SestaMIBI) scan (44%), other routinely used imaging modality, for detection of multiglandular parathyroid disease of MEN1.[11] This finding may also be extrapolated to multiglandular sporadic disease, and CECT may have better sensitivity to identify multiglandular involvement in sporadic PHPT patients. However, most of the studies report less sensitivity of CECT for multiglandular PHPT and varies from 29% to 85%.[14] Although ^{68}Ga-DOTA-NOC/TATE PET/CT had comparable sensitivity to CECT in our initial experience with a smaller number of subjects, larger data from this study suggest poor sensitivity of ^{68}Ga-DOTA-NOC/TATE PET/CT for the detection of parathyroid lesions.[9] Similar studies reporting poor sensitivity of ^{68}Ga-DOTA-NOC/TATE PET/CT have been published previously.[5,7] In patients with recurrence of PHPT, we prefer CECT over (99m) Tc-sestaMIBI. (18) F-Fluorocholine (18 F-FCh) PET/CT has shown better sensitivity (92%) compared Tc-99m-sestaMIBI SPECT/CT (sensitivity 49%).[15] The performance of 18 F-FCh PET/CT was superior particularly in patients with multiple lesions or hyperplasia. One study has shown preoperative localization with FCh-PET and focused parathyroidectomy in patients with single adenoma gives very high success rate even without intraoperative parathyroid hormone testing.[16] We could not do 18 F-FCh PET/CT due to nonavailability.

In MEN1 patients, GEP-NET and thymic carcinoids are two common tumors with malignant potential that contribute to their reduced life span.[17] Reported sensitivities of CT and SSTR based imaging are 85% and 50%–85.7%, respectively.[18] In our study, ^{68}Ga-DOTA-NOC/TATE PET/CT did not show SSTR uptake in thymic carcinoid in one patient (size: 1.6 cm), but it was visible on the CT component. Moreover, even in the detected lesions, the SUVmax in thymic carcinoids was low with faint visualization of the lesions. Thymic carcinoids are most often rapidly progressing, and their early detection at a smaller size is important.[17]

In our series, ^{68}Ga-DOTA-NOC/TATE PET/CT had numerically higher sensitivity than CECT, both in per-patient (89.2% vs. 71.4%) and per-lesion (74.1% vs.

63.7%) analyses, for the detection of GEP-NET. However, the difference was not statistically significant. Per-patient sensitivity of CECT for localizing sporadic GEP-NET has been reported to be 73%,[19] which is comparable to the per-patient sensitivity in our study. However, per-patient sensitivity is not an accurate measure of sensitivity in MEN1 due to its association with multifocal GEP-NET.[2] Hence, per-lesion sensitivity is a better indicator of disease extent and helps in patient management. In our study, the sensitivity of CECT for GEP-NET was lower in per-lesion analysis (63.7%) than per-patient analysis (71.4%). The per-lesion sensitivity of CECT for GEP-NET in our study was comparable to that of previously published literature [Table 3].

The literature on sensitivity of ^{68}Ga-DOTATATE PET/CT in different subgroups of GEP-NETin MEN1 patients is limited. The performance of ^{68}Ga-DOTATATE PET/CT was better than CECT for gastrinomas, as reported previously.[20] Although sensitivity of ^{68}Ga-DOTATATE PET/CT was higher for the detection of NF-NET than CECT, it was not statistically significant. This may be due to small sample size. On the contrary, the sensitivity of CECT was numerically higher than ^{68}Ga-DOTATATE PET/CT for the detection of insulinomas. This may be due to poor expression of SSTR2 by insulinomas demonstrated in *in vitro* studies.[21]

Currently, in SSTR PET, three major ^{68}Ga-DOTA-peptides are used for imaging: Tyr3-Octreotide (TOC), 1-NOC, and TATE. There is differential binding of these peptides to different SSTRs (SSTR 2, SSTR 3, and SSTR 5). All three can bind to SSTR2 and SSTR5, while only NOC has good affinity for SSTR3.[22] This difference may indicate NOC as a better peptide for clinical imaging, but in our study, NOC and TATE showed similar sensitivity.

We showed that the use of combined imaging significantly increases the sensitivity to detect GEP-NET than any single modality. However, we have not studied whether aggressive imaging using both modalities would improve the outcome. Moreover, performing both imaging modalities at regular intervals will significantly increase radiation exposure. Studies have demonstrated increased radiation exposure in MEN1 patients with aggressive monitoring, and excess radiation exposure itself may increase the risk of malignant tumors in MEN1 patients.[23] Hence, radiological surveillance in MEN1 patients could be a double-edged sword. A recent study showed that the combination of triple-phase CT with ^{68}Ga-DOTATOC PET delivers highly synergistic information in sporadic NET.[24] Hence, combining CECT (triple phase) with the ^{68}Ga-DOTA-NOC/TATE PET/CT may give a single better modality for disease mapping in MEN1. This imaging modality can reduce the number of imaging as well as the time required for evaluation. Although conclusion on the optimal duration of interval imaging cannot be drawn from this study. However, this proposal needs evaluation in larger prospective studies comprising MEN1 patients.

In addition to GEP-NET, ^{68}Ga-DOTA-NOC/TATE PET has been claimed to give a panoramic view of MEN1-associated lesions at one assessment with a good sensitivity (75%) and specificity (83%) for them (pituitary adenomas and adrenal adenomas).[20] However, in our study, ^{68}Ga-DOTA-NOC/TATE PET showed SSTR uptake in only four adrenal nodules, but all were seen on the CT component of ^{68}Ga-DOTA-NOC/TATE PET. Another benefit of ^{68}Ga-DOTA-NOC/TATE PET/CT is for identification of distant metastases (liver and bone, distant lymph nodes, and soft tissues) from GEP-NET and thymic carcinoids. Although ^{68}Ga-DOTA-NOC/TATE PET/CT was more sensitive to for the detection of distant metastatic lesions from thymus than CECT.

^{68}Ga-DOTA-NOC/TATE PET/CT shows physiological uptake in pituitary and is not helpful in the detection of pituitary tumors. In addition, a recent study has demonstrated the prognostic advantage of ^{68}Ga-DOTA-NOC/TATE PET in GEP-NET. The study showed that SUVmax measured on ^{68}Ga-DOTA-NOC PET/CT is an independent, positive prognostic factor for predicting progression-free survival in NET.[25]

Table 3: Comparison of our study with literature for gastroenteropancreatic neuroendocrine tumors in multiple endocrine neoplasia Type 1

Study	Type	Number of patients	^{68}Ga-DOTA-NOC/TATE PET/CT		CECT	
			Sensitivity (%)	PPV	Sensitivity (%)	PPV (%)
Lastoria *et al*.[5]	Prospective	18	100	-	60	-
Morgat *et al*.[6]	Prospective	19	76	-	60	-
Froeling *et al*.[7]	Retrospective	21 (19-MEN 1, 1-MEN 2A and 1-MEN 2B)	81	-	56.8	
Lewis *et al*.[8]	Retrospective	52 (CT was available in 43)	-	-	70 (per patient sensitivity)	97.1
Our study Per Lesion Analysis	Retrospective	34	74.1	100	63.7	100

PPV: Positive predictive value; GEP-NET: Gastroenteropancreatic neuroendocrine tumors; MEN 1: Multiple endocrine neoplasia Type 1; ^{68}Ga-DOTANOC/TATE PET/CT: ^{68}Ga DOTA-Nal3-Octreotide/tyr3-octreotate positron emission tomography/computed tomography

Limitations of our study include a small sample size and retrospective nature. Our study had selection bias because, in few of our MEN1 patients, the lesions were not histologically proven. This selection bias might have overestimated the PPV.

CONCLUSION

^{68}Ga-DOTA-NOC/TATE PET was more sensitive for the detection of gastrinomas and metastases than CECT, whereas it was less sensitive for the detection of parathyroid lesions than CECT. The combined use of both the imaging modalities significantly increases the sensitivity for GEP-NETs. Combined imaging can be used at diagnosis of MEN1 syndrome to map disease burden.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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