PET/CT imaging of neuroendocrine tumors with 68Gallium-labeled somatostatin analogues: An overview and single institutional experience from India

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ABSTRACT

Neuroendocrine tumors (NETs) are rare neoplasms characterized by overexpression of somatostatin receptors (SSTRs). Functional imaging plays a crucial role in management of NETs. Recently, positron emission tomography/computed tomography (PET/CT) with 68Gallium (68Ga)-labeled somatostatin analogues has shown excellent results for imaging of NETs and better results than conventional SSTR scintigraphy. In this review we have discussed the utility of 68Ga-labeled somatostatin analogue PET/CT in NETs for various established and potential indications. In addition we have also shared our own experience from a tertiary care center in India.

Keywords: 68Gallium-labeled [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-NaI3-octreotide, 68Gallium-labeled [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-Phe^1-Tyr^3-Octreotide, 68Gallium-labeled [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-Tyr^3-Octreotate, Neuroendocrine tumor, PET/CT, somatostatin receptor

INTRODUCTION

Neuroendocrine tumors (NETs) are rare tumors arising from the neuroendocrine cells dispersed through the body derived from the neural crest. The incidence of these tumors appears to be rising. An analysis of the Surveillance, Epidemiology, and End Results (SEER) database indicates an increase in the reported annual age-adjusted incidence of NETs from 1.09/100,000 (1973) to 5.25/100,000 (2004).[1] This may be in part due to the improvement in imaging and biochemical methods for detection of NETs. These tumors can originate from endocrine glands such as the pituitary and adrenal medulla, as well as endocrine cell clusters in the thyroid or the pancreas and widely dispersed endocrine cells in the gastrointestinal and respiratory tract as well as skin.[2] As these tumors belong to the amine precursor uptake and decarboxylation (APUD) cell

system, they can concentrate and secrete a wide variety of amines and peptides. The presence of hormone syndromes related to secreted amine/hormone production, allows the differentiation of NET into functional (33-50% of cases) or nonfunctional subgroups. Another characteristic feature of NET cells is the expression of several receptors in high quantities.[3] Apart from location, NETs are also graded according to proliferation activity (G1: Ki67 < 2%, G2: Ki67 2-20%, and G3: Ki67 > 20%) which can have strong impact on prognosis and therapy.[4]

Because of the small lesion size, variable anatomical location, and low metabolic rate; conventional imaging of such tumors is often difficult. Computed tomography (CT), ultrasound (US), and magnetic resonance imaging (MRI) are often unable to characterize or sometimes unable to detect such tumors.[5] Therefore, functional imaging plays a crucial role in management of NETs. Somatostatin receptor scintigraphy (SRS) is an important tool for imaging of NETs and has been shown to be superior as compared to other morphological imaging modalities, for the detection of both primary NET and their metastatic lesions in a landmark study by Krenning et al., with more than 1,000 patients.[6] A few years back, novel 68Gallium (68Ga) labeled somatostatin analogues were developed as positron emission tomography (PET) tracers for NETs and have shown

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excellent results. In this review we will discuss the methods and implications of PET with these ^{68}Ga-labeled somatostatin analogues for imaging of NETs and share our experience in this regard [Table 1].

PRINCIPLE OF IMAGING WITH [68]GA-LABELED SOMATOSTATIN ANALOGUES

These ^{68}Ga-labeled somatostatin analogues are generally short peptide analogues of somatostatin which are linked to the positron emitter ^{68}Ga by a bifunctional chelate, usually 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA). The ^{68}Ga-DOTA-peptides bind to the somatostatin receptors (SSTRs) overexpressed on NETs cells. Six different SSTRs have been identified.[7] These are SSTR1, 2A, 2B, 3, 4, and 5. These SSTRs are G-protein coupled transmembrane receptors and are internalized after binding to specific ligand.[7] Among these SSTR2 and 5 are predominantly overexpressed

Table 1: Brief overview of patients who underwent ^{68}Ga-labeled analogue PET/CT for known or suspected NET

	No. (%) of patients
Total number	1,260 (100)
Age (years)	
Mean	42.3±11.9
Range	6–78
Sex	
Male	764 (60.6)
Female	496 (39.4)
Primary tumor site	
GEP-NET	509 (40.3)
Pancreas	171 (13.5)
Stomach	56 (4.4)
Duodenum	68 (5.3)
Jejunum	31 (2.4)
Ileum	98 (7.7)
Colon	28 (2.2)
Rectum	18 (1.4)
Multiple	39 (3)
Bronchopulmonary	85 (6.7)
MTC	127 (10)
Pheochromocytoma	111 (8.8)
Paraganglioma	59 (4.6)
Meningioma	21 (1.6)
Cervix	3 (.02)
Pituitary adenoma	3 (.02)
Larynx	1 (.01)
Paranasal sinus	1 (.01)
Breast	1 (.01)
Prostate	1 (.01)
Ectopic ACTH syndrome	32 (2.5)
Tumor induced osteomalacia	22 (1.7)
Hereditary syndrome	30 (2.3)
MEN 1	10 (0.7)
MEN 2	19 (1.5)
VHL	1 (.01)
Cancer of unknown primary	118 (9.3)
Suspected NET	166 (13.1)

Gallium, PET/CT: Positron emission tomography/computed tomography, NET: Neuroendocrine tumor, GEP: Gastroenteropancreatic, MTC: Medullary thyroid carcinoma, ACTH: Adrenocorticotropic hormone, MEN: Multiple endocrine neoplasia, VHL: Von-Hippel Lindau, [68]Ga=68

in NETs, while normal tissue majorly express SSTR3 and 5. Three major ^{68}Ga-DOTA-peptides are currently available for imaging: ^{68}Ga-DOTA-Phe[1]-Tyr[3]-Octreotide (TOC), ^{68}Ga-DOTA-NaI[3]-Octreotide (NOC), and ^{68}Ga-DOTA-Tyr[3]-Octreotate (TATE). The main difference among these three tracers (DOTA-TOC, DOTA-NOC, and DOTA-TATE) is their variable affinity to SSTR subtypes.[8] All of them can bind to SSTR2 and SSTR5, while only DOTA-NOC shows good affinity for SSTR3.[9] This has clinical implication in the form that a wide spectrum ligand (^{68}Ga-DOTA-NOC) may be preferred for imaging. However, there is currently no evidence of a clinical impact of these differences in SSTR binding affinity, and therefore no preferential use of one compound over the others can be advised.[10]

ADVANTAGES OVER CONVENTIONAL SRS

With the advent of ^{68}Ga-DOTA peptide PET/CT there is a trend toward shifting from conventional scintigraphy to PET/CT. Many studies have already shown the superiority of ^{68}Ga-DOTA peptide PET/CT over conventional SRS for imaging NETs.[11,12] This is because ^{68}Ga-DOTA peptide PET/CT offers several advantages over conventional SRS. Firstly, the synthesis of ^{68}Ga-DOTA peptides is relatively easy and economical, and does not require a cyclotron. On the other hand, the production of ^{111}In-Octreotide requires a cyclotron and is relatively costly. Secondly, PET/CT imaging requires less time than SRS (2 h, instead of the 4 plus 24 h acquisition). Thirdly, the higher spatial resolution of the PET as compared to the single photon emission computed tomography (SPECT) (3-6 mm versus 10-15 mm), providing better visualization of small lesions. Fourthly, ^{68}Ga-DOTA-petides have about ten-fold higher affinity for SSTRs as compared to ^{111}In-Octreotide. Also, the ^{68}Ga-DOTA-NOC has broad spectrum affinity for SSTRs (SSTR2, 3, and 5) as compared to ^{111}In-Octreotide (SSTR2 only). Finally, PET provides the possibility of quantification of the tracer uptake in a given region of interest. This can be achieved by measuring the standardized uptake value (SUVmax) which can be used for response monitoring and prognostication.[13,14]

SYNTHESIS OF [68]GA-LABELED SOMATOSTATIN ANALOGUES

The synthesis process is relatively easy. [68]Ga can be easily eluted from a commercially available [68]Ge/^{68}Ga generator. At our center we have a 30-50 mCi [68]Ge/^{68}Ga generator (Cyclotron Co. Ltd.; Obninsk, Russia). The long half-life of the mother radionuclide [68]Ge (270.8 days) makes it possible to use the generator for approximately 6-12 months depending on use and can be eluted as early as every 3 h.[15] [68]Ga ($T_{1/2}$ = 68 min) is a positron emitter with 89% positron emission and negligible gamma emission (3.2%). For labeling, the [68]Ge/^{68}Ga generator is eluted using 0.1 M HCL. The eluent is loaded onto a cation exchange cartridge to preconcentrate and prepurify (using 80% acetone/0.15 M HCL). Purified ^{68}Ga is then directly eluted with 97.7% acetone/0.05 M HCL into the reaction vial containing

30-50 μg of DOTA-TOC/DOTA-NOC. Synthesis is carried out at approximately 126°C for 10-15 min. This is followed by removal of labeled peptide from unlabeled peptide using reverse phase C-18 column with 400 μl of ethanol. This solution is further diluted with normal saline and passed through 0.22 μm filter to get sterile preparation for injection. Radiolabeling yields of >95% can usually be achieved within 15 min. The radiation exposure to the radiochemist is within limits prescribed.[16] With availability of automated modules the synthesis has become safer.

IMAGING PROTOCOL OF 68GA-LABELED SOMATOSTATIN ANALOGUE PET/CT

Guidelines are available with respect to PET/CT imaging with 68Ga-DOTA-peptides.[17] The discontinuation of somatostatin analogue treatment before PET/CT is desired but not mandatory and has been shown not to influence results.[18] Fasting is not required. The recommended dose of 68Ga-DOTA-peptides is usually 132-222 MBq (4-6 mCi), but should not be less than 100 MBq.[17] PET/CT is acquired 45-60 min post injection, with the general consensus that best images are obtained at 60 min. Images are acquired from skull (must include the pituitary gland) to mid-thigh. Additional views can be taken as and when required. Use of intravenous contrast during CT part of PET/CT is controversial, with few studies advocating their use.[19] At our center we do not routinely use intravenous CT contrast and reserve its use in selected cases. The images are reconstructed using iterative reconstruction using standard protocols.

NORMAL BIODISTRIBUTION AND DOSIMETRY

As 68Ga-DOTA peptide binds to cell surface SSTRs, it is physiologically distributed in organs which normally express high levels of SSTRs.[20] It is important to have knowledge of the physiologic tracer distribution before attempting to interpret the pathologic sites of uptake. Normal tracer uptake is seen in the pituitary, salivary glands, thyroid, liver, spleen, adrenals, pancreas, kidneys, ureters, and bladder [Figure 1]. The spleen shows the highest tracer uptake, while the uptake in liver is usually variable and mild. Uptake in exocrine pancreas is a problem, is variable, and can lead to false positive results.[21] In general, pancreatic uptake similar to liver is usually physiological.[22] Another pitfall is physiological uptake in adrenal glands which might interfere with diagnosis of adrenal NETs. The dosimetry of 68Ga-DOTA-peptides is still under evaluation. The whole body effective dose usually varies between 1.7 and 2.5 × 10^{-2} mSv/MBq and the urinary system receives the highest absorbed dose.[23]

GASTROENTEROPANCREATIC NETS (GEP-NETS)

68Ga-DOTA peptide PET/CT has been shown to be extremely useful for imaging of GEP-NETs. The majority of these tumors contain high number of SSTRs, homogeneously distributed

Figure 1: Maximum intensity projection image of 68Gallium-labeled [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-NaI3-octreotide (68Ga-DOTANOC) positron emission tomography (PET) done in a 45-year-old male after resection of an ileal carcinoid reveals normal radiotracer distribution in pituitary gland, spleen, liver, bilateral adrenal glands, kidneys, ureters, and urinary bladder

throughout the tumor, and expressed at both primary and metastatic sites.[24] The utility of 68Ga-DOTA peptide PET/CT is well-established and can influence many aspects of GEP-NET management including staging patients with already diagnosed NETs, detection of sites of recurrence in patients with treated NETs (restaging), diagnosis of patients suspected of having NET based on clinical features or biochemical evidence of hormone excess, selection of potential candidates for cold somatostatin analogue or peptide receptor radionuclide therapy (PRRT), and monitoring response to therapy in such patients.

Diagnosis, staging and restaging

A recent meta-analysis by Treglia et al., evaluated 16 studies comprising 567 patients with GEP and thoracic NETs.[25] The pooled sensitivity and specificity of 68Ga-DOTA peptide PET or PET/CT in detecting NETs were 93% (95% confidence interval (CI): 91-95%) and 91% (95% CI: 82-97%), respectively, on per patient-based analysis. They advised that this accurate technique should be considered as first-line diagnostic imaging methods in patients with suspicious thoracic and/or GEP NETs. Ambrosini et al., reviewed their experience of imaging GEP-NETs in 1,239 patients.[26] The sensitivity was 92% and specificity was 98% for the detection of NET. The mean SUVmax of positive lesions was 22.8 ± 18.6 (2.2-150.0), reflecting high SSTR expression by GEP-NETs. Our experience has been similar [Figures 2 and 3]. In a prospective analysis of 109 patients done at our center, 68Ga-DOTA-NOC PET/CT has shown a sensitivity and specificity of 78.3 and 92.5% for primary tumor and 97.4 and 100% for metastases, respectively.[27] It changed the management strategy in 21 patients (19%) and supported management decisions in 32 patients (29%). It was better than conventional imaging modality for the detection of both primary tumor ($P < 0.001$) and metastases ($P < 0.0001$). In that study 68Ga-DOTA-NOC PET/CT was superior to conventional imaging for the detection of lymph node ($P < 0.0001$) and
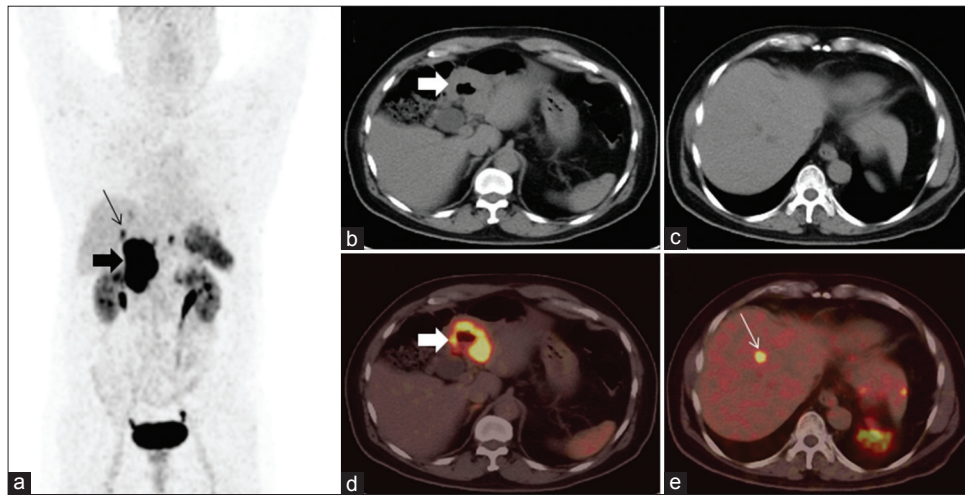
Figure 2: A 60-year-old man, diagnosed case of duodenal carcinoid underwent ⁶⁸Ga-DOTANOC PET/computed tomography (CT) for evaluation of suspected liver metastasis. Maximum intensity projection PET image (a) shows intense tracer uptake in right upper part of abdomen (bold arrow) and focal areas of tracer uptake in liver (arrow). Transaxial images show circumferential duodenal thickening (b and c, bold arrow) with increased tracer uptake. Also noted small foci of increased tracer uptake in liver in PET-CT (E, arrow), with no corresponding lesion on noncontrast CT (d), suspicious for metastasis. This liver lesion was confirmed to be metastatic on contrast CT
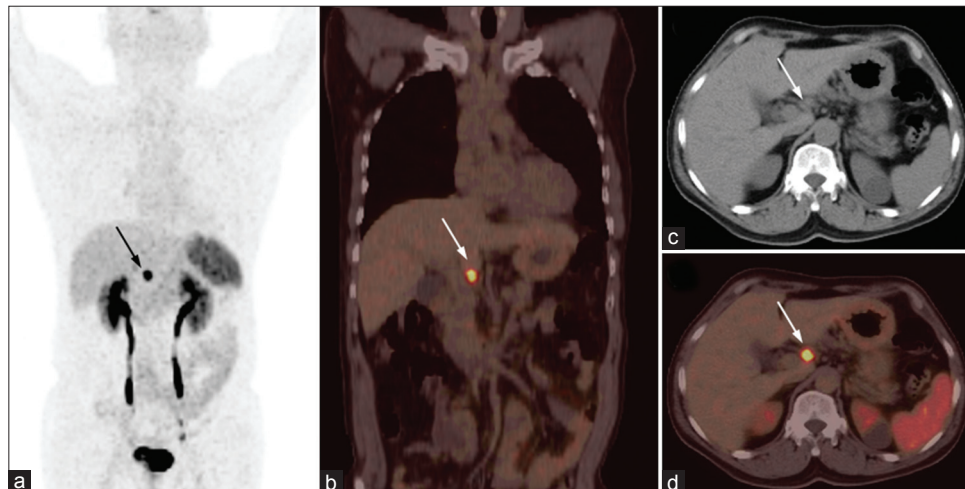

Figure 3: A 50-year-old male, operated case of gastrinoma of stomach, presented with recurrent abdominal pain and raised serum gastrin levels. CT findings were suspicious for recurrence in thickened gastric folds. ⁶⁸Ga-DOTANOC PET/CT was done for restaging. Maximum intensity projection PET image (a) shows a focal area of increased radiotracer uptake in abdomen near midline (arrow), confirmed as positive portal lymph node on PET/CT (b-d, arrow). No abnormal radiotracer uptake was noted in region of stomach

bone ($P = 0.002$), but not liver metastases ($P = 1.000$). These findings were similar to those reported by Putzer *et al.*[28] Kumar *et al.*, from our center prospectively compared ⁶⁸Ga-DOTA-TOC PET/CT and contrast enhanced CT (CECT) for diagnosis and staging of 20 patients with pancreatic NET.[29] The detection rate of CECT was lower than ⁶⁸Ga-DOTA-TOC PET-CT, both for primary tumor (20 vs 15) and metastatic disease (13 vs 7). Another of our studies addressed subgroup of gastrinoma patients with negative or equivocal CECT findings.[30] ⁶⁸Ga-DOTA-NOC PET/CT showed a detection rate of 68% overall, 92.8% in those with equivocal CT findings and 36.4% in those with negative CT. Diagnostic performance of ⁶⁸Ga-DOTA-NOC PET/CT was superior in patients with equivocal CECT findings than that in patients with negative CECT ($P = 0.010$). Frilling *et al.*, have also demonstrated the superiority of ⁶⁸Ga-DOTA-TOC PET/CT over conventional imaging (CT/MRI) in GEP-NETs.[31] In that

series of 52 patients, PET/CT altered the treatment plan in 31 (59.6%) patients.

Suspected NET

An important subgroup of these patients present with clinical, biochemical, or imaging suspicion of NET. In these patients a histopathological diagnosis of NET is still not available. Given the high sensitivity and specificity of ⁶⁸Ga-DOTA-peptide PET/CT in these patients it can be employed to confirm or rule out NET. Ambrosini *et al.*, have shown high sensitivity of 89.5% and specificity of 100% for ⁶⁸Ga-DOTA-NOC PET/CT in patients with clinical/biochemical/radiological suspicion of NET.[32] In that population, increased blood markers and clinical signs/symptoms were associated with the lowest frequency of true-positive findings, highlighting that NETs are frequently suspected but rarely diagnosed. On the contrary, a

positive radiological finding was more commonly associated with positive 68Ga-DOTA-NOC PET/CT. The authors concluded that 68Ga-DOTA-NOC PET/CT in not routinely indicated in patients with clinical/biochemical suspicion of NET. Another similar study by Haug et al., on the contrary, advocated the use of 68Ga-DOTA-TATE PET/CT in these patients.[33] 68Ga-DOTA-TATE PET/CT showed a sensitivity of 81% and specificity of 90% in their study. Our experience is similar. We did a retrospective analysis of 164 patients with suspected NET based on clinical/biochemical/imaging findings. In that series 68Ga-DOTA-NOC PET/CT showed a sensitivity of 94.8% and specificity of 86.5%. The accuracy of PET-CT was 90.4% in patients with clinical signs/symptoms, 86.7% in those with raised biochemical markers, and 92.7% in those with suspicious imaging findings. We must remember the threshold for imaging in patients with suspected NET varies from center to center and hence no definite guideline can be provided at present. However, it appears that in appropriately selected patient population the yield can be high as reported by Haug et al.,[33] and our experience.

Selection of therapy and monitoring response

A major role of 68Ga-DOTA-peptide therapy is selection of patients for SSTR based therapy with cold or radiolabeled somatostatin analogues. In a study by Miederer et al., in 18 patients, 68Ga-DOTA-TOC PET/CT scans were quantified by SUV calculations and correlated to a cell membrane-based SSTR2-immunohistochemistry (IHC) score (0-3).[34] They found that negative IHC scores were consistent with SUV values below 10, and all scores of 2 and 3 specimens corresponded with high SUV values (above 15). This validates the use of 68Ga-DOTA-peptide PET/CT for selection of somatostatin analogues (cold/PRRT) therapy as high uptake is associated with high levels of SSTR expression. The uptake of somatostatin analogues has been shown to be dependent on a number of variables; the most important among these is cellular differentiation.[35] The system proposed for GEP-NETs by the European Neuroendocrine Tumor Society (ENETS) and also now recommended by the World Health Organization (WHO) uses either mitotic rate or Ki-67 labeling index.[36] Ki-67 index is calculated by using MIB-1 monoclonal antibody against the Ki-67 antigen. The MIB-1 labeling index is the fraction of tumor cells that are labeled by Ki-67. Tumors with higher Ki-67 expression are associated with poorer prognosis. Adams et al., have showed a linear relationship between higher proliferative rate (Ki-67) and uptake of the glucose metabolic tracer 18F-Fluorodeoxyglucose (18F-FDG).[37] Such patients with high 18F-FDG uptake, and thus a high Ki-67 index and cellular proliferation will respond poorly to somatostatin analogues but might respond to chemotherapy. A comparison of 68Ga-DOTANOC and 18F-FDG studies done at our center in 26 patients has shown that well-differentiated GEP-NETs with low Ki-67 index have higher tumor uptake, while uptake on 18F-FDG PET is higher in poorly differentiated tumors. Therefore, at our center we routinely perform both 18F-FDG and 68Ga-DOTANOC PET/CT in patients with metastatic NETs as this combination can provide insights into both therapeutic strategy and prognosis. In addition, 68Ga-DOTANOC PET/ CT can also be used for monitoring response to treatment in GEP-NETs, although the results have been variable.[13,38]

Prognosis

The prognostic ability of 68Ga-DOTA-peptides PET/CT results from its inverse association with cellular proliferation.[39] As NET becomes more aggressive, it loses its ability of SSTR expression. Campana et al., have demonstrated the prognostic value of SUV on 68Ga-DOTA-NOC in patients with NET.[14] A SUVmax $\geq$ 19.3 was found to be a significant predictor of survival on multivariate analysis. Haug et al., on the other hand found change in tumor-to-spleen SUV ratio ($\Delta SUV_{T/S}$) to be an independent predictor of progression free survival after PRRT.[13] In their study, $\Delta SUV_{T/S}$ was superior to $\Delta SUVmax$ for prediction of outcome. In our analysis of 40 patients with NETs, we found SUVmax on 68Ga-DOTA-NOC PET/CT and histopathological grades to be significantly associated with progression free survival on multivariate analysis. The SUVmax cutoff obtained in our study was 4, which was less than that reported by Campana et al.[14] Heterogeneity between the patient populations might have caused this difference.

PULMONARY NETS

Pulmonary NETs are second most common site for NETs after GEP-NETs and account for 22-27% of such tumors. The WHO classification of pulmonary NETs classifies these neoplasms in order of increasing malignant potential into typical carcinoids, atypical carcinoids, and large cell and small cell NETs.[40] Most of these are typical carcinoids with metastases in only 15% and a high 5 year survival rate of over 90%.[41] While typical carcinoids are commonly seen in young adults, the less common atypical carcinoids are more frequent in elderly and are more often associated with metastasis.[42] The differentiation of pulmonary NETs is associated with SSTR expression, with better differentiated tumors showing higher SSTR expression.[43] Many studies in the past have explored 68Ga-labeled somatostatin analogue PET/CT in patients with pulmonary NETs, often in conjunction with 18F-FDG. Ambrosini et al., evaluated 68Ga-DOTA-NOC PET/CT in 11 patients with bronchial carcinoid.[44] PET/CT detected at least one lesion in nine of 11 patients and was negative in two. PET/CT and CECT were discordant in eight of 11 patients. On a clinical basis, PET/ CT provided additional information in nine of 11 patients leading to the changes in the clinical management of three of nine patients. Jindal et al., form our center found 68Ga-DOTA-TOC PET/CT to be very useful for detection of pulmonary carcinoids and commented that it can play an important role in management of such tumors.[45] Kayani et al., compared 68Ga-DOTATATE and 18F-FDG PET/CT in 18 patients with pulmonary NET.[46] In that series, typical carcinoids showed significantly higher uptake of 68Ga-DOTA-TATE and significantly less uptake of 18F-FDG than did tumors of higher grade (P = 0.002 and 0.005). In addition, 68Ga-DOTA-TATE was superior to 18F-FDG for discriminating endobronchial tumor from distal collapsed lung. We at our center found similar results. In a prospective study at our center, the

SUVmax in typical carcinoids on ^{68}Ga-DOTA-TOC-PET/CT was significantly higher (SUVmax, 8.8-66) compared with atypical carcinoids (SUVmax, 1.1-18.5; P = 0.002).[47] It appears that different uptake patterns on ^{68}Ga-DOTA-TOC PET/CT and ^{18}F-FDG PET/CT and the ratio of SUVmax may be helpful in differentiating between typical and atypical carcinoids.

METASTATIC NET WITH UNKNOWN PRIMARY

NETs account for about 2-4% of carcinoma of unknown primary site (CUP) and are often mentioned separately because this entity belongs to a treatable subset.[48] Identification of the primary site is of prime importance as many aspects of tumor management are dependent on it, ranging from disease prognosis, treatment outcome, and survival rates. Morphological imaging, though routinely performed, may not be very useful because of their low sensitivity for NETs. Conventional SRS has been explored to detect occult primary sites in patients with metastatic GEP-NETs with a detection rate of 39%.[49] Prasad *et al.*, were the first to evaluate the role of ^{68}Ga-DOTA-NOC PET/CT for CUP-NET.[50] They demonstrated that ^{68}Ga-DOTA-NOC PET-CT was able to localize the primary tumor in 59% of the patients. Moreover, there was change in management in 10% of the patients. The experience from our center is similar [Figure 4]. In a prospective evaluation in 20 patients, we found that ^{68}Ga-DOTANOC PET-CT was able to localize the primary tumor in 12/20 (60%) patients.[51] The most common site of primary was midgut. Even in patients where no primary tumor was localized, additional sites of metastatic disease were observed when compared to conventional imaging, mostly in lymph nodes and bones. There was a change in management in 3/20 patients (15%), who underwent surgery. In the remaining 17 patients, demonstration of SSTR expression by PET-CT made them suitable candidate for PRRT.

MEDULLARY CARCINOMA THYROID

Medullary thyroid carcinoma (MTC) is a NET originating in the parafollicular cells (C cells) of the thyroid, which are derived from the neural crest. MTC secretes calcitonin as well as other polypeptides such as carcinoembryonic antigen (CEA) which can be used as tumor markers. The reported prevalence is 3-12% of thyroid cancers and may occur in either sporadic (75-80% of cases) or inherited forms (20-25%), which include multiple endocrine neoplasia (MEN) types IIA and IIB and isolated familial MTC.[52] Lymph nodes are the most common site of metastases throughout the clinical course[53] followed by bones, liver, and lungs.[54] Surgery remains the primary mode of treatment.[55] Residual/recurrent tumor after surgery is usually suggested by elevated basal serum calcitonin and CEA.[56] Localization of recurrent tumor is extremely difficult even with high resolution morphological imaging and a wide array of radiopharmaceuticals such as ^{99m}Tc (V)-Dimercaptosuccinic acid, ^{99m}Tc-Sestamibi, and $^{131/123}$I-Metaiodobenzylguanidine have been evaluated with variable success.[57,58] ^{18}F-FDG PET/CT has been shown to be a useful imaging tool in such patients, though the results have been variable. A recent meta-analysis by Cheng *et al.*, showed pooled sensitivities of 0.68 (95% CI: 0.64-0.72) for ^{18}FDG PET and 0.69 (95% CI: 0.64-0.74) for ^{18}FDG PET/CT.[59]

MTC cells are also known to express SSTRs owing to their neuroendocrine origin and behavior.[60] Conventional SRS with ^{111}In-pentreotide have been used in MTC with variable success.[61] More recently, PET/CT with ^{68}Ga-DOTA-peptides has been evaluated in MTC [Figure 5]. Conry *et al.*, compared the accuracy of ^{68}Ga-DOTA-TATE and ^{18}F-FDG PET/CT for detection of recurrent MTC and mapping the extent of disease in 18 patients.[62] Per patient based sensitivity of 72.2%
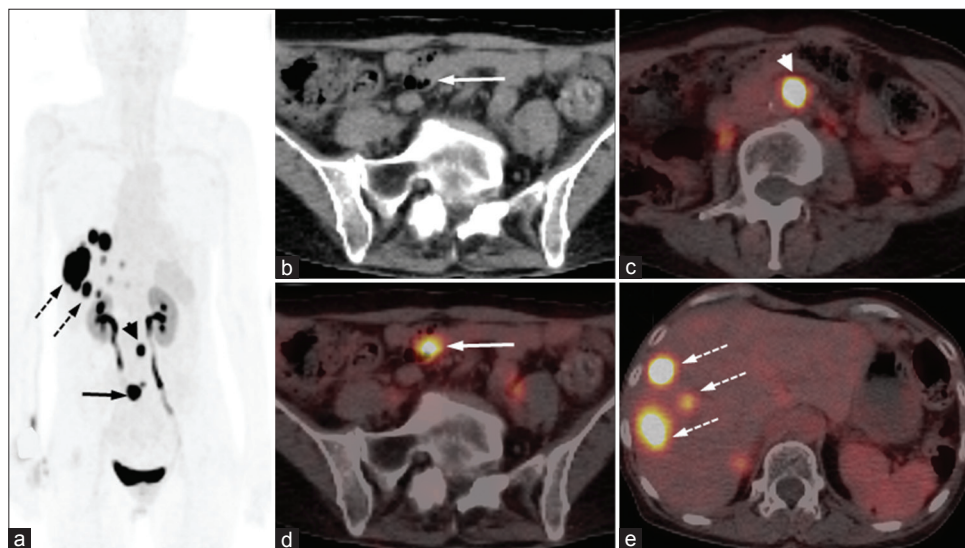

Figure 4: A 35-year-old female presenting with recurrent pain abdomen and multiple hepatic space occupying lesions on ultrasound. Fine needle aspiration cytology from liver lesions demonstrated metastatic neuroendocrine tumor (NET). ^{68}Ga-DOTANOC PET/CT was done to localize the primary. Maximum intensity projections PET image (a) showed multiple liver lesions (broken arrows) along with two discrete foci in abdomen (arrow and arrowhead). Axial CT (b) and PET/CT (c) images of the abdomen revealed focal tracer uptake in ileum with minimal wall thickening (arrow). Also noted are ^{68}Ga-DOTANOC avid retroperitoneal lymph node metastasis (d, arrowhead) and multiple liver metastases (e, broken arrows). The ileal lesion was proven to be carcinoid at histopathology
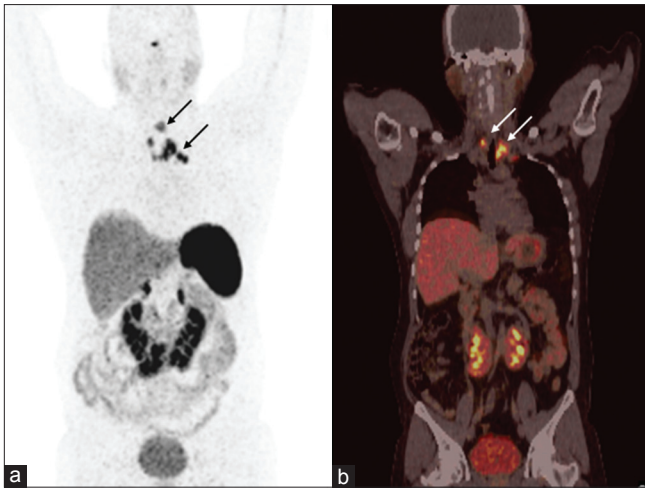
Figure 5: A 31-year-old male with medullary carcinoma thyroid post total thyroidectomy, central neck dissection, and right side radical neck dissection. He presented with rising calcitonin level. 68Ga-DOTANOC PET/CT was done for restaging. Maximum intensity projection PET image (a) revealed presence of multiple focal areas of increased radiotracer uptake (arrows) in cervical and high mediastinal region, confirmed as SSTR positive cervical and high mediastinal lymph nodes on PET/CT (b, arrows). Resurgery confirmed the diagnosis. In addition, horseshoe kidney was incidentally detected on PET/CT

for 68Ga-DOTA-TATE versus 77.8% for 18F-FDG PET/CT was seen and the difference was not significant. While 18F-FDG PET/CT detected more lesions, in 10 patients a discordant tracer pattern of per-region and/or per-lesion distribution of recurrent disease was observed. The authors concluded that the role of two tracers is complimentary. We have prospectively compared 68Ga-DOTA-NOC and 18F-FDG PET/CT in 41 patients with recurrent MTC.[63] In our study, 68Ga-DOTA-NOC PET/CT proved superior to 18F-FDG PET-CT with a higher sensitivity (75.61 vs 63.4%). However, the difference was not statistically significant ($P = 0.179$). 68Ga-DOTA-NOC PET/CT was superior to 18F-FDG PET-CT for detecting recurrence in cervical lymph nodes ($P < 0.001$), but not for other sites. Discordance was observed in 25% patients between the two imaging agents, mainly for lymph nodal lesions. Although, no cutoff for serum calcitonin could be obtained for disease detection on PET/CT, values > 500 pg/ml was more commonly associated with distant metastasis. At present it appears wise to evaluate patients with recurrent MTC using dual tracers (68Ga-DOTA-NOC and 18F-FDG) and their role appears complimentary in such patients.[64] There is small difference between our study and that by Conry et al.,[62] which might be because of the different receptor affinity profile of tracers used. 68Ga-DOTA-NOC has an affinity profile for broader SSTR subtypes: SSTR2, SSTR3, and SSTR5; whereas 68Ga-DOTA-TATE is more active at SSTR2 and SSTR3.[9]

PHEOCHROMOCYTOMA/PARAGANGLIOMA

Paragangliomas are tumors that develop from endocrine cells derived from pluripotent neural crest stem cells and are associated with neurons of the autonomic nervous system. Those developing from adrenal medulla are most common (~90%)

and called pheochromocytoma.[64] Pheochromocytomas are a feature of certain disorders with an autosomal dominant pattern of inheritance (e.g. MEN2) in about one-fourth of unselected cases.[65] They are rare (~1%), but treatable cause of hypertension. About 10-20% of these tumors are malignant. Paragangliomas may also arise anywhere from the sympathetic nervous system or the parasympathetic nervous system. While those arising from sympathetic nervous system (abdominothoracic paraganglioma) are frequently associated with catecholamine overproduction, those arising from parasympathetic system (head and neck paraganglioma) rarely do so.[66] Paragangliomas are familial in 9% cases.[67] They can be multicentric in 10% sporadic cases and 32% of familial cases.[68] Precise localization of these tumors is mandatory for management as surgery is the mainstay of treatment.

The diagnosis of pheochromocytoma is established biochemically by measuring the level of urinary and plasma catecholamines and their metabolites (24-h total metanephrine and/or catecholamine).[69] Imaging is important for the localization of tumor and excluding possibility of multifocal lesions before surgery. CT or MRI provide excellent morphologic details and have high sensitivity in the depiction of pheochromocytoma, but their specificity is low. 123/131 I-Metaiodobenzylguanidine (MIBG) scintigraphy is currently the functional imaging method of choice for the localization of pheochromocytomas and paragangliomas. It provides high sensitivity and specificity, but is not without limitations.[70] From in vitro and in vivo studies, it has been established that SSTR 2, 3, and 4 are expressed in pheochromocytoma and paraganglioma.[71] Usually the expression of SSTR receptors is increased in malignant pheochromocytomas and paragangliomas.[72] Previous studies with 111In-Octerotide have shown higher sensitivity for detecting metastatic pheochromocytoma than for detecting benign pheochromocytoma, but the overall sensitivity remains low (~30%).[72] Limited literature is available with respect to 68Ga-DOTA-peptide imaging in pheochromocytoma and paraganglioma, majority from our center. Win et al., compared 68Ga-DOTA-TATE PET with 123I-MIBG in five patients with pheochromocytoma and showed that 68Ga-DOTA-TATE PET showed more lesions, with higher uptake and better resolution.[73] Maurice et al., compared 68Ga-DOTA-TATE PET with 123I-MIBG in 15 patients with pheochromocytoma/paraganglioma.[74] They recommended that 68Ga-DOTA-TATE PET should be used as the first line investigation for paraganglioma and metastatic disease. In the largest study till date, Naswa et al., from our center showed the superiority of 68Ga-DOTA-NOC PET/CT over 131I-MIBG in 35 patients with pheochromocytoma/paraganglioma.[75] 68Ga-DOTA-NOC PET/CT showed a diagnostic accuracy of 97.1% on per-patient and 98% on lesion-wise analysis [Figure 6]. No significant relationship was however observed between the degree of tracer uptake (SUVmax) and lesion size and no difference was seen between adrenal and extra-adrenal lesions. A combination of 68Ga-DOTA-NOC PET/CT and 18F-FDG PET/CT is able to preoperatively characterize indeterminate adrenal masses.[76]

Naswa et al., have also shown the utility of 68Ga-DOTA-NOC PET/CT for imaging of carotid body chemodectoma, by demonstrating additional lesions or metastasis.[77] A recent study by Sharma et al., from our center has shown the superiority of 68Ga-DOTA-NOC PET/CT over conventional imaging (CT/MRI) and 131I-MIBG in head and neck paraganglioma.[78] In that series of 26 patients, 68Ga-DOTA-NOC PET/CT showed more lesions as compared to 131I-MIBG ($P < 0.0001$) and conventional imaging ($P = 0.015$). More importantly, a combination of CT/MRI and 131I-MIBG scintigraphy detected only 53/78 (67.9%) lesions and was also inferior to PET/CT ($P < 0.0001$). Other PET tracers like 18F-FDG, 18F-FDOPA, and 11C-hyroxyephidrine have been evaluated with variable results in pheochromocytoma/

Figure 6: A 28-year-old male with uncontrolled hypertension and left adrenal mass. Urinary metanephrine was mildly elevated. He underwent 68Ga-DOTANOC PET/CT for characterization of the adrenal mass. MIP PET image (a) show intense tracer uptake in left suprarenal region (arrow). Transaxial CT (b) and PET/CT (c) images showed increased tracer uptake in the large left suprarenal mass with central necrosis (arrow) suggesting pheochromocytoma. Postoperative histopathology confirmed pheochromocytoma

paraganglioma and their role viz-à-viz 68Ga-DOTA-peptides needs to be evaluated.[79]

HEREDITARY SYNDROMES WITH NET

A wide variety of hereditary syndromes can present with NET. These include MEN syndromes (1 and 2), familial paraganglioma syndrome, von-Hippel Lindau (VHL) syndrome, succinate dehydrogenase (SDH) mutation, and neurofibromatosis type 1. MEN 1 syndrome is the most common and GEP-NETs are often associated. They are usually functional and commonly include gastrinomas (60%) and insulinomas (10%), although carcinoid tumors are also known to occur.[80] MEN2 syndrome on other hand is associated with MTC and pheochromocytoma.[81] As most of these tumors express SSTRs, 68Ga-DOTA-peptide PET/CT can play an important role in management of these disorders. Froeling et al., evaluated and reported the utility of 68Ga-DOTA-TOC PET/CT in 21 patients with MEN1 syndrome.[82] PET/CT was superior to contrast CT for detection of NET lesions ($P < 0.001$) and impacted therapeutic strategy in almost half of the patients. Our experience is similar [Figure 7]. It appears to be especially useful in asymptomatic relatives of index patients. Further evaluation of 68Ga-DOTA-peptides in these hereditary syndromes is warranted.

OTHER NETS

68Ga-DOTA-peptide PET/CT has been shown to be useful for a wide range of other rare tumors of neuroendocrine origin. These include pituitary adenoma, hemangioblastoma, meningioma, melanoma, and others.[83-86] It has also been employed for locating the primary tumor in patients with tumor induced osteomalacia and ectopic adrenocorticotropic hormone (ACTH) producing tumors. A recent study by Clifton-Bligh et al., have shown the utility of 68Ga-DOTA-TATE PET/CT imaging in six patients
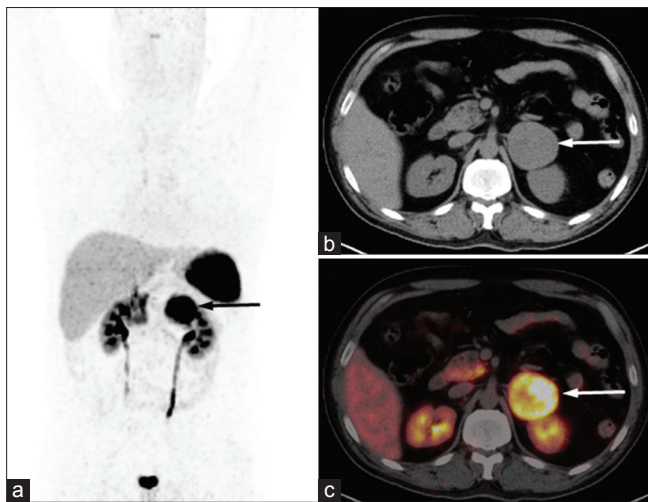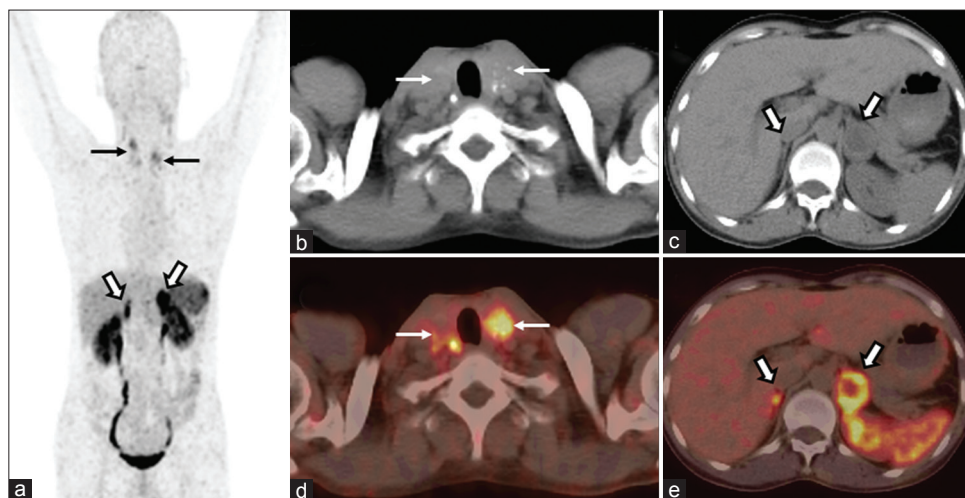

Figure 7: A 35-year-old man, suspected case of MEN 2A syndrome, with known bilateral adrenal masses and cervical lymphadenopathy underwent 68Ga-DOTANOC PET/CT for characterization of the lesions. MIP PET (a) image shows intense tracer uptake in bilateral cervical (arrows) and adrenal regions (bold arrows). Transaxial CT (b) and PET/CT (c) images showed increased tracer uptake in the bilateral calcified thyroid masses (bold arrows). Also noted were bilateral adrenal masses with increased tracer uptake (d and e, arrows). The diagnosis of MEN 2A was confirmed on genetic analysis

with tumor induced osteomalacia.[87] Our experience is similar, with PET/CT being able to show culprit tumor in a significant proportion of these patients. No systemic study is available regarding utility of 68Ga-DOTA-peptide PET/CT in ectopic ACTH producing tumor. Results from our center have also not been too encouraging. Only four of our patients (of 32) so far have shown localization (lungs in three patients, pancreas in one). Further studies are required in future addressing these tumors.

CONCLUSION

68Ga-labeled somatostatin analogue PET/CT has emerged as an important imaging tool for NET. It can influence many aspects of management of such tumors and has the potential to be the first-line imaging investigation for their evaluation, especially for GEP-NETs.

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