Gallium-68-dotatate PET/CT is better than CT in the management of somatostatin expressing tumors: First experience in Africa

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Abstract

Objectives: In this study we aimed to present our experience on the use of Gallium-68-dotatate with positron emission tomography, computed tomography (^{68}Ga-dotatate PET/CT) in the management of neuroendocrine tumors (NET) and other somatostatin expressing tumors. **Subjects and Methods:** We retrospectively reviewed patients with histologically confirmed or biochemically suspected NET and other somatostatin expressing (SSTR) tumors imaged at our department with ^{68}Ga-dotatate PET/CT. We determined the performance of this imaging technique as well as its impact on patients management. A total of 203 patients were studied: 103 females, 100 males median age 52years. **Results:** The commonest tumor type was gastroenteropancreatic NET (41% of patients) and the commonest sites of distant metastases were lymph nodes and the liver 34.0% and 30.5% respectively. Positron emission tomography detected foci of disease in 19 patients where CT was falsely negative. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of ^{68}Ga-dotatate PET/CT imaging of NET and other SST expressing tumors were 94.16%, 91.89%, 95.55%, 89.47% and 96.55% respectively. **Conclusion:** Gallium-68-dotatate PET/CT was better than CT in detecting primary sites of the disease and highly sensitive and specific for diagnosis and treatment of NET and other SSTR expressing tumors.

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Introduction

Neuroendocrine tumors (NET) are a diverse group of slow growing tumors that overexpress the somatostatin receptors (SSTR). They derive from the ectodermal neural crest cells [1]. The wide dispersal of the neural crest cells explains the ubiquity of NET affecting almost all organs of the body. Neuroendocrine tumors have been traditionally described as rare tumors with an incidence of 2.5-5/100,000 in the US [2]. However, their incidence has been on the increase in most regions of the world over the course of the last four decades [3]. This has been largely attributed to increase in the rate of disease detection [4]. In the US, the age-adjusted incidence of gastroenteropancreatic NET increased from 1.00 to 3.65 between the years 2003 and 2007 [5]. In the UK, a rise in the incidence of gastrointestinal NET of 4.8 in males and of 3.8 in females was reported in the years between the 1970 and early 2000 [6]. Similar rise has been reported in other parts of the world [3]. Neuroendocrine tumors are generally less agressive compared to tumors of other histologies of the same organ [7].

Neuroendocrine tumors can be described as secretory or non-secretory tumors. The secretory NET produce different vasoactive peptides owing to their ability to take up amines precursors and decarboxylate them. They therefore become symptomatic even when they are quite small and their localization during imaging is challenging. Conversely, non-secretory NET may remain undetectable until they are advanced or widely metastatic or as a result of pressure symptoms or complications.

Functional imaging with nuclear medicine techniques have studied the overexpression of SSTR tumors as well as their ability to uptake amines [8] and is useful in localizing initial staging or re-staging following treatment and in selecting patients for peptide receptor radionuclide therapy (PRRT) [9].

Somatostatin analogue imaging of NET and other SSTR tumors is done using gallium-68 datatate in positron emission tomography/computed tomography (^{68}Ga-dotatate PET/CT) imaging. Dotatate is an acronym where dota stands for 1, 4, 7, 10 tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid which is a bi-functional chelator that binds an analogue of octreotide (D-Phe^{1}-Tyr^{3}-Thr^{8}-octrotide)) to the radionuclide gallium-68. Tate

stands for D-Phe[1]-Tyr[3]-Thr[8]-octrotide which is a synthetic analogue of somatostatin. This radiopharmaceutical used in PET imaging performs better than anatomic imaging only with CT or magnetic resonance imaging (MRI) [10-12]. Traditionally, functional imaging of NET uses single photon emission tomography (SPET) technique with indium-111 conjugated with diethyl triamine penta-acetic acid to octreotide (^{111}In-DTPA-octreotide) or radioiodine-123 or -131 labeled metaiodobenzylguanidine (^{123,131}I-MIBG) [13-15]. ^{68}Ga-dotatate PET/CT imaging has however been shown to outperform SPET imaging [16] as the imaging modality of choice in the management of NET leading to change in patient management in up to 81% of patients [17, 18].

The aim of this study was to report our experience on using ^{68}Ga-dotatate PET/CT scans in the management of patients with NET and other SSTR tumors. To the best of our knowledge, this is the first such study reported from Africa.

Subjects and Methods

This was a retrospective study of ^{68}Ga-dotatate PET/CT imaging done in patients with NET and other SSTR tumors grades I and II between November 2011 and February 2017 carried out in the Department of Nuclear Medicine, Steve Biko Academic Hospital, Pretoria, South Africa.

Dotatate was mixed with ^{68}Ga to prepare the radiopharmaceutical and was administered intravenously (i.v.) in a dose of 150 to 250MBq with purity greater than 95% [19]. Concentration of dotatate injected varied from 20μg to 50 μg. Patients on treatment with short or with long acting somatostatin analogues discontinued their medication for 24 hours or for 3 to 4 weeks prior to imaging.

Gallium-68-dotatate PET/CT scan was performed according to European Association of Nuclear Medicine guidelines [20]. Imaging was acquired on a Biograph 40 TruePoint PET/CT scanner (Siemens Medical Solution, Illinois, USA). Whole-body (vertex to mid-thigh) CT imaging commenced after about 65 min. (range: 55 to 70min). Thirty mL of gastrografin (Bayers, Isando, South Africa) in 1 liter of water was given orally over 1 hour prior to imaging. For an intravenous contrast agent, 100mL of Omnipaque (GE Healthcare, Wisconsin, USA) which contains 350mg of iodine was given. PET scan was acquired in 3D-mode with acquisition time of 4min per bed position. Computed tomography data were used for attenuation correction. Image reconstruction was done with iterative reconstruction algorithm. No side effects were noticed.

Image interpretation

Reconstructed images were displayed on a workstation equipped with syngo, image processing software (Siemens Medical Solutions, Illinois, USA). Reconstructed axial, coronal and sagittal images were viewed as PET, CT and fused PET/CT images. Areas of abnormally increased tracer accumulation were considered as positive for the presence of SSTR tumors and were correlated with the CT images. Areas of disparity between PET and CT findings were noted. Findings on PET/CT images were compared with the pre-imaging treatment plan. Image interpretation was done by two experienced nuclear medicine physicians. Areas of disagreement were resolved by a third physician. Presence or absence of malignant disease was determined by biopsy and histological examination and disease progression by imaging. Positron emission tomography findings were considered as true positive, if histologically confirmed as SSTR tumors or if their size and tracer uptake increased on the subsequent images. Findings were considered as false positive when there was ^{68}Ga-dotatate uptake in inflammatory changes. Unequivocal CT lesions but histologically positive for SSTR were considered as false negative.

Statistical analysis

Descriptive data were presented as mean±standard deviation (M±SD) when normally distributed and as median (range) for skewed data. Categorical data were presented as frequency (percentage). A two by two table was used to determine sensitivity and specificity of the ^{68}Ga-dotatate PET/CT scan. The number of patients in which imaging led to upstage of disease and to change in treatment was expressed.

Results

A total of 203 patients were included in this study, females: 103 (50.7%), males: 100 (49.3%), mean age: 49.31±18.70. Mid-gut SSTR tumors were the commonest tumour subtype 39 patients, 19.2%.

Image findings by histology were confirmed in 107 patients (52.70%). Follow-up imaging was used as gold standard in 96 patients (47.30%).

In total, there were 129 true positive cases, 68 true negative, 6 false positive and 8 false negative cases. Overall sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 94.16%, 91.89%, 95.55%, 89.47% and 96.55%, respectively.

The ^{68}Ga-dotatate PET/CT study was most often performed for re-staging of the disease in patients treated before. Table 1 shows the detailed demographics as well as histopathological characteristics of the patients. A total of 68 patients (33.50%) were scanned for restaging by ^{68}Ga-dotatate PET/CT imaging: 26 to evaluate the completeness of surgical resection, 28 to evaluate the response to PRRT with lutetium-177 (^{177}Lu)-dotatate and 14 to evaluate response to other forms of treatments including chemotherapy and radiotherapy.

Of all 203 patients, 129 had metastases, with 81 patients (63%) having five or more sites of malignant disease. Lymph nodes and liver were the commonest sites of distant metastatic spread detected in almost half of the study population. Table 2 shows the detailed findings of PET/CT imaging.

Positron emission tomography outperformed contrast enhanced CT in 19 patients (9.4%) by detecting lesions not detected by CT. The liver and the pancreas were the commo-

Table 1. *Demographic and pathology data of the 203 patients*

Variable	Frequency (N=203)	Percent
Age (years)		
Mean±SD	49.31±18.70	
Median (range)	52.00 (1.00 – 87.00)	
Gender		
Male	100	49.26
Female	103	50.74
Type of Tumour		
Foregut NET	14	6.70
Midgut NET	39	19.21
Hindgut NET	8	3.94
Bronchial Carcinoid	11	5.41
Pancreatic NET	23	11.33
Metastatic carcinoid primary unknown	15	7.39
Biochemically suspected carcinoid tumour	30	14.78
Pheochromocytoma/ Paraganglioma	21	10.34
Neuroblastoma	5	2.46
Biochemically suspected pheochromocytoma	11	5.41
Medullary thyroid carcinoma	6	3.00
Ovarian NET	3	1.48
NET of the cervix	3	1.48
NET of the breast	2	0.99
Merkel cell carcinoma	2	0.99
Oncogenic osteomalacia	2	0.99
Meningioma	1	0.49
Medulloblastoma	1	0.49
NET of the parotid gland	1	0.49
NET of the larynx	1	0.49
Dedifferentiated papillary thyroid carcinoma	1	0.49
NET of the thymus	1	0.49
Rosai-Dorfman disease	1	0.49
Indications		
Initial Staging	49	24.14
Re-staging	68	33.50
Evaluate suitability for PRRT	16	7.88
Recurrence	14	6.90
Localize primary site of tumour	56	27.59

SD,standarddeviation;NET,Neuroendocrinetumour;PRRT,Peptide receptorradionuclidetherapy

nest sites of falsely negative CT scan. Figure 1 shows the distribution of false negative CT findings.

In nine out of the 49 patients imaged for initial staging of the disease, ^{68}Ga-dotatate PET/CT detected additional sites of disease leading to up-staging of the disease. In 20 other patients there was only one site of disease, so that surgical resection was a possible treatment. On the whole, management was altered in 29 patients (14.3%). The primary tumor was localized in 11 cases. Figure 2 shows the yield of positive imaging in localizing NET.

Galium-68-dotatate PET/CT demonstrated 100% sensitivity and specificity in localizing oncogenic osteomalacia but failed to localize iodine refractory papillary thyroid cancer.

Table 2. Image findings on ^{68}Ga dotatate PET/CT scans

Variable	Analogy (N=203)
Number of lesions on positive scans (n = 129) (%)	
1	20(16)
2	13(10)
3	11(9)
4	4(3)
≥5	81(13)
Site of metastases on positive scans	
Lymph node	69
Liver	62
Bone	30
Lung	13
Pancreas	7
Peritoneum	5
Brain	4
Adrenal gland	4
Bowel	3
Thyroid	1
Prostate	1
Type of gold standard (%)	
Histology	107 (53)
Follow-up	96 (49)

Discussion

In our study gastroenteropancreatic NET was by far the commonest tumor type accounting for 41% of our study population (84/203) with the mid-gut being the commonest site of primary tumor in this subpopulation (39/84) [22, 23].

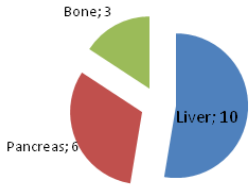

Figure 1. Distribution of organs with true positive findings on PET images but false negative CT findings.

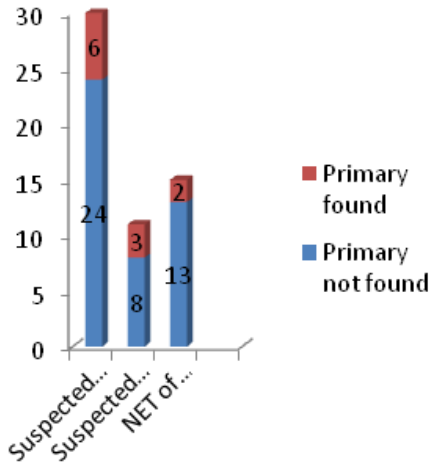

Figure 2. The yield of ^{68}Ga-dotatate PET/CT in identifying the site of primary lesions among 56 patients with biochemical suspicion or of unknown NET primary.

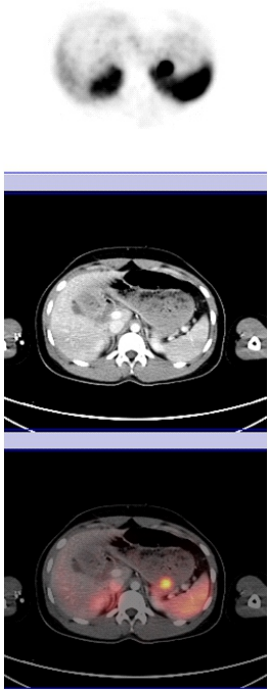

Figure 3. A 24 years old female with persistent symptomatic hypoglycemia associated with hyperinsulinaemia. ^{68}Ga-dotatate PET/CT scan done to localize possible insulinoma showed a polypoid arising from the posterior wall of the stomach and protruding into its lumen. Histological examination confirmed the diagnosis of insulinoma.

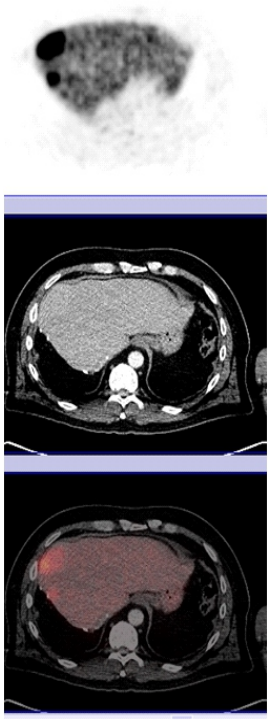

Figure 4. A 64 years old male with metastatic pancreatic neuroendocrine tumor. Axial PET/DET/CT and fused PET/CT images through the upper abdomen are shown. Two foci of liver metastases are seen on the PET image. No corresponding morphologic abnormality is seen in the CT image.

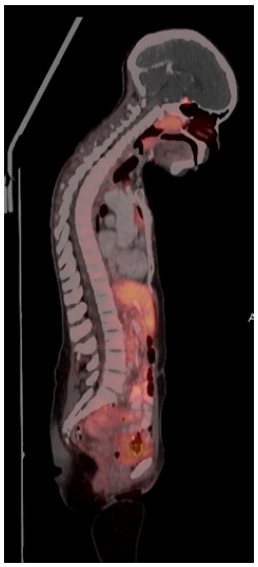

Figure 5. False positive findings in a 34 years old HIV positive female with severe hypertension associated with elevated urinary vanilmandelic acid and homovanilic acid. She was evaluated with ^{68}Ga-dotatate on suspicion of possible pheochromocytoma/paraganglioma. Sagittal fused PET/CT image shows two pharyngeal masses with avidity for ^{68}Ga-dotatate. Histological examination showed features consistent with pyogenic granuloma.

There were 26 patients (12.8%) with tumors of the sympathetic-adrenal axis (pheochromocytomas/paragangliomas: 21, neuroblastomas: 5). These tumors have traditionally been imaged and treated by ^{131}I-MIBG. Recent studies have however demonstrated better diagnostic accuracy with ^{68}Ga-labeled peptides [24, 25].

The primary site of disease was found in 11/56 unknown or doubtful sites (19.6%). This low yield has similarly been reported in other studies [26].

Analysis of images showed findings not demonstrated on contrast enhanced CT (Figures 1, 4). This is in accord with previous reports that have demonstrated the superiority of ^{68}Ga-dotatate PET/CT and other ^{68}Ga-labeled peptides over anatomic imaging in the evaluation of NET [12, 29]. Another study also reported the superiority of ^{68}Ga-dotatate PET/CT over enhanced CT [12]. Another study with limited population showed that, ^{68}Ga-dotatate detected more lesions compared to anatomic CT or MRI imaging [29].

Imaging with ^{68}Ga-dotatate PET/CT led to up-staging of disease in 9 patients and in 9% of patients PET demonstrated lesions not seen on CT. Imaging impacted on management in 29/203 patients (14.8%). This finding is much lower than what is reported in the literature (47% to 81%) [17, 18, 30, 31]. This lower impact is likely to have resulted from the large proportion of our patients with known distant metastases at the time of imaging. Almost 63% of all patients with positive scan findings in our study population had five or more lesions detected on imaging. Finding additional sites of disease involvement is unlikely to lead to a change in the stage of disease or have an impact on management to any significant proportion in this setting.

All 6 cases of false positive findings were due to tracer uptake in inflammatory lesions (Figure 5). The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of ^{68}Ga-dotatate demonstrated in our study are comparable to what have been previously reported [21, 23, 32].

In conclusion, PET imaging with ^{68}Ga-dotatate has a sensitivity, specificity, positive predictive value, negative predictive and accuracy of 94.16%, 91.89%, 95.55%, 89.47% and 96. 55%, respectively. Out of 56 patients with unknown sites of primary disease we detected using 68Ga-dotatate PET/CT scan primary tumor NET sites in 19.6%. Widespread metastases were found in 63% of which 40% had 5 or more metastases. Primary NET tumors were by 9% better diagnosed by the ^{68}Ga-dotate PET scan than by CT.

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The authors of this study declare no conflict of interest

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DEPARTEMENT OF ERRORS

In the paper under the title: "An ultrasound image navigation robotic prostate brachytherapy system based on US to MRI deformable image registration method", published in the 3rd issue of 2016, on pages 223-230, the correct formulas (number 1 to 5 and number 8 to 11) are as follows:

$$\min \sum_{i=1}^{n} \left\| p_{P,i} - {}^{P}M_{Q} \cdot p_{Q,i} \right\|^2 \quad (1), \qquad \min \sum_{i=1}^{n} \left\| {}^{\text{inn}}p'_{\text{mod}i} - M_{\text{inn}} \cdot {}^{\text{inn}}p_{\text{mod}i} \right\|^2 \quad (2), \qquad {}^{\text{add}}p'_{\text{mod}} = M_{\text{inn}}\, {}^{\text{add}}p_{\_\text{ar}} \quad (3), \qquad \min \sum_{i=0}^{n} \left\| {}^{\text{add}}p'_{\text{mod}i} - M_{\text{add}} \cdot {}^{\text{add}}p_{\text{mod}i} \right\|^2 \quad (4),$$

$$\text{MCC}(X,Y) = \sup_{f,g\ V} \text{CC}(f(X), g(Y'') \quad (5), \qquad S_u^f = \sum_{i=1}^{m} \alpha_i K_\delta(S_u(x), \xi_i'), T^g(x) = \sum_{i=1}^{m} \beta_i K_\delta(T(x), \eta_i') \quad (8), \qquad \text{MCC}(S_u, T) = \sup_{f,g} \text{CC}(S_u^f, T^g) \quad (9),$$

$$\min_{u,\alpha,\beta} \lambda \int_{\Omega} |\nabla u(x)|^2 dx + |\Omega|(1 - \text{MCC}(S_u, T))^p \quad (10), \qquad \text{TRE} = \sqrt{\frac{1}{N} \sum_{i=1}^{N} \|P_{MRi} - P_{USi}\|^2} \quad (11)$$