Gallium-68 dotatate PET/CT is superior to other imaging modalities in the detection of medullary carcinoma of the thyroid in the presence of high serum calcitonin

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Abstract

Objective: Medullary carcinoma of the thyroid (MTC) is a rare neuroendocrine tumour (NET) that expresses somatostatin receptors on the cell membrane and secretes calcitonin. Surgery is the primary curative modality but is achieved only when the diagnosis is timely so there is a high rate of persistent and recurrent disease indicated by a rise in the serum calcitonin levels. Successful management of recurrent disease requires accurate localisation with cross sectional and functional imaging. The introduction of gallium-68-Dotatate (^{68}Ga-Dotatate) peptides positron emission tomography/computerized tomography (PET/CT) has significantly improved the detection of NET and has been reported as a valuable adjunct in MTC localisation. We retrospectively reviewed our cases of MTC to correlate the detectability of ^{68}Ga-Dotatate in relation to calcitonin levels and assess suitability of inoperable patients for peptide receptor radionuclide therapy (PRRT). **Subjects and methods**: Seven patients (age range 31-66 years, M:F 3:4) with raised calcitonin (mean=7,143pg/mL) were referred for ^{68}Ga-Dotatate PET/CT scan for localisation of persisting recurrent MTC. Six patients were known to have MTC treated with thyroidectomy and one patient was presenting for the first time. All patients had multiple imaging including ultrasound (US), CT, magnetic resonance imaging (MRI), fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT and iodine-123-metaiodobenzylguanidine (^{123}I-MIBG). Positive findings were defined as areas of increased uptake other than the organs of normal distribution and were correlated with results of biopsies, other imaging, long term monitoring of calcitonin and clinical follow-up. **Results**: In 6/7 patients with very high serum calcitonin (range= 672-37,180, mean=8,320pg/mL) ^{68}Ga-Dotatate PET/CT confirmed the presence of active disease seen on other modalities or detected hitherto unsuspected lesions. In at least 3 cases, ^{68}Ga-Dotatate PET/CT showed many more lesions compared to other imaging combined. In 1/7 patient ^{68}Ga-Dotatate PET/CT was negative in line with a relatively low calcitonin level (80pg/mL) and negative disease on fine needle aspiration. **Conclusion**: ^{68}Ga-Dotatate PET/CT is an effective tool for localising metastatic spread of MTC. It appears to be most effective in the presence of higher levels of serum calcitonin, probably in excess of 500pg/mL. The results of our small cohort had an impact on staging and management with the introduction of peptide receptor radionuclide therapy for inoperable disease.

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Introduction

Medullary carcinoma of the thyroid (MTC) is a rare neuroendocrine tumour (NET) which originates from parafollicular cells, and produces calcitonin. Medullary thyroid carcinoma may occur in sporadic (75%) or hereditary (25%) forms, the latter is associated with rare but fascinating syndromes such as Multiple Endocrine Neoplasia 2A, familial MTC and Multiple Endocrine Neoplasia 2B. Medullary thyroid carcinoma is commonly associated with mutations in the rearranged during transfection (RET) proto-oncogene, which was discovered in 1985 [1]. Like other NET, MTC expresses human somatostatin receptors (hSSTR) on their cell membrane. There are five human somatostatin receptors (hSSTR1-5), of which hSSTR2 is most commonly expressed in NET including MTC [2].

Though rare, MTC is a medically challenging malignancy that has a high recurrence rate of up to 50% [3]. Calcitonin level measurements are invaluable in the follow-up of patients with MTC, and reflect the volume of disease present but does not localise the site of the recurrent or metastasized disease. Selective venous catheterisation is useful in locating the site of disease but its invasiveness is a limiting factor [4]. Imaging remains

the main aid of localising recurrent MTC in general practice and the American Thyroid Association (ATA) recommends a neck US if serum calcitonin is <150pg/mL. If the level is >150pg/mL, other imaging modalities may be employed since the sensitivity of detecting a larger or functionally more active tumour improves [5]. This involves the use of a combination of modalities, including ultrasound (US), computerised tomography (CT) and magnetic resonance imaging (MRI). Nuclear medicine procedures are mandatory in outlining the functional status of these lesions. Current functional imaging include planar imaging and single photon emission tomography (SPET) with iodine-123 labelled metaiodobenzylguanidine (^{123}I-MIBG) and positron emission tomography (PET) imaging with ^{18}F-fluorodeoxyglucose (^{18}F-FDG). Technetium-99m-pentavalent dimercaptosuccinic acid (^{99}mTc-DMSA-V) and indium-111-octreotide (^{111}In-Octreotide) are less commonly used due to reduced sensitivity and unavailability [6-9].

Despite the combined use of various imaging techniques, recurrence is only detected in 40% of cases [7]. Surgery is the primary curative modality but is achieved only when the diagnosis is timely, and therefore early localisation is crucial in patient management.

The recent introduction of gallium-68 (^{68}Ga) labelled somatostatin analogue peptides (Dotatate, Dotatoc and Dotanoc) in PET/CT imaging has been regarded as a major step in the detection and localisation of NET. The combination of PET imaging with ^{68}Ga, with its improved resolution, and the high affinity of the new generation of DOTA peptides to various hSSTR, particularly hSSTR2, has been shown to significantly improve the sensitivity of this technique [10-12].

The successful imaging of NET is exploited through their increased expression of somatostatin receptors, and ^{68}Ga-Dotatate PET/CT imaging has been shown to be more sensitive than other imaging modalities such as octreotide scans, ^{123}I-MIBG scintigraphy and conventional imaging [11] as well as ^{18}F-FDG PET/CT in the imaging of well-differentiated NET [13]. Furthermore, other groups have shown that ^{68}Ga peptides PET/CT are useful in detecting recurrent MTC [14-18] with the prospect of offering peptide receptor radionuclide therapy (PRRT) to inoperable disease that shows good uptake on ^{68}Ga peptides PET/CT [19].

Our aim was to review our cases of MTC and correlate our ^{68}Ga-Dotatate PET/CT detection rate with serum calcitonin levels and to assess if our improved detection rate fits in with the ATA's management guidelines for MTC [5]. Our secondary aim was to select patients with inoperable disease and positive ^{68}Ga-Dotatate PET/CT for consideration of PRRT treatment with lutetium-177 labelled peptides.

Subjects and methods

Seven patients (age range 31-66 years, mean age 45 years, M:F 3:4) were referred for ^{68}Ga-Dotatate PET/CT between 2008 and 2014 due to rising calcitonin levels with a range of 80-37,180pg/mL (Normal level at our institution=0-11.5pg/mL). The purpose of referral was to detect disease recurrence in six patients who had histopathology confirmed MTC and previous complete thyroidectomy, and to establish initial diagnosis of MTC in one patient with very high calcitonin.

All patients had previous investigations with a combination of US, CT, MRI, ^{123}I-MIBG and ^{18}F-FDG PET/CT.

Gallium-68-Dotatate was produced and provided by Mallinckrodt, formerly part of Covidien (Dublin, Ireland) and delivered on the day of the scan.

Gallium-68-Dotatate PET/CT was acquired on a Siemens Biograph 16 PET/CT scanner (Siemens Healthcare, Erlangen, Germany). The tracer was administered intravenously (Dose range 52-89MBq, mean dose 72MBq). Imaging started after an uptake time of 45min.

Low dose CT was acquired for anatomic localization and attenuation correction, followed by PET (six fields of view, 3-4min per 21.9cm axial field of view in a 3D acquisition). Positron emission tomography and CT images were acquired from mid thighs to vertex. Positron emission tomography images were corrected for tissue attenuation using the CT data and were reconstructed using iterative reconstruction.

Interpretation criteria

The scintigraphic studies were classified as negative when the tracer was confined to organs of normal uptake (pituitary, spleen, urinary bladder, liver) and with no sites of abnormal uptake observed. A positive scan was reported as active disease or recurrence/relapse when at least one focus of abnormal intense uptake characterized by visual inspection and/or SUV measurements was observed. By adopting these interpretation criteria, it was possible to clarify all the scans as either frankly positive or frankly negative for recurrence.

No statistical analysis was performed due to the small sample size.

Results

In 6/7 patients, ^{68}Ga-Dotatate PET/CT confirmed the presence of suspected lesions seen on other modalities or detected hitherto unsuspected lesions (Table 1 patients 1-4 and 6-7). All these patients had very high serum calcitonin levels (range=672-37,180 mean: 8,320pg/mL). In 1/7 patient, ^{68}Ga-Dotatate imaging was true negative in a case of minimal and relatively low calcitonin (80pg/mL) and FNA negative disease. A selection of five interesting cases is discussed below.

Patient number 1 (Table 1, Figure 1) had total thyroidectomy in 2001 and a neck dissection in 2003 for local recurrence. A neck ultrasound and ^{18}F-FDG PET/CT performed in 2010 for a calcitonin rising to >4000 were negative. In 2014, the calcitonin continued to rise, and by this time measured >8000. A neck US demonstrated right cervical lymphadenopathy and FNA of these showed metastatic MTC. Computerized tomography also showed subcarinal lymphadenopathy. Given the high calcitonin level, other sites of disease were suspected therefore a ^{99m}Tc-hydroxymethylene diphosphonate (HDP) bone scan was performed and was negative. A subsequent ^{68}Ga-Dotatate PET/CT revealed several bone metastases in the left humerus and both proximal femora, as well as disease at the surgical thyroid bed and cervical and mediastinal lymph nodes.

Patient number 2 (Table 1, Figure 2) had total thyroidectomy in 2000. Following a rise in serum calcitonin to 265 in 2011, an US was performed demonstrating small right cervical nodes. These had low-level metabolic activity on ^{18}F-FDG PET/CT. Fine needle aspiration and biopsy of the right cervical nodes were reactive. A study with ^{123}I-MIBG was done with a negative result. Gallium-68-Dotatate PET/CT demonstrated low-level ^{68}Ga-Dotatate uptake in the right cervical nodes, but intense uptake in the left L5 pedicle. An MRI of the lumbar spine was performed demonstrating a lesion in the left L5

Table 1. *Demographic, clinical and biochemical data of all patients with corresponding findings on ^{68}Ga-Dotatate PET/CT compared to other imaging*

Patient	Age	Gender	Previous surgery	Presenting complaint	Calcitonin pg/mL (range)	Value of ^{68}Ga-Dotatate PET/CT compared to other imaging
1 PE	61	F	Total thyroidectomy	High calcitonin	(1474-8940)	Confirmed bone lesions not detected by other imaging
2 SG	66	F	»	High calcitonin	(265-672)	Detected L5 pedicle lesion not detected on bone scan or CT. Bone biopsy confirmed metastatic MTC
3 MS	58	M	Nil (Initial diagnosis)	Cervical nodes and high calcitonin	37180	Confirmed disease foci not detected on other imaging including ^{18}F-FDG PET/CT
4 AF	61	M	Total thyroidectomy	Cervical nodes	(542-742)	Confirmed active disease in cervical and mediastinum nodes
5 JR	35	F	»	High calcitonin	80	Ruled out disease recurrence
6 JC	61	F	»	High calcitonin	(758-1700)	Confirmed active disease seen on CT and was superior to ^{18}F-FDG PET/CT
7 AC	31	M	»	High calcitonin	(212-684)	Confirmed active disease in biopsy confirmed recurrent MTC

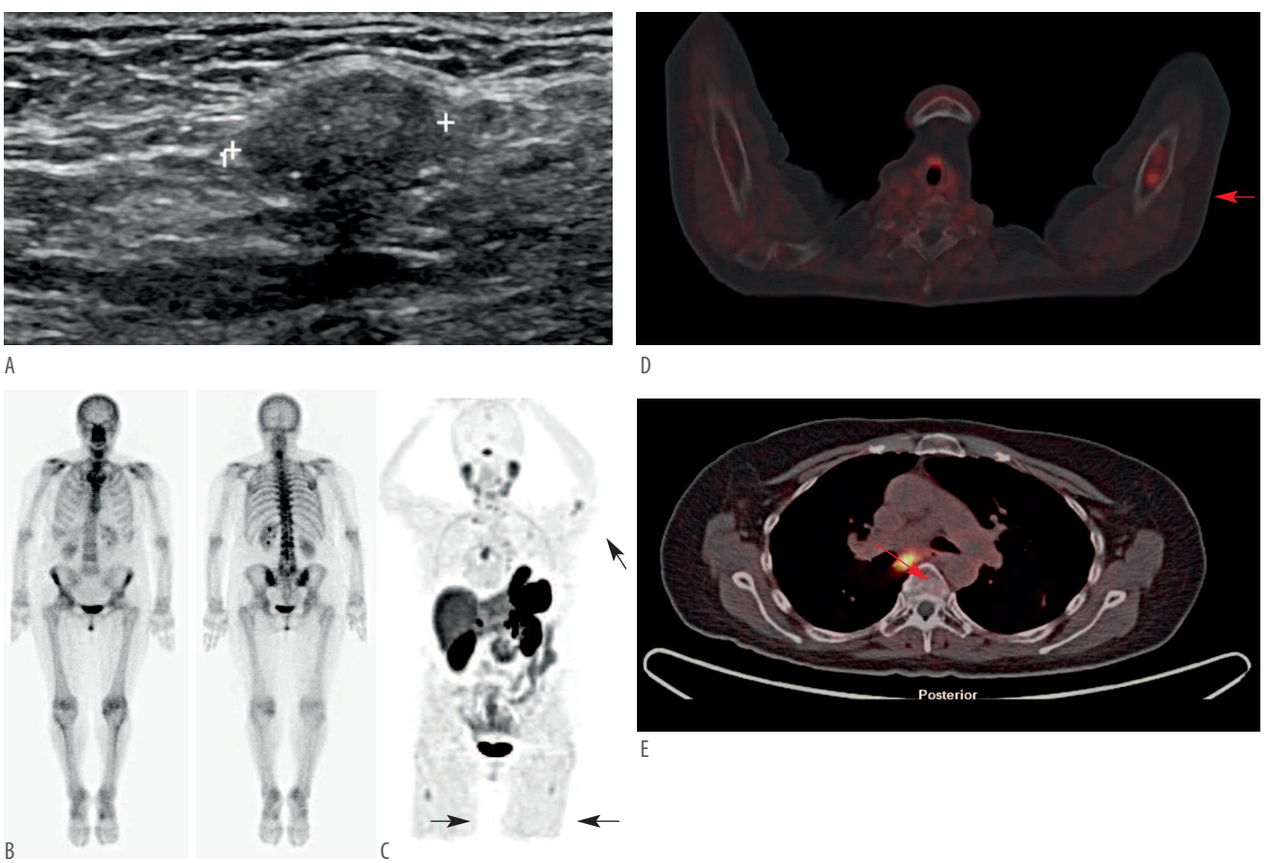

Figure 1. Recurrent MTC. A neck ultrasound demonstrated right cervical lymphadenopathy. (A). Very high calcitonin suggested bone metastases but ^{99m}Tc-HDP bone scan was negative (B). ^{68}Ga-Dotatate PET/CT maximum intensity projection (MIP) (C) showing several bone metastases (black arrows). Fused transverse views showing lesions in the left humerus (D) and mediastinum (E) (red arrows).

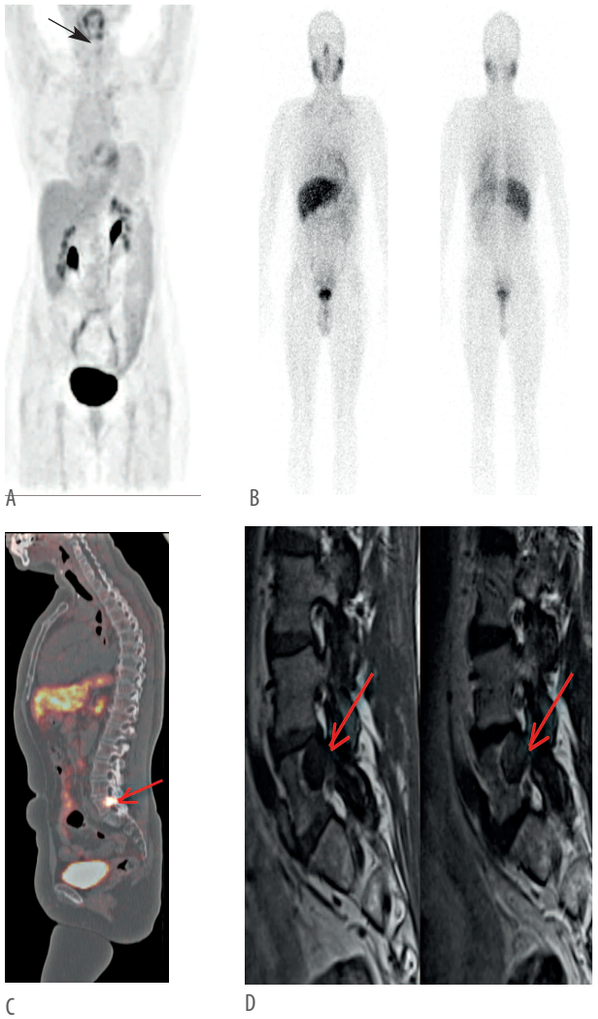

Figure 2. Recurrent MTC presenting with small right cervical nodes. ^{18}F-FDG PET/CT MIP showing low-level metabolic activity in cervical nodes (arrow) (A). ^{123}I-MIBG scan was negative (B). ^{68}Ga-Dotatate PET/CT fused sagittal view showed intense uptake in the left L5 pedicle (C). An MRI of the lumbar spine (D) was performed demonstrating a lesion in the left L5 pedicle (red arrows) and a bone biopsy showed recurrent metastatic MTC.

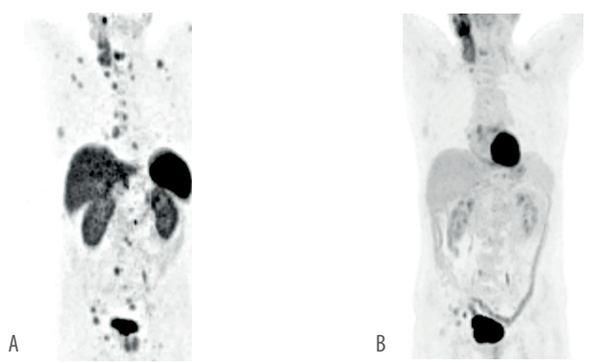

Figure 3. A patient with MTC presenting for the first time. Staging CT demonstrated multi-site lymph node and bone metastases (not shown) with very high calcitonin. (A) ^{68}Ga-Dotatate PET/CT MIP showing uptake in more sites of cervical, mediastinal and pelvic lymph nodes, as well as bone metastases in the spine, ribs and pelvis. ^{18}F-FDG PET/CT MIP (B) showed significantly less uptake within nodal and bone metastases.

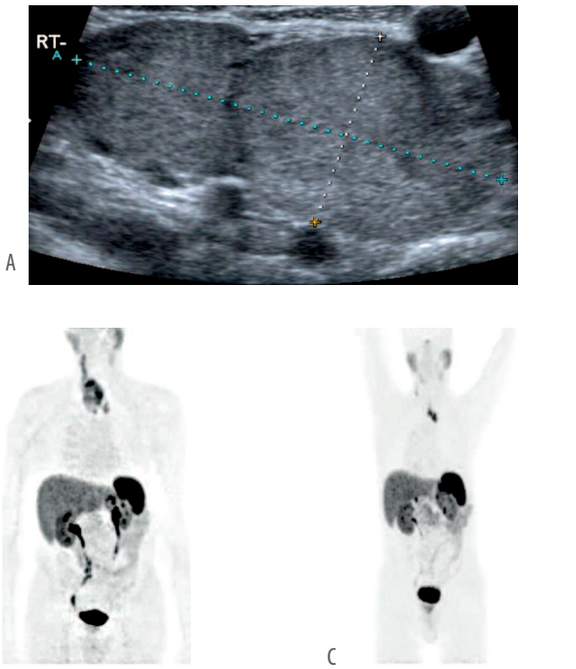

Figure 4. MTC presenting in 2011 with recurrence in cervical nodes on US (A) and further sites of disease in the superior mediastinum on ^{68}Ga-Dotatate PET/CT MIP (B). Post-surgical second recurrence in 2014 in cervical nodes and superior mediastinum on US and CT. ^{68}Ga-Dotatate PET/CT MIP (C) confirming findings on CT and US.

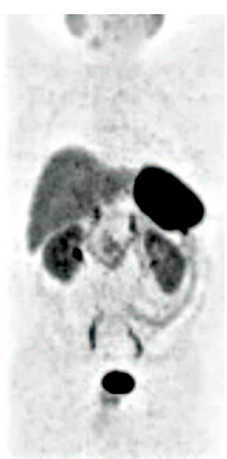

Figure 5. A case of MTC post thyroidectomy with modest and stable rise of calcitonin to 80pg/mL over 2 years and small volume right cervical nodes on US and CT. ^{68}Ga-Dotatate PET/CT MIP did not show significantly high uptake in cervical nodes or elsewhere. FNA of a left cervical node was negative.

pedicle and a bone biopsy showed recurrent metastatic MTC.

Patient number 3 (Table 1, Figure 3) was initially investigated for clinically palpable right cervical lymphadenopathy demonstrated on US. A staging CT demonstrated cervical, paraoesophageal, retrocrural and pelvic lymphadenopathy together with bone metastases. Serum calcitonin was 37,810pg/mL and the patient was suspected of having advanced MTC. Fluorine-18-FDG PET/CT showed metabolically active disease in cervical and pelvic lymphadenopathy. Gallium-68-Dotatate PET/CT demonstrated uptake in more sites of nodal disease and within bone metastases. Histology confirmed MTC of the right cervical nodes.

The differences in uptake on ^{68}Ga-Dotatate and ^{18}F-FDG PET/CT highlights the superior sensitivity of ^{68}Ga-Dotatate PET/CT in detecting many more lesions compared to CT and

^{18}F-FDG PET/CT.

These three cases demonstrate that ^{68}Ga-Dotatate PET/CT has provided invaluable information in the detection of recurrent metastatic MTC compared to all other imaging techniques.

Patient number 4 (Table 1, Figure 4) had thyroidectomy for MTC, presented with an abnormal node in the right thyroid bed along with right sided cervical lymphadenopathy confirmed on ultrasound and a rising serum calcitonin to 5150pg/mL in 2011. Gallium-68-Dotatate PET/CT demonstrated further sites of disease in the superior mediastinum. This significantly influenced the approach undertaken at the time of surgery. Post-surgical histopathology confirmed recurrent metastatic MTC. Despite the reduction in serum calcitonin level (542pg/mL), the patient presented in 2014 with recurrent/residual disease. Ultrasound demonstrated abnormal nodes in the right thyroid bed and cervical regions and CT showed abnormal nodes in the superior mediastinum. Serum calcitonin started to rise again to 742pg/mL and a repeat ^{68}Ga-Dotatate PET/CT was performed. Tracer uptake in the right thyroid bed, right cervical and superior mediastinal nodes was demonstrated, confirming disease recurrence.

Patient number 5 (Table 1, Figure 5) had a previous total thyroidectomy for MTC and was initially investigated with an US of the neck for a rise in calcitonin. There were small volume right cervical nodes, which were also demonstrated on a subsequent CT. A ^{68}Ga-Dotatate PET/CT did not show significantly high uptake in those nodes. There were no other sites of significant uptake. Combined with an FNA of a left cervical node and a stable calcitonin from 2012-2013 at 80pg/mL, ^{68}Ga-Dotatate PET/CT helped to confirm that there was no evidence of disease recurrence. However, the presence of microscopic disease leading to the stable and modest rise of calcitonin could not be ruled out.

Discussion

Medullary carcinoma of the thyroid (MTC) is a rare neuroendocrine tumour (NET) with fascinating hereditary and genetic links. It makes up 3%-10% of all thyroid cancers and 13.4% of all thyroid-related deaths [3, 5]. It arises from the parafollicular thyroid cells and produces calcitonin in abundance, leading to a rise in serum levels that can be used as a tumour marker. Surgical excision is curative in solitary or accessible disease but recurrences are encountered in 50% of cases and are associated with a rise in calcitonin levels that prompts the clinicians to set a management plan. Surgery is again the primary curative modality but is achieved only when the diagnosis is timely so there is a high rate of persistent and recurrent disease indicated by a rise in the serum calcitonin levels.

Unfortunately, the rise in calcitonin carries no clue to the site of the disease and this obstacle may delay surgery. To overcome this, a variety of imaging procedures are employed for localisation, starting with a neck US. The ATA recommends neck US alone when calcitonin levels are <150pg/mL with optional use of other modalities. If calcitonin level is >150pg/mL, then other cross sectional imaging such as CT and MR as well as functional imaging should be performed.

Radiopharmaceuticals that were historically used in the detection of MTC are less commonly used now. Technetium-99m-DMSA-V was mainly used in the detection of MTC but the sensitivity was counterbalanced by instability of the component and low specificity with non-tumoural uptake such as in areas of inflammation, bone fractures and other types of tumours. It is now unavailable commercially [6, 7]. Indium-111-octreotide has demonstrated variable sensitivity ranging from 37% to 75% [8, 9, 20] and has been replaced by ^{68}Ga-Dotatate peptides.

In practical clinical setting, the most commonly used functional imaging include ^{123}I-MIBG SPET/CT, which detects uptake in intra-cellular granules, and ^{18}F-FDG PET/CT which detects increased metabolic activity and utilisation of glucose by tumour cells. However, and despite the combined use of anatomical and functional imaging, recurrences are only detected in 40% of cases.

Medullary thyroid carcinoma expresses somatostatin receptors on its cell membrane, with hSSR2 (the most common receptors on tumour cell membrane) being the most prevalent of the five known human receptors. This allows for the use of PET/CT imaging with ^{68}Ga labelled somatostatin-analogue peptides. These radiopharmaceuticals (^{68}Ga-Dotatate, ^{68}Ga-Dotatoc, ^{68}Ga-Dotanoc) benefit from the improved resolution of PET compared to SPET imaging with ^{123}I-MIBG or ^{111}I-octreotide, and the improved affinity of the DOTA peptides to somatostatin receptors.

Since its introduction into clinical practice in the beginning of this century [21], ^{68}Ga-peptides PET/CT has provided a dramatic improvement in the detection and management of NET. It has been shown to provide clear superiority over other functional imaging such as ^{111}In-Octreotide and ^{18}F-FDG PET/CT [9, 10]. In addition, the higher rate of detection with DOTA peptides has demonstrated a high impact on disease management. In a study of 52 patients with NET, ^{68}Ga-Dotatoc PET/CT influenced treatment decision in more than every second patient [12]. Gallium-68-Dotatate has also been shown to detect bone metastases that were not suspected clinically or radiologically [22].

There are increasing numbers of reports of patients with MTC demonstrating the added value of ^{68}Ga-peptides PET/CT in detecting active/recurrent or metastasised disease, particularly bony metastases, that were not detected by other imaging modalities. Nicolini et al (2012) published a case report in which ^{68}Ga-Dotanoc PET/CT identified recurrent MTC in a C6 vertebral body [14]. Similar findings were also demonstrated by Lapinska et al (2011) using ^{68}Ga-Dotatate in four cases of MTC [15].

In a group of eight patients, Palyga et al (2010) showed that ^{68}Ga-Dotatate PET/CT localised recurrent MTC within cervical lymph nodes, confirmed after resection, while ^{18}F-FDG PET/CT was negative. However, the detection was limited to a small number of patients (2 out of 8 cases) who had the highest levels of calcitonin (>500pg/mL) [16]. Conry et al (2010) compared ^{68}Ga-Dotatate and ^{18}F-FDG PET/CT in 18 patients with recurrent MTC and reported marginal benefit for imaging with ^{18}F-FDG compared to ^{68}Ga-Dotatate. However, their patients had a wide range of calcitonin (38-

15,600pg/mL) and only 50% of them had calcitonin level >150pg/mL [17]. Their imaging results were contradicted by Naswa et al (2012), who demonstrated superiority of ^{68}Ga-Dotatoc PET/CT in detecting recurrent MTC, with a sensitivity of 75.6% compared to 63.4% for ^{18}F-FDG PET/CT. Their patients also had a wide spectrum of calcitonin levels (range 50-30,000pg/mL). They could not define a cut-off calcitonin level that could predict recurrence [18].

The detection of MCT with ^{68}Ga-Dotatate peptides has gained further interest with the increasing trend of treating patients with positive ^{68}Ga-Dotatate peptides PET/CT with ^{90}Yttrium and ^{177}Lutetium labelled somatostatin analogues [19].

Our series of 7 patients with raised calcitonin showed a higher yield with 6/7 true positive cases in correlation with biopsies, other imaging and long term clinical follow up and calcitonin monitoring. They all had very high calcitonin levels (range 672pg/mL to 37,180pg/mL, mean 7,143pg/mL). Imaging with ^{68}Ga-Dotatate was superior to that with ^{18}F-FDG in 3 patients.

In 1/7 patient, ^{68}Ga-Dotatate was negative in association with a negative biopsy and stable calcitonin at 80pg/mL. However, in this particular case, the presence of microscopic disease that is undetected by imaging could not be excluded and therefore we cannot assume that it is a true negative case.

Due to the small number of patients, and the predominance of very high calcitonin levels, we were unable to recommend a cut off value for the calcitonin levels beyond which imaging with ^{68}Ga-Dotatate PET/CT would be recommended. However, our data and those of Palyga et al (2010) [16], suggest that high levels of calcitonin (>500pg/mL) is needed before embarking on this imaging.

In our clinical setting, our findings were fundamental in the early detection and assessment of the extent of disease and strongly influenced decisions regarding resectibility and prognosis. In addition, they have a substantial impact on treatment since inoperable and wide spread metastases will be treated with peptide receptor radionuclide therapy (PRRT) using ^{90}Yttrium and ^{177}Lutetium labelled somatostatin analogues.

In conclusion, our results in this small series demonstrate that ^{68}Ga-Dotatate PET/CT was fundamental in the early detection and assessment of the extent of disease recurrence in MTC with a positive impact on resectibility and prognosis. However, the use of this imaging modality should only be considered when the serum calcitonin levels are persistently high and probably in excess of 500pg/mL. Of the positive cases, those with inoperable disease will be offered PRRT.

The authors declare that they have no conflicts of interest.

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