The Value of Ga68-DOTATATE PET/CT in Diagnosis and Management of Suspected Pituitary Tumors

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Abstract

Backroud Gallium 68-tetraazacyclododecane-tetraacetic acid-octreotate (Ga-68-DOTATATE) is a selective somatostatin analogue ligand, which shows increased affinity for somatostatin receptor subtype (SSTR) 2 and has been used routinely for imaging neuroendocrine tumors with PET/CT. We investigated the utility of Ga-68-DOTATATE positron emission tomography/computed tomography (PET/CT) in patients with suspected pituitary pathology. We reviewed imaging for twenty consecutive patients (8 men, 12 women, mean age of 48.2, range: 14-78) with suspected pituitary pathology who were referred for Ga-68-DOTATATE PET-CT.

Results Nine patients presented with recurrent Cushing's syndrome following surgical resection of pituitary adenomas due to recurrent Cushing's disease (seven patients) and ectopic ACTH secreting tumor (2 patients). All seven patients with recurrent Cushing's disease showed positive pituitary Ga-68-DOTATATE uptake while both cases of ectopic hormonal secretion had absent pituitary uptake. In 1 of these 2 patients Ga-68-DOTATATE was able to localize the source of ectopic ACTH tumor.

Six patients presented de novo with Cushing's due to ectopic ACTH secretion; Ga-68-DOTATATE PET/CT was able to localize ectopic tumors in six of eight patients (3 lungs, 2 pancreases, 1 mid-gut)

There was high uptake Ga-68-DOTATATE in 3 cases of recurrent central hyperthyroidism (SUVmax 6.6-14.3) and 2 cases of prolactinoma (SUVmax 5.5 and 11.3).

Conclusion Absent Ga-68-DOTATATE activity in the pituitary fossa is useful in excluding pituitary disease in recurrent Cushing's. Recurrent pituitary thyrotropinomas and prolactinomas showed moderate to high pituitary activity. In addition, in Cushing's syndrome Ga-68-DOTATATE is useful for detection of ectopic sources of ACTH production, especially where anatomic imaging is negative.

Introduction

Neuroendocrine tumors (NET) cover a heterogeneous group of tumors, which originate from endocrine glands (pituitary, parathyroid, adrenal medulla) or other endocrine organs like thyroid, pancreas, respiratory and gastrointestinal tissue.

As most NET's express somatostatin receptors, they can be adequately targeted and visualized with somatostatin receptor radio-labelled analogues in vivo (1-4).

The use of Ga-68-DOTATATE labelled for the somatostatin receptor scintigraphy (SRS) is based on the increased affinity of Ga-68-DOTATATE labelled somatostatin receptor ligands relative to ¹¹¹In-octreotide (2-6). European Neuroendocrine Tumor Society guidelines (5, 7) recommend the use of PET/CT for the localization of the primary tumor in metastatic NET's (8).

The aim of our study was to evaluate the utility of Ga-68-DOTATATE PET/CT imaging scan in patients with suspected pituitary pathology. Patients were divided into two broad groups; those with ACTH

dependent Cushing's syndrome and those with recurrent prolactinomas and thyrotropinomas.

Cushing's syndrome is a hormonal imbalance due to abnormally increased levels of cortisol hormone in blood. Cushing's syndrome is divided into 2 types: ACTH-dependent and ACTH-independent forms. In ACTH-dependent type, there is over-synthesis of ACTH from pituitary adenoma, called Cushing's disease (CD), or ectopic secretion of ACTH from peripheral tumors (9). CD is the most common form of endogenous Cushing's syndrome, accounting for approximately 70% of cases (10-11). Ectopic ACTH secretion is a cause of approximately 15-20% of ACTH-dependent Cushing's syndrome (12). In the literature, several small case series studies have reported on use of Ga-68-peptide ligands to evaluate ectopic ACTH secreting tumors (13-16). Prolactinomas are relatively common primary pituitary neoplasm's whereas thyrotropinomas are rare. In both cases, however, there is very limited literature on use of somatostatin receptor imaging in vivo.

Methods

Patients

A search of our Institutional database over 5-year period between 2008 and 2013 revealed 20 consecutive patients (8 male, 12 females with mean age 48.2 years (range: 14-78 years)) who underwent Ga-68-DOTATATE PET/CT for evaluation of pituitary pathology.

The indication for Ga-68-DOTATATE PET/CT were: (Table 1)

- a) Suspected recurrent Cushing's disease following previous surgical resection
- b) ACTH dependent Cushing syndrome secondary to suspected ectopic ACTH production
- c) Recurrent central hyperthyroidism
- d) Recurrent prolactinoma

PET/CT acquisition parameters

Images were acquired 45-60 min after injection of 120–200 MBq of Ga-68-DOTATATE. Imaging was performed using a dedicated GE Discovery STE camera combining a PET unit and a 16-slice CT unit; whole-body examinations (brain to mid-thigh) were performed with the patient supine. The CT exposure factors for all examinations were 120 kVp and 80 mA in 0.8 s. Maintaining patient position, we performed a whole-body PET emission scan covering an area identical to that covered by CT. PET scans were acquired at a rate of 4 min per bed position, and PET images were reconstructed using CT for attenuation correction. The Ga-68-DOTATATE PET acquisitions were performed in 3 dimensions with a 5-slice overlap between consecutive bed positions. Ga-68-DOTATATE PET images were reconstructed using an ordered-subsets expectation maximization algorithm with 3 iterations and 25 subsets. The CT data for Ga-68-

DOTATATE were reconstructed to axial slices 3.75 mm thick with a soft-tissue reconstruction algorithm and 2.5 mm thick with a lung reconstruction algorithm.

Image analysis

The documented clinical reports were used to determine results of Ga-68-DOTATATE PET/CT scans. In addition, scans were retrospectively reviewed to document standardized uptake value (SUVmax) in all lesions.

Histological confirmation of tumor type was available for all patients except for one case where ectopic ACTH source for Cushing syndrome was unknown.

All patients had informed consent, and institutional board ethics approval was received for this retrospective study.

Results

Tumor Overview, histology assessment and Ga-68-DOTATATE uptake is summarized in Table 2.

15 patients had Cushing's syndrome. Of these 15, nine presented with recurrent Cushing's following surgical treatment for Cushing's disease. 6/15 patients presented de novo with ectopic ACTH dependent Cushing's syndrome. In 7/9 patients with recurrent Cushing's syndrome there was recurrent pituitary disease. In 2/9 patient's recurrent Cushing's syndrome was due to ectopic ACTH producing tumor.

The source of ectopic ACTH was due to bronchial carcinoid (3 patients), pancreatic NET's (2 patients) and mid gut NET (1 patient). Of 3 bronchial carcinoid tumors, 2 were typical carcinoid (0.8 and 1.7 cm) and 1 was atypical carcinoid (1.5 cm). In one patient, ectopic source of ACTH production was unknown.

In all seven patients with recurrent Cushing's secondary to recurrent Cushing's disease there was positive uptake of Ga-68-DOTATATE within pituitary (SUVmax 2.3-6.1, mean 4.1). In both cases of recurrent Cushing's due to ectopic ACTH production there was absent uptake of Ga-68-DOTATATE in the pituitary. Pituitary uptake in those with recurrent pituitary adenomas was less than intense than pituitary uptake seen in patients presenting de novo with ectopic Cushing's (SUVmax 4.8-8.9, mean 6.2).

Ga-68-DOTATATE was able to depict source of ectopic ACTH production in six of eight patients (1/2 patients with recurrent Cushing's syndrome, and 5/6 patients presenting de novo). Ga-68-DOTATATE showed positive but low uptake (Fig.1) in all three bronchial carcinoids (SUVmax 1.4-2.0). There was high Ga-68-DOTATATE uptake in 1/2 Pancreatic NET's (SUVmax 35.5) and one Mid-Gut NET (SUVmax 25.3) (Fig.2).

In one with negative Ga-68-DOTATATE uptake, ectopic source of tumor was not shown on any imaging modality, ectopic tumor ACTH production was diagnosed biochemically and on basis of complete resection of pituitary tissue (shown on MRI) as well absent pituitary Ga-68-DOTATATE activity (Fig.3). In

another with pancreatic NET there was negative Ga-68-DOTATATE uptake as well as negative CT and MRI with tumor depicted only on EUS.

In one case with unknown primary site on conventional CT/MRI imaging Ga-68-DOTATATE showed site of primary tumor (in terminal ileum).

Three patients presented with recurrent central hyperthyroidism due to thyroid stimulating hormone (TSH) secreting adenoma following previous surgical resection, with increased TSH and free-thyroid hormone levels, and residual pituitary macro adenomas on MRI (size 13 mm, range 11-15 mm). All patients with recurrent thyrotropinomas showed high tracer uptake (Fig.4) within pituitary (mean SUVmax 9.2, range: 6.7-14.3). Two patients with pituitary adenoma secondary to prolactinoma showed moderate to high Ga-68-DOTATATE uptake in pituitary gland (SUVmax 5.5 and 11.3).

Discussion

Our study suggests that, in selected indications, Ga-68-DOTATATE has a useful role in evaluating patients with suspected pituitary pathology.

Ga-68-DOTATATE activity within the pituitary fossa is a marker for functioning pituitary tissue, a property which can help assess patients with recurrent Cushing's syndrome following resection of corticotrophin secreting pituitary tumors. Positive pituitary uptake indicates the presence of functioning pituitary tissue; in all seven patients with recurrent Cushing's disease there was positive uptake within pituitary although this was less than normal pituitary activity seen in those with Cushing's due to ectopic ACTH secretion. Our findings are in keeping with Zhao et al. who showed that Ga-68-DOTATATE had higher uptake in normal remaining pituitary tissue than in recurrent or residual pituitary adenomas (17). In contrast both patients with recurrent Cushing's syndrome due to ectopic ACTH secretion had no uptake within pituitary, in keeping with treated pituitary disease.

The diagnosis of Cushing's disease can be challenging. The best imaging modality, MRI may be normal in up to 40% of patients (18). Inferior petrosal sinus sampling (IPSS) is the gold standard for differentiating between pituitary and non-pituitary sources of corticotrophin, with diagnostic accuracy of 87% (18) but is a highly skilled and invasive technique, requiring placement of catheters in both inferior petrosal sinuses (19). Ga-68-DOTATATE is also useful in localization of ectopic ACTH producing tumors. Ectopic ACTH secretion is an infrequent cause of ACTH-dependent Cushing's syndrome. It often presents a major diagnostic difficulty because it is hard to differentiate Cushing's disease from ectopic tumors and is often difficult to localize. Ga-68-DOTATATE could detect ectopic ACTH source in 5/6 patients presenting de novo with ACTH dependent Cushing's and 1/2 patients with treated pituitary Cushing's. Three with ectopic Cushing's had lung carcinoid. Although pulmonary carcinoids showed positive uptake of Ga-68-DOTATATE, the level of accumulation was unusually low (SUVmax 1.4-2.0).

There are varying results regarding use of conventional single photon somatostatin receptor scintigraphy (SRS) for evaluating patients with ectopic Cushing syndrome with majority of published studies (12, 13,

20-28) reporting sensitivity of between 40-60%. In the two largest published studies by Zemskova et al. and Ilias et al. SRS could detect ectopic tumor in (17/30) 57% and (21/43) 49% (23, 24). Studies comparing SRS with diagnostic CT/MRI have found limited role for SRS as no additional lesions were detected with SRS relative to CT/MRI (7, 20-21).

Studies evaluating Ga-68-DOTATATE labelled somatostatin ligands are limited to a small number of case reports and very small case series (20, 27-35). The sensitivity of Ga-68-DOTATATE in detecting source of ectopic ACTH secretion from previously published cases is approximately 72% (18/25 patients) (Table 3). Ozkan et al. (20) found positive Ga-68-DOTATATE uptake in only 2/5 patients with ectopic ACTH syndrome, one patient showed false positive uptake. In contrast Gilardi et al. reported that Ga-68-DOTATATE revealed the source of ectopic lesions in 5/5 patients with ectopic ACTH syndrome (28). In 3/5 patients SRS with ¹¹¹In-pentetreotide had failed to localize the source of ACTH secretion. Kakade et al. reported that Ga-68-DOTATATE was positive in 4/6 ectopic ACTH secreting tumor including two which had negative CT (27). In our series 6 of 8 ectopic ACTH secreting tumors were detected with Ga-68-DOTATATE, in one case ectopic primary tumor was not seen on CT but was depicted with Ga-68-DOTATATE.

Thyrotropinomas are a rare cause of hyperthyroidism in clinical practice often diagnosed as macro adenomas due to delayed diagnosis. Suppression of TSH secretion is mediated via both SSTR 2 and SSTR 5 subtypes (36). Long acting somatostatin analogue drugs reduce TSH secretion and normalize FT4 and FT3 levels in 90% of patients suffering with pituitary TSH secreting tumors (37). In 25 percent of thyrotropinoma cases there is autonomous secretion of a second pituitary hormone (38). One of our 9 patients with recurrent Cushing's syndrome also had the symptoms of central hyperthyroidism with final diagnosis of plurihormonal pituitary adenoma with expression of ACTH, FSH and TSH (case 7, Table 2). In a study published by Foppiani et al. all 3 patients with TSH-oma were positive in octreoscan (39). Despite previous pituitary surgery there was moderate increased Ga-68-DOTATATE uptake in patient with recurrent Cushing's and thyrotropinoma and intense uptake in 3 cases of recurrent thyrotropinomas (Fig. 4). Moderate to high pituitary uptake was also seen in both patients with recurrent prolactinomas.

Conclusion

Ga-68-DOTATATE, with integrated PET/CT, is a useful diagnostic modality for the evaluation of patients with suspected pituitary pathology. Recurrent Cushing's disease is associated with positive pituitary uptake of Ga-68-DOTATATE. Although in these cases it would not be possible to distinguish pathological from physiological uptake, positive Ga-68-DOTATATE is useful as it indicates the presence of functioning pituitary tissue. Absence of pituitary uptake in patients with recurrent Cushing's suggests source of ACTH is ectopic. Moderate to high pituitary tracer uptake of Ga-68-DOTATATE was seen in patients with recurrent thyrotropinomas and prolactinomas indicating Ga-68-DOTATATE may be useful for detection of disease post-surgery.

Ga-68-DOTATATE may be helpful in detecting source of ectopic lesion in Cushing's syndrome particularly in those where CT imaging is negative. Finally, locally aggressive or metastatic pituitary tumors may show Ga-68-DOTATATE uptake and therefore indicate potential for treatment with radio labelled somatostatin receptor analogues such as ¹⁷⁷Lu-DOTATATE.

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Tables

Table 1. Patients demographic and clinical characteristic

Total Number of Enrolled Patients	20
Gender of Patients	
Male	8
Female	12
Clinical Presentation	
Suspicious Recurrent Cushing Disease	9
ACTH Dependant Ectopic Cushing Syndrome	6
Recurrent Central Hyperthyroidism	3
Recurrent Galactorrhea	2

Table 2. Summary of tumour characteristic and finding

<i>Patients No</i>	<i>Age, Sex</i>	<i>Referral Presentation</i>	<i>Previous treatment (PS/RT)</i>	<i>Tumour site/⁶⁸Ga-PET/CT Uptake</i>	<i>Final Diagnosis/ Histology</i>
1	68, M	Suspected Recurrent Cushing Disease	PS	Pituitary fossa (SUVmax 2.3)	CD/ Pituitary Adenoma with expression of ACTH
2	37, M	Suspected Recurrent Cushing Disease	PS	Pituitary Fossa (SUVmax 4.2)	CD/ Pituitary Adenoma with expression of ACTH
3	57, F	Suspected Recurrent Cushing Disease	PS	Pituitary Fossa (SUVmax 4.2)	CD/ Atypically Pituitary Adenoma with expression of ACTH
4	49, F	Suspected Recurrent Cushing Disease	PS	Pituitary Fossa (SUVmax 3.1)	Pituitary adenocarcinoma with expression of ACTH
5	26, M	Suspected Recurrent Cushing Disease	PS	Pituitary Fossa (SUVmax 6.1)	CD/ Pituitary Adenoma with expression of ACTH
6	78, F	Suspected Recurrent Cushing Disease	PS + RT	Pancreas (SUVmax 8.4)	Pancreatic NET's with expression of ACTH
7	30, F	Suspected Recurrent Cushing Disease, Central Hyperthyroidism	PS	Pituitary Fossa (SUVmax 5.2)	CD+ TSH-oma / Plurihormonal Pituitary adenoma with expression of TSH, FSH and ACTH
8	68, F	Suspected Recurrent Cushing Disease	PS	Pituitary Fossa (SUVmax 3.9)	Cyclical CD / Adenoma with expression of ACTH
9	67, F	Suspected Recurrent Cushing Disease	PS	Negative	Ectopic ACTH secreting tumour, unknown source
10	73,	Ectopic Cushing	NO	Negative	Pancreatic NET's with

	F	Syndrome			expression of ACTH
11	14, M	Ectopic Cushing Syndrome	NO	Lung Nodule (SUVmax1.4)	Atypical lung Carcinoid with expression ACTH
12	58, M	Ectopic Cushing Syndrome	NO	Lung-Nodule (SUVmax 1.9)	Typical Lung Carcinoid with expression of ACTH
13	22, F	Ectopic Cushing Syndrome	NO	Lung Nodule (SUVmax 2.0)	Typical Lung Carcinoid with expression of ACTH
14	42, F	Ectopic Cushing Syndrome	NO	Small Bowel (SUVmax 25.3)	Metastatic Mid-Gut NET's with expression of ACTH
15	49, F	Ectopic Cushing Syndrome	NO	Head of Pancreas (SUVmax 35.5)	Pancreatic NET's with expression of ACTH
16	27, M	Recurrent Central Hyperthyroidism	PS	Pituitary Fossa (SUVmax 6.6)	TSH-Oma/Pituitary adenoma with expressing of TSH
17	48, M	Recurrent Central Hyperthyroidism	PS	Pituitary Fossa (SUVmax 6.7)	TSH-Oma/Pituitary adenoma with expressing of TSH
18	50, F	Recurrent Central Hyperthyroidism	PS	Pituitary Fossa (SUVmax 14.3)	TSH-Oma/Pituitary adenoma with expressing of TSH
19	23, M	Pituitary Mass	EBRT	Pituitary Fossa (SUVmax 5.5)	Prolactinoma /Pituitary Adenoma with expression of Prolactin
20	34, F	Recurrent Galactorrhea	NO	Pituitary Fossa	Prolactinoma/Pituitary Adenoma with expression of Prolactin

PS pituitary surgery, EBRT external beam radiation therapy, CD cushing's disease, ACTH adrenocorticotrophic hormone, TSH thyroid stimulating hormone, NET neuroendocrine tumour

Table 3. Study of Ectopic ACTH PET-CT scan with ^{68}Ga -DOTA peptides

Studies	Patients	Positive Uptake within ectopic tumour	Negative Uptake within ectopic tumour	Tracer	Tumour Types
Veit et al (14)	1	1	0	⁶⁸ Ga-DOTANOC	Paranasal Adenoma
Singer et al (15)	1	1	0	⁶⁸ Ga-DOTATOC	Ileum Carcinoma
Ozkan et al (20)	5	2	3*	⁶⁸ Ga-DOTATATE	Bronchial Carcinoid -1, Metastatic Atypical Carcinoid -1
Kakade et al (27)	6	4	2	⁶⁸ Ga-DOTATATE	Bronchial Carcinoid -1, PNET -1, MTC -2
Gilardi et al (28)	5	5	0	⁶⁸ Ga-DOTATOC	Bronchial Carcinoid
Venkitaraman et al (29)	3	3	0	⁶⁸ Ga-DOTATOC	Bronchial Carcinoid
Treglia et al (30)	1	1	0	⁶⁸ Ga-DOTANOC	PNET
Darr et al (31)	1	1	0	⁶⁸ Ga-DOTATATE	Bronchial Carcinoid
Thomas et al (32)	1	1	0	⁶⁸ Ga-DOTATATE	Nasal Paraganglioma
Willhauck et al (33)	1	1	0	⁶⁸ Ga-DOTATATE	Sphenoid Adenoma
Schalin-Jäntti et al (34)	1	0	1	⁶⁸ Ga-DOTATOC	Bronchial Carcinoid
Gani et al (35)	1	0	1	⁶⁸ Ga-DOTATOC	Bronchial Carcinoid
Our Study	8	6	2	⁶⁸ Ga-DOTATATE	Bronchial Carcinoid - 3, Ileum Carcinoma -1, PNET -2

MTC medullar thyroid carcinoma, PNET pancreatic neuroendocrine tumour

*One false positive

Figures

Figure 1

A 58-y-old man was presented with ectopic ACTH secreting Cushing Syndrome. FDG PET/CT images (a-c) showed a non-avid lung nodule. MIP, trans-axial CT, PET and fused PET/CT images (d-g) show mild focal Ga-68-DOTATATE uptake (SUVmax 1.9) in right lower lobe nodule (black filled arrows). Post-surgery histological diagnosis was typical bronchial carcinoid secreting ACTH. After surgery Cushing's symptoms is cured. Uptake is also seen with FDG (b-c) and Ga-68-DOTATATE (d, f-g) PET/CT due to a rib fracture (black dashed arrows).

Figure 2

A 2 Ga-68-DOTATATE PET MIP (a-b) images in two female patients, 42-y and 49-y-old, with ectopic ACTH secreting Cushing Syndrome due to metastatic neuroendocrine tumors. Primary tumor sites in both patients were identified by 68Ga-DOTATATE as shown by focal intense uptake (SUVmax 25.3 and 35.5) at small bowel (filled arrow) and head of pancreas (dashed arrow). Both patients subsequently underwent for somatostatin receptor radionuclide therapy.

Figure 3

A 67-y-old woman history of surgical resection for ACTH pituitary macro-adenoma was referred with suspected recurrent Cushing disease. PET MIP (a), trans- axial CT, PET and fused PET/CT images (b-d) show no Ga-68- DOTATATE uptake in pituitary fossa in keeping with prior curative resection. MRI showed no glandular tissue in pituitary fossa. The source of recurrent ACTH in this case was unknown.

Figure 4

A 50-y-old woman was referred with recurrent central hyperthyroidism, 2 year post pituitary surgery for a TSH secreting micro-adenoma. Ga-68-DOTATATE PET MIP (a-b), trans-axial PET and fused PET/CT images (c-d) clearly depict increased focal uptake (SUVmax 14.3) in pituitary fossa. The patient underwent repeat surgical resection of recurrent pituitary adenoma (Thyrotropinoma).