



Comparison of ⁶⁸Ga-DOTANOC PET/CT and contrast-enhanced CT in localisation of tumours in ectopic ACTH syndrome

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Abstract

Background: Localising ectopic adrenocorticotrophic hormone (ACTH) syndrome (EAS) tumour source is challenging. Somatostatin receptor-based PET imaging has shown promising results, but the data is limited to case reports and small case series. We reviewed here the performance of ⁶⁸Ga-DOTANOC positron emission tomography (PET)/computed tomography (CT) and contrast-enhanced CT (CECT) in our cohort of 12 consecutive EAS patients.

Materials and methods: Retrospective data analysis of 12 consecutive patients of EAS presenting to a single tertiary care centre in a period between January 2013 and December 2014 was done. CECT and ⁶⁸Ga-DOTANOC PET/CT were reported (blinded) by an experienced radiologist and a nuclear medicine physician, respectively. The performance of CECT and ⁶⁸Ga-DOTANOC PET/CT was compared.

Results: Tumours could be localised in 11 out of 12 patients at initial presentation (overt cases), whereas in one patient, tumour remained occult. Thirteen lesions were identified in 11 patients as EAS source (true positives). CECT localised 12 out of these 13 lesions (sensitivity 92.3%) and identified five false-positive lesions (positive predictive value (PPV) 70.5%). Compared with false-positive lesions, true-positive lesions had greater mean contrast enhancement at 60s (33.2 vs 5.6 Hounsfield units (HU)). ⁶⁸Ga-DOTANOC PET/CT was able to identify 9 out of 13 lesions (sensitivity 69.2%) and reported no false-positive lesions (PPV 100%).

Conclusion: CECT remains the first-line investigation in localisation of EAS. The contrast enhancement pattern on CECT can further aid in characterisation of the lesions. ⁶⁸Ga-DOTANOC PET/CT can be added to CECT, to enhance positive prediction of the suggestive lesions.

Key Words

- ▶ EAS
- ▶ ⁶⁸Ga-DOTANOC PET/CT
- ▶ CECT
- ▶ Cushing's syndrome
- ▶ lung carcinoid
- ▶ pulmonary paraganglioma
- ▶ DIPNECH

Endocrine Connections
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Introduction

Ectopic adrenocorticotrophic hormone (ACTH) syndrome (EAS) is a rare disorder, accounting for 5–15% cases of endogenous Cushing's syndrome (CS) (1, 2). Although

initially construed to be caused by malignant tumours (such as small-cell carcinoma of lung), majority of cases of EAS are now reported to be caused by neuroendocrine



tumours (NETs) that include carcinoid tumours of bronchopulmonary system, thymus, and gastrointestinal tract; pancreatic NETs; medullary thyroid carcinoma and pheochromocytoma/paraganglioma (1, 3). Localisation of these tumoral sources of ectopic ACTH secretion is a challenging task. With time, the localisation strategies have evolved from chest X-rays to advanced anatomical imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) followed by functional imaging modalities (4). The functional imaging modalities that have been studied in EAS include metaiodobenzylguanidine scans in earlier days, followed by single-photon emission computed tomography (SPECT)-based octreotide scintigraphy (¹²³I-Tyr-3-octreotide and ¹¹¹In-DTPA-pentetreotide) and more recently PET-based imaging such as ¹⁸F-FDG PET/CT scan and ⁶⁸Ga-based somatostatin receptor (SSTR) positron emission tomography (PET)/CT scans (2, 4). Despite these advances, ectopic source remains occult in 9–27% of cases (2), even as high as in 50% in some series (5, 6, 7). Although of proven value in NETs (8, 9), the literature for the newer PET-based imaging, especially ⁶⁸Ga SSTR scans in EAS is limited to few case reports/series (10, 11, 12, 13, 14, 15, 16). We hereby report our experience regarding the performance of ⁶⁸Ga-DOTANOC PET/CT and contrast-enhanced CT (CECT) in 12 consecutive EAS patients managed at our centre.

Patients and methods

Medical records of 48 consecutive patients of ACTH-dependent CS treated at the Department of Endocrinology, KEM Hospital, Mumbai, India, between January 2013 and December 2014 were reviewed retrospectively. Twelve patients diagnosed as EAS were included in the study (none of these patients had been a part of our previously published cohort) (17). The diagnosis of EAS was established after a stepwise evaluation as described previously (17). All EAS cases (negative/equivocal pituitary MRI and a peripheral ACTH gradient on corticotrophin-releasing hormone-stimulated inferior petrosal sinus sampling) have initially undergone CECT scan of the neck, chest, abdomen, and pelvis for localisation of the ectopic source. Helical CT was obtained with section collimation of 1–3 mm by the Philips Brilliance (Amsterdam, The Netherlands) 64-slice CT scanner. The contrast enhancement was obtained with 80 mL of iodinated material (Accupaque 300) injected with a mechanical power injector at a rate of 2.7 mL/s. Scanning from the neck to the pelvis was performed at baseline and 60s after initiation of contrast

infusion. ⁶⁸Ga-DOTANOC PET/CT scan was an additional imaging test for all patients. ⁶⁸Ga was obtained from in-house ⁶⁸Ge–⁶⁸Ga generator. This was then labelled with DOTA-conjugated peptide (DOTANOC), which is a somatostatin analogue in the automated synthetic module. Whole-body (head to toe) scans were obtained with acquisition post 1–1.5 h of intravenous injection of 3–5 mCi ⁶⁸Ga-DOTANOC. PET scan was performed after CT scan acquisition. Scans were acquired on dedicated PET/CT scanner (STE-16, BGO crystal, 16-slice CT scanner, GE Healthcare). Vertex-to-mid-thigh acquisitions in hands above the head position were obtained. PET scan was acquired in 7–8 min overlapped body position with 3 min acquisition per body position. CT data were used for attenuation correction and fusion imaging. The images were reconstructed in the standard display consisting of trans-axial, sagittal and coronal projections. CT-guided biopsy of the suspected EAS lesion was done before surgical resection. Final diagnosis of tumoural source of EAS (true-positive lesions) was confirmed on the basis of histopathologically proven NETs with ACTH immunohistochemistry positivity and/or demonstration of significant reduction in hypercortisolemia, after resection of the suggested lesion.

For the purpose of this study, CECT images were retrospectively reported by an experienced radiologist who was blinded for the final outcomes of the patients. Reporting was done in a predefined format, which included common sites of EAS such as the thyroid, thymus, lungs, pancreas and adrenals. The lesions were reported as ‘suggestive lesions’ if their CT characteristics were suggestive of tumoural origin and provoked specific diagnostic action like biopsy. The other lesions, such as atelectasis, fibrotic nodule and calcified lymph nodes, that did not warrant any action were regarded as ‘non-specific lesions’. Although these non-specific lesions were recorded, they were excluded from the analysis of diagnostic accuracy of CT. The CT characteristics of true-positive and false-positive lesions were compared in terms of morphological features and contrast enhancement (difference between postcontrast Hounsfield units (HU) at 60s and baseline HU).

Similarly, ⁶⁸Ga-DOTANOC PET/CT images were retrospectively reviewed by a nuclear medicine physician who was blinded to patient outcomes. Any area of uptake with intensity greater than background that could not be identified as physiological activity (pituitary gland, spleen, liver, adrenal glands, and uncinate process of pancreas, thyroid, and urinary tract) was considered to be positive. The sensitivity and PPV were compared with CECT.

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Table 1 Baseline characteristics of patients, lesions reported on CECT and ⁶⁸Ga-DOTANOC PET/CT, histopathology, and final outcome.

Case no	Age/sex	EAS lesions	CECT			⁶⁸ Ga-DOT-ANOC PET/CT		Final histopathology	Outcome		
			Suggestive lesions			Number of lesions (SUV max)	Plasma ACTH (pg/mL)			LDDS cortisol (µg/dL)	
			True positive*	False positive	Non-specific lesions						
1	45/F	2.5 cm nodule in the left inferior hilar region of the lung (Fig. 1A1 and A2)	1	1 (7 mm liver nodule)	1 (LN)	1 (TP) (3.4)	203	8.81	+	BPC	Remission
2	28/F	0.8 cm nodule in the medial segment of the middle lobe of the right lung (Fig. 1B1 and B2)	1	0	0	1 (TP) (2.4)	252	13.4	+	BPC	Remission
3	41/F	0.9 cm nodule in the apical segment of the right lower lobe of the lung (Fig. 1C1 and C2)	1	0	0	1 (TP) (1.5)	304	29.4	+	Bronchial paraganglioma	Remission
4	56/M	2.6 cm nodule in the superior segment of the right lower lobe of the lung (Fig. 1D1 and D2)	1	1 (thyroid nodule)	2 (LN, FL)	1 (TP) (4.4)	314	34.5	NA	NA	Partial remission after RFA
5	23/M	1 cm nodule in the apicoposterior segment of the left upper lobe of the lung (Fig. 2E1 and E2)	1	0	1 (LN)	0	98.6	15.46	+	BPC	Remission
6	43/F	1.2 cm nodule in the medial segment of the right middle lobe of the lung (Fig. 2F1 and F2)	1	0	2 (atelactasis, adrenal adenoma)	0	72.9	23.19	+	BPC	Remission
7	34/F	Multiple confluent solid nodules of 1–1.5 cm in the upper lobe of the right lung (taken as a single lesion) (Fig. 2G1 and G2)	1	0	2 (LN, FL)	0	244	16.5	+	DIPNECH	Remission
8	33/F	1 cm nodule in the apical segment of the right lower lobe of the lung (Fig. 2H1 and H2)	1	0	1 (fibrocavitatory lesion)	0	864	52.4	+	BPC	Remission
9	37/F	Two 5.8 and 1 cm retroperitoneal masses (Fig. 3I1 and I2)	2	0	0	2 (TP) (19.4, 19)	1250	58.4	+	RPC	Remission
10	22/M	3 cm mass in the body of pancreas (Fig. 3J1 and J2)	1	0	1 (FL)	1 (TP) (3.2)	314	31	+	PNET	Remission
11	36/M	(a) 1.9 cm nodule in the medial segment of the right middle lobe of the lung (b) 0.7 cm nodule in the lower lobe of the left lung (Fig. 3K1, K2 and K3)	1 (TP a)	0	1 (LN)	2 (TP a and b) (2, 3.5)	319	65.8	+	SCLC	Bilateral adrenalectomy and chemotherapy
12	29/M	No definite lesion identified#	0	3 (lung nodules)**	0	0	107	53	NA	–	Bilateral adrenalectomy

ACTH, adrenocorticotropic hormone; LDDS, low-dose dexamethasone suppression; BPC, bronchopulmonary carcinoid; DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; FL, fibrotic lesion; LN, calcified mediastinal lymph node; NA, not available; PNET, pancreatic neuroendocrine tumor; RPC, retroperitoneal carcinoid; SCLC, small-cell lung carcinoma; SUV max, standardized uptake value maximum.

*The true positive lesions are the same as the true positives described in the adjacent column; **Lesions were non-enhancing and disappeared after the course of antibiotics; #Patient with occult disease at last follow-up.



Results

In our series, the mean age at presentation was 35.5 years (range 22–45 years) with five males and seven females (Table 1). Out of 12 patients, EAS source could be localised in 11 patients at the first evaluation (overt cases), whereas 1 patient remained occult till last follow-up (18 months). In these 11 patients, a total of 13 lesions (10 intra-thoracic, 3 intra-abdominal) were found to be true-positive EAS source (Figs 1, 2 and 3). Two patients had two lesions each, resulting in 13 lesions in 11 patients (patient 11 had small-cell carcinoma in the middle lobe of the right lung, with metastasis to the left lung, and patient 9 was reported to have two distinct adjacent lesions on both CECT and ⁶⁸Ga-DOTANOC PET/CT, which was later confirmed as a single retroperitoneal carcinoid intra-operatively).

CECT

The radiologist reported 28 lesions in total, with 17 as 'suggestive lesions' and 11 as 'non-specific' ones (Table 1). Compared with the final outcome, 12 of these 17 suggestive lesions were true positive, and the remaining 5 were false positive. The false-positive lesions included three infective pulmonary nodules in patient 12 (which cleared on repeat imaging after antibiotic therapy), one thyroid nodule in

patient 5 (which was cytologically Bethesda category 2) and one 7 mm liver nodule in patient 1 (which remained static even after patient achieved remission post-resection of bronchial carcinoid). Thus, CECT has sensitivity of 92.3% (12/13) for overt cases, and positive predictive value (PPV) of 70.5% (12/17) for 'suggestive' lesions (Table 2). However, the PPV dropped down to 42.8% (12/28) with inclusion of non-specific lesions. Difference between post-contrast HU at 60s and baseline HU was 33.2HU (range 26.0–62.5) for true-positive lesions and 5.6HU (range 2–8) for false-positive lesions.

⁶⁸Ga-DOTANOC PET/CT

The nuclear medicine physician reported 9 lesions (out of 13 true positive lesions) in seven patients. Thus, PPV of ⁶⁸Ga-DOTANOC PET/CT per lesion was 100% (Table 2). It failed to identify four lesions (one lesion each in patients 5, 6, 7 and 8; Fig. 2), thus making a sensitivity of 69.2%. The mean standardised uptake value maximum in the positive lesions was 5.79 (range 1.5–19.4).

Management and outcome

The management strategies included resection of the suspected lesions in nine patients, radiofrequency

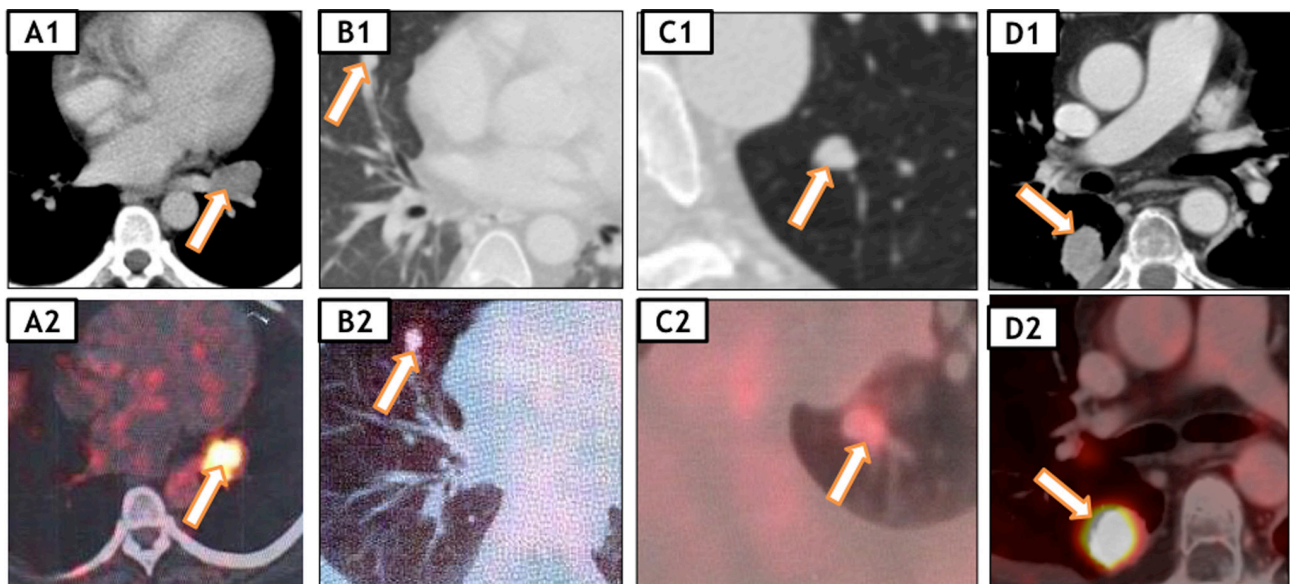
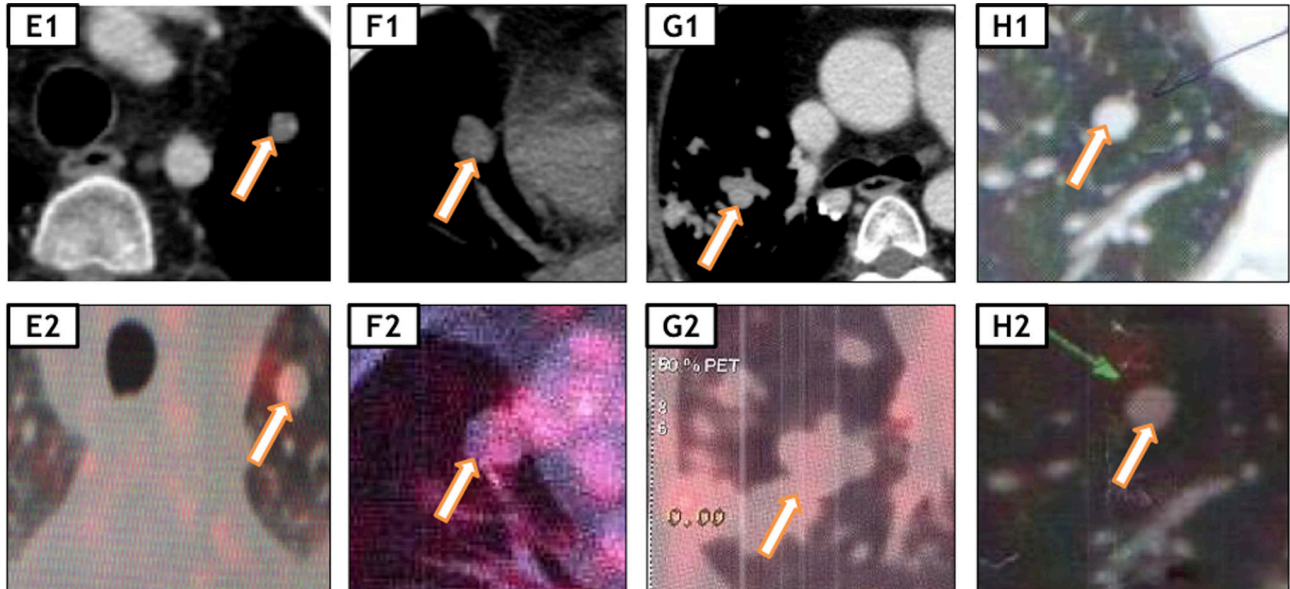


Figure 1

Representative CECT and ⁶⁸Ga-DOTANOC PET/CT images for patients 1 (A1 and A2), 2 (B1 and B2), 3 (C1 and C2) and 4 (D1 and D2). All four patients had bronchopulmonary carcinoids (BPC) with corresponding uptake on ⁶⁸Ga-DOTANOC PET/CT scans. Details given in Table 1.

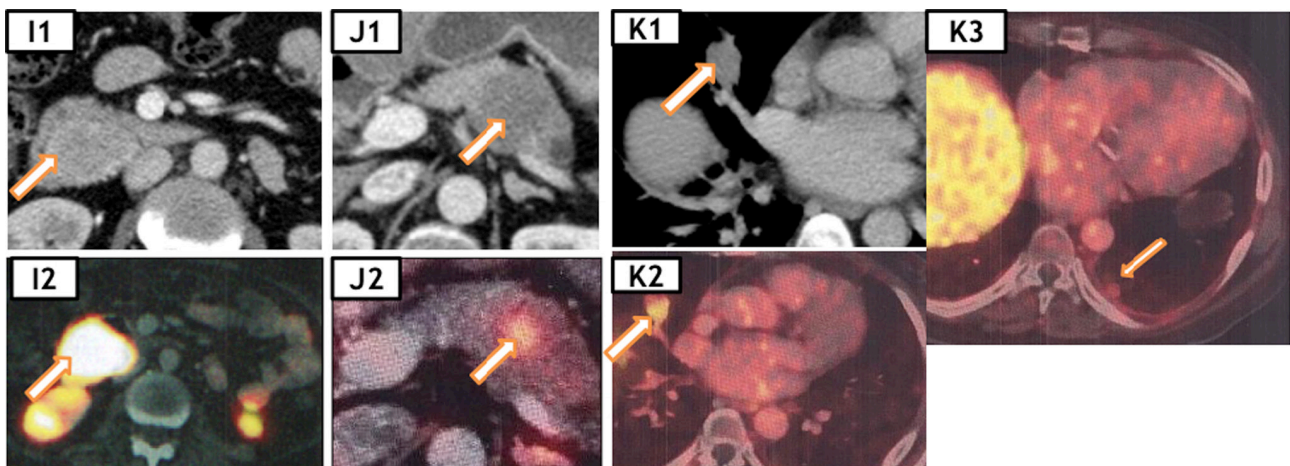
**Figure 2**

Representative CECT and ⁶⁸Ga-DOTANOC PET/CT images for Case 5: BPC showed on CECT (E1) with no uptake on ⁶⁸Ga-DOTANOC PET (E2) Case 6: BPC showed on CECT (F1) with no uptake on ⁶⁸Ga-DOTANOC PET (F2) Case 7: DIPNECH showed on CECT (G1) with no uptake on ⁶⁸Ga-DOTANOC PET (G2) Case 8: BPC showed on CECT (H1) with no uptake on ⁶⁸Ga-DOTANOC PET (H2) Details given in Table 1.

ablation of lung nodule (patient 4, high surgical risk) and chemotherapy for metastatic small-cell lung carcinoma (patient 11). Patient 12 underwent bilateral adrenalectomy to control hypercortisolism, because tumour remained occult at last follow-up (18 months). Details of outcome are shown in Table 1.

Histopathology

Histopathology was available in all patients except one (patient 4). Patient 4 underwent CT-guided biopsy of suspected lung lesion at the time of radiofrequency ablation (RFA), but the biopsied specimen was inadequate

**Figure 3**

Representative CECT and ⁶⁸Ga-DOTANOC PET/CT images for Case 9: Retroperitoneal carcinoid positive on both scans (I1 and I2) Case 10: NET at the body of pancreas with atrophic tail positive on both scans (J1 and J2) Case 11: Small cell carcinoma of right lung (K1 and K2) with metastasis to opposite lung (K3) Details given in Table 1.

Table 2 Sensitivity and PPV of CECT and ⁶⁸Ga-DOTANOC PET/CT (total true-positive lesions = 13).

	True positive	False positive	False negative	Sensitivity (%)	PPV (%)
CECT	12	5	1	92.3	70.5
⁶⁸ Ga-DOTANOC PET/CT	9	0	4	69.2	100

for histopathological diagnosis. However, there was significant reduction in hypercortisolaemia post-RFA; hence, it was considered as the true EAS source. All other patients ($n=10$) had histopathologically confirmed NET with positive immunostaining for synaptophysin, chromogranin and ACTH. The histopathological diagnosis included bronchopulmonary carcinoids ($n=5$), diffuse idiopathic pulmonary neuroendocrine cell hyperplasia ($n=1$), pulmonary paraganglioma ($n=1$), small-cell carcinoma lung ($n=1$), gastroenteropancreatic neuroendocrine tumor (GEP-NET) ($n=1$) and retroperitoneal carcinoid ($n=1$).

Discussion

The localisation of tumours causing EAS has always been a challenge. In an editorial review, de Herder and coworkers (18) have suggested that no single imaging modality is of sufficient accuracy to allow singular use, and various modalities especially anatomical and functional imaging have to be used in combination. This older review is still held true by recent systemic analyses (2). Among the functional imaging modalities, maximum data are on SPECT-based octreotide scintigraphy (10). In general, PET-based imaging offers a better modality over SPECT-based imaging (19). SSTR-based PET imaging has shown promising results in localisation of EAS. However, the data on this modality is limited to case reports and some case series (11, 12, 13, 14, 15, 16). We reviewed here the performance of ⁶⁸Ga-DOTANOC PET/CT imaging in detecting the source of ectopic ACTH secretion in 12 consecutive patients of EAS presented to our centre between 2013 and 2014. Given the inherent bias of reporting only positive cases in case reports, our study is important as it is the largest report of use of this modality in consecutive patients of EAS and its comparison with CECT.

⁶⁸Ga-DOTANOC PET/CT

In our study, ⁶⁸Ga-DOTANOC PET/CT localised 9 out of 13 lesions with overall sensitivity of 69.2%; site-specific

sensitivity was 60% (6/10) for lung lesions and 100% (3/3) for GEP-NET. As there are no similar series for comparison, we compared the performance of ⁶⁸Ga-DOTANOC PET/CT in our study with a recent individual patient-based systematic review done by Isidori and coworkers (2). They analysed studies on EAS localisation, which have included at least one conventional and one nuclear medicine investigation. In this systematic review, data on ⁶⁸Ga-SSTR PET/CT use was available for EAS patients ($n=23$). They reported similar CECT sensitivity of 81.8% (18/22) for histopathologically proven lesions, 77.8% (7/9) for lung lesions and 100% (4/4) for GEP NET. Better performance of ⁶⁸Ga-DOTANOC PET/CT is well reported in GEP-NET (sensitivity approaching up to 95%) (20).

Additionally, in our study, no false-positive lesions were reported in ⁶⁸Ga-DOTANOC PET/CT, making its PPV 100%. This is comparable with the lower false-positive rate (4.3%) reported by Isidori and coworkers (2). Our finding of high PPV of ⁶⁸Ga-DOTANOC PET/CT is particularly important as it may consolidate the findings of CECT (which, though more sensitive, has lower PPV). This substantiates the suggested role of functional imaging to back up the findings of anatomical imaging and facilitate therapeutic decision making (18, 21). We suggest that a convincing uptake on ⁶⁸Ga-DOTANOC PET/CT in suspected lesions might obviate the need for preoperative biopsy to establish ACTH source, although this needs to be studied in a larger prospective cohort.

CECT

In our study, CECT has sensitivity of 92.3% in overt cases and PPV of 70.5% for 'suggestive' lesions. Various series have reported the sensitivity of CECT ranging from 66 and 93% (2, 3, 21). The probable reasons for better sensitivity observed by us (92.3%) might be a small sample size, technical differences in the CT scanning, referral bias for severe cases and the lower number of occult cases in our cohort. As the tumours responsible for EAS are often small, the resolution of CT scan as determined by the slice thickness of CT acquisition is an important determinant. Whenever specified, different series have used variable slice thicknesses ranging from 1 to 10 mm (3, 21). We have used thin sections of 1–3 mm, which might partly explain the better sensitivity observed in our study. Another important confounding factor is the proportion of occult cases in the studied cohort. This is evident in a study by Zemskova and coworkers (21) in which they did a comprehensive prospective analysis of imaging modalities in 41 EAS patients. They reported that



the sensitivity of CT reduced from 93% (when restricted to tumour-found group) to 63% (when occult cases were included in the analysis).

In our study, CECT had a PPV of 70.5% (with a false-positive rate of 29.5%), which is similar to that reported by Zemskova and coworkers (66%) (21). However, the false-positive rate is considerably higher than that reported by Isidori and coworkers (a false-positive rate of only 3.7%) (4). Although the reason for this disparity remains unknown, one notable difference is the higher sensitivity of CECT (92.3%) in our study compared with that by Isidori and coworkers (66.2% overall and 81.8% for histologically confirmed cases). Given the fact that high sensitivity often comes at a cost of high false-positive rate, use of sensitive acquisition parameters of thin CT sections (1–3 mm) at our centre might have contributed to higher false-positive rate. Notably, we have excluded the non-specific lesions (which did not evoke any diagnostic action like biopsy) from our analysis. This factor has an important bearing on the PPV analysis. As predicted, the PPV of CECT reduced to 42.8% after inclusion of such lesions. Because NETs are highly vascular structures and have good contrast enhancement (23), we analysed the contrast enhancement characteristics of our true-positive lesions. We found that true-positive lesions had better enhancement compared with false-positive lesions. We suggest that consideration of this characteristic may enhance the predictivity of suggestive lesions on CECT.

Finally, all our patients with positive functional imaging had a corresponding lesion well evident on conventional CT scans. Tabarin and coworkers (24) have questioned the additional utility of SSTR-based functional imaging, arguing that in most positive reported cases, the source of ectopic ACTH was already evident on conventional CT/MRI scans. They have shown the limited utility of SSTR imaging (octreotide-based SPECT imaging) over CECT in a carefully selected cohort of 12 patients with occult EAS on conventional imaging. Given that the functional imaging scans have limited availability, this objection seems pertinent. The sensitivity of CT scans will always be higher than that of functional scans because it is not biologically plausible to have a tracer uptake on the functional scan without a corresponding anatomical substrate on CT/MRI. However, for clinical relevance, suggestive lesions on CT should not only escape an overlook but also be convincing enough to provoke therapeutic intervention. Reports of initially overlooked lesions on CECT, which were retrospectively confirmed after a positive SSTR scan, substantiate the former concern (5). Notably patient 2, (Fig. 1B) had a 0.8 cm nodule in the

middle lobe of the right lung lying along the course of pulmonary vessels. The difficulty encountered in detecting such lesions is well described (25). Although it was reported as probable lesion by the radiologists at our centre, her scans were repeatedly reported negative at the referring centre. The attempts at biopsy failed due to difficult location. The convincing uptake shown on ⁶⁸Ga-DOTANOC PET/CT consolidated the diagnosis and facilitated the decision of surgery. Similar facilitation with a positive functional scan was reported by More and coworkers (26) in a patient with severe bronchiectasis that defied CECT localisation of two bronchial carcinoids. Additionally, ⁶⁸Ga-DOTANOC PET/CT has helped to change the management strategy in one of our patients. In patient 11 (Fig. 3), identification of an additional focus on ⁶⁸Ga-DOTANOC PET/CT changed the stage of the disease (from localised disease to metastatic) and treatment (from surgery to palliative chemotherapy).

Given the limited availability of ⁶⁸Ga-DOTANOC PET/CT, the commonly used functional imaging modality is octreoscan (¹²³I-Tyr-3-octreotide and ¹¹¹In-DTPA-pentetreotide scans). However, there are no studies of direct comparison of these octreoscans with ⁶⁸Ga-DOTANOC PET/CT in a cohort of EAS patients. Technically, ⁶⁸Ga-DOTANOC PET/CT has better sensitivity and image quality than SPECT-based octreoscan due to improved spatial resolution and better signal-to-noise ratios attributable to PET-based acquisition parameters (19). In their review, Isidori and coworkers reported lower sensitivity of octreoscan (48.9%) compared with ⁶⁸Ga-DOTANOC PET/CT (81.8%) in the overall cohort (2).

The limitations of our study include small sample size and lower number of occult cases. Also, majority of our tumours were intra-thoracic. This may influence the sensitivity analysis because tumour site-specific differences in sensitivity of imaging modalities are well described (2). We emphasise the need for a larger prospective study on ⁶⁸Ga-based SSTR PET/CT in EAS patients with varied tumour types. Also, our sample may not be representative of general population, because ours being an established referral centre for CS, the possibility of preferential reference of difficult patients with CS who were not localised by the routine workup could not be refuted, and this may account for higher proportion of ectopic CS cases in our total CS cohort.

In sum, based on our retrospective experience, our current approach to localisation of EAS is to initiate with a thin-slice (1–3 mm) conventional CECT scan from the neck to the pelvis (owing to its higher sensitivity) followed by ⁶⁸Ga-DOTANOC PET/CT scan for confirmation of positive lesions (due to its higher PPV). In case of unavailability



of ⁶⁸Ga-DOTANOC PET/CT scans, we suggest a careful study of contrast enhancement pattern on CECT to characterise the lesions and guide better targeting of lesions for biopsy (with ACTH staining). Conversely, positive ⁶⁸Ga-DOTANOC PET/CT scans may obviate the need for preoperative biopsy.

To conclude, in the current era of functional imaging, conventional imaging with thin-section CECT still holds promise in EAS localisation. The need for experienced radiology services cannot be overemphasised. ⁶⁸Ga-DOTANOC PET/CT images help to consolidate the CT localisation findings.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

- 1 Wajchenberg BLEO, Mendonca BB, Liberman B, Pereira MAA, Carneiro PC, Wakamatsu A & Kirschner MA. Ectopic Adrenocorticotrophic hormone syndrome. *Endocrine Reviews* 1994 **15** 752–787. (doi:10.1210/edrv-15-6-752)
- 2 Isidori AM, Sbardella E, Zatelli MC, Boschetti M, Vitale G, Colao A, Pivonello R & ABC Study Group. Conventional and nuclear medicine imaging in ectopic Cushing's syndrome: a systematic review. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 3231–3244. (doi:10.1210/JC.2015-1589)
- 3 Ilias I, Torpy DJ, Pacak K, Mullen N, Wesley RA & Nieman LK. Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 4955–4962. (doi:10.1210/jc.2004-2527)
- 4 Isidori AM, Kaltsas GA, Pozza C, Frajese V, Newell-Price J, Reznick RH, Jenkins PJ, Monson JP, Grossman AB & Besser GM. The ectopic adrenocorticotropin syndrome: clinical features, diagnosis, management, and long-term follow-up. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 371–377. (doi:10.1210/jc.2005-1542)
- 5 Özkan ZG, Kuyumcu S, Balköse D, Ozkan B, Aksakal N, Yilmaz E, Sanli Y, Türkmen C, Aral F & Adalet I. The value of somatostatin receptor imaging with In-111 Octreotide and/or Ga-68 DOTATATE in localizing Ectopic ACTH producing tumours. *Molecular Imaging and Radionuclide Therapy* 2013 **22** 49–55. (doi:10.4274/MIRT)
- 6 Hernández I, Espinosa-de-los-Monteros AL, Mendoza V, Cheng S, Molina M, Sosa E & Mercado M. Ectopic ACTH-secreting syndrome: a single center experience report with a high prevalence of occult tumour. *Archives of Medical Research* 2006 **37** 976–980. (doi:10.1016/j.arcmed.2006.05.015)
- 7 Torpy DJ, Chen CC, Mullen N, Doppman JL, Carrasquillo JA, Chrousos GP & Nieman LK. Lack of utility of ¹¹¹In-pentetreotide scintigraphy in localizing ectopic ACTH producing tumours: follow-up of 18 patients. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 1186–1192. (doi:10.1210/jcem.84.4.5576)
- 8 Jensen RT, Cadiot G, Brandi ML, De Herder WW, Kaltsas G, Komminoth P, Scoazec JY, Salazar R, Sauvanet A & Kianmanesh R. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumour syndromes. *Neuroendocrinology* 2012 **95** 98–119. (doi:10.1159/000335591)
- 9 Phan AT, Oberg K, Choi J, Harrison LH Jr, Hassan MM, Strosberg JR, Krenning EP, Kocha W, Woltering EA, Maples WJ & North American Neuroendocrine Tumour Society (NANETS). NANETS consensus guideline for the diagnosis and management of neuroendocrine tumours: well-differentiated neuroendocrine tumours of the thorax (includes lung and thymus). *Pancreas* 2010 **39** 784–798. (doi:10.1097/MPA.0b013e3181ec1380)
- 10 Santhanam P, Taieb D, Giovannella L & Treglia G. PET imaging in ectopic Cushing syndrome: a systematic review. *Endocrine* 2015 **50** 297–305. (doi:10.1007/s12020-015-0689-4)
- 11 Thomas T, Zender S, Terkamp C, Jaekel E & Manns MP. Hypercortisolaemia due to ectopic adrenocorticotrophic hormone secretion by a nasal paraganglioma: a case report and review of the literature. *BMC Research Notes* 2013 **6** 331. (doi:10.1186/1756-0500-6-331)
- 12 Treglia G, Salomone E, Petrone G, Giaccari A, Rindi G & Rufini V. A rare case of ectopic adrenocorticotrophic hormone syndrome caused by a metastatic neuroendocrine tumour of the pancreas detected by ⁶⁸Ga-DOTANOC and ¹⁸F-FDG PET/CT. *Clinical Nuclear Medicine* 2013 **38** e306–e308. (doi:10.1097/RLU.0b013e318279ec68)
- 13 Willhauck MJ, Pöpperl G, Rächinger W, Giese A, Auernhammer CJ & Spitzweg C. An unusual case of ectopic ACTH syndrome. *Experimental and Clinical Endocrinology & Diabetes* 2012 **120** 63–67. (doi:10.1055/s-0031-1297967)
- 14 Venkitaraman B, Karunanithi S, Kumar A, Bal C, Ammini AC & Kumar R. ⁶⁸Ga-DOTATOC PET-CT in the localization of source of ectopic ACTH in patients with ectopic ACTH-dependent Cushing's syndrome. *Clinical Imaging* 2014 **38** 208–211. (doi:10.1016/j.clinimag.2013.10.007)
- 15 Gilardi L, Colandrea M, Fracassi SL, Sansovini M & Paganelli G. (⁶⁸Ga-DOTA(0)-Tyr(3) octreotide (DOTATOC) positron emission tomography (PET)/CT in five cases of ectopic adrenocorticotropin-secreting tumours. *Clinical Endocrinology* 2014 **81** 152–153. (doi:10.1111/cen.12313)
- 16 Karageorgiadis AS, Papadakis GZ, Biro J, Keil MF, Lyssikatos C, Quezado MM, Merino M, Schrupp DS, Kebebew E, Patronas NJ, et al. Ectopic adrenocorticotrophic hormone and corticotropin-releasing hormone co-secreting tumours in children and adolescents causing Cushing syndrome: a diagnostic dilemma and how to solve it. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 141–148. (doi:10.1210/jc.2014-2945)
- 17 Kakade HR, Kasaliwal R, Jagtap VS, Bukan A, Budyal SR, Khare S, Lila AR, Bandgar T, Menon PS & Shah NS. Ectopic ACTH-secreting syndrome: a single-center experience. *Endocrine Practice* 2013 **19** 1007–1014. (doi:10.4158/EP13171.OR)
- 18 de Herder WW & Lamberts SW. Tumour localization – the ectopic ACTH syndrome. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 1184–1185. (doi:10.1210/jcem.84.4.5690)
- 19 Rahmin A & Zaidi H. PET versus SPECT: strengths, limitations and challenges. *Nuclear Medicine Communication* 2008 **29** 193–207. (doi:10.1097/MNM.0b013e318282f3a515)
- 20 Treglia G, Castaldi P, Rindi G, Giordano A & Rufini V. Diagnostic performance of Gallium-68 somatostatin receptor PET and PET/CT in patients with thoracic and gastroenteropancreatic neuroendocrine tumours: a meta-analysis. *Endocrine* 2012 **42** 80–87. (doi:10.1007/s12020-012-9631-1)
- 21 Zemskova MS, Gundabolu B, Sinaii N, Chen CC, Carrasquillo JA, Whately M, Chowdhury I, Gharib AM & Nieman LK. Utility of various functional and anatomic imaging modalities for detection of ectopic adrenocorticotropin-secreting tumours. *Journal of Clinical*



- Endocrinology and Metabolism* 2010 **95** 1207–1219. (doi:10.1210/jc.2009-2282)
- 22 Pacak K, Ilias I, Chen CC, Carrasquillo JA, Whatley M & Nieman LK. The role of [(18)F]fluorodeoxyglucose positron emission tomography and [(111)In]-diethylenetriaminepentaacetate-D-Phe-pentetreotide scintigraphy in the localization of ectopic adrenocorticotropin-secreting tumours causing Cushing's syndrome. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 2214–2221. (doi:10.1210/jc.2003-031812)
- 23 Chong S, Lee KS, Kim BT, Choi JY, Yi CA, Chung MJ, Oh DK & Lee JY. Integrated PET/CT of pulmonary neuroendocrine tumours: diagnostic and prognostic implications. *AJR American Journal of Roentgenology* 2007 **188** 1223–1231. (doi:10.2214/AJR.06.0503)
- 24 Tabarin A, Valli N, Chanson P, Bachelot Y, Rohmer V, Bex-Bachelier V, Catargi B, Roger P & Laurent F. Usefulness of somatostatin receptor scintigraphy in patients with occult ectopic adrenocorticotropin syndrome. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 1193–1202. (doi:10.1210/jcem.84.4.5583)
- 25 Doppman JL, Pass HI, Nieman LK, Findling JW, Dwyer AJ, Feuerstein IM, Ling A, Travis WD, Cutler GB Jr, Chrousos GP, *et al.* Detection of ACTH-producing bronchial carcinoid tumours: MR imaging vs CT. *AJR American Journal of Roentgenology* 1991 **156** 39–43. (doi:10.2214/ajr.156.1.1845787)
- 26 More J, Young J, Reznik Y, Raverot G, Borson-Chazot F, Rohmer V, Baudin E, Coutant R & Tabarin A. Ectopic ACTH syndrome in children and adolescents. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 1213–1222. (doi:10.1210/jc.2010-2276)

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