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ORIGINAL ARTICLE

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The Clinical Impact of [^{68}Ga]-DOTATATE PET/CT for the Diagnosis and Management of Ectopic Adrenocorticotropic Hormone – Secreting Tumours

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Abstract

Objectives: Localization of ectopic ACTH-secreting tumours causing Cushing syndrome (ECS) is essential for clinical management, yet often difficult. [^{68}Ga]-DOTATATE PET/CT ([^{68}Ga]-DOTA-(Tyr^3)-octreotate)] is an FDA-approved high-resolution diagnostic tool for imaging neuroendocrine tumours. Data on the clinical utility of [^{68}Ga]-DOTATATE in patients with ECS, however, are scarce. The objectives of this study were to determine the efficacy for ECS localization and the clinical benefit of [^{68}Ga]-DOTATATE imaging.

Method: We conducted a retrospective review of all cases with ECS evaluated with [^{68}Ga]-DOTATATE from November 2016 through October 2018 at three referral centres. The clinical benefit of [^{68}Ga]-DOTATATE was based on detection of new tumours and resultant changes in management.

Results: Over the study period, 28 patients with ECS underwent [^{68}Ga]-DOTATATE: 17 for identification of the primary tumour and 11 during follow-up. [^{68}Ga]-DOTATATE identified the suspected primary ECS in 11/17 patients (65%). Of these, nine patients underwent surgery: eight with confirmed ECS (5 bronchial, 1 thymic, 1 pancreatic and 1 metastatic neuroendocrine tumour of unknown primary origin) and one patient with a false-positive scan (adrenal gland). Of the 11 patients with ECS who underwent [^{68}Ga]-DOTATATE evaluation during follow-up, the study led to changes in clinical management in 7/11 (64%) patients.

Conclusions: [^{68}Ga]-DOTATATE is sensitive in detecting primary and metastatic ECS, often identifies occult tumours after conventional imaging, and impacts clinical care in the majority of patients.

KEYWORDS

[68Ga]-DOTATATE PET, CT, Cushing syndrome, ectopic ACTH secretion, somatostatin receptor, tumour localization

1 | INTRODUCTION

Ectopic ACTH-secreting tumours often lead to fulminant Cushing syndrome (ECS) and are associated with higher mortality compared to other causes of cortisol excess.[1] Prompt identification and treatment of ECS are imperative for optimal clinical outcomes. Surgical cure, however, is achieved in less than half of patients with ECS, partly due to unresectable metastases

and also because many such tumours are small and difficult to localize.[2-6]

Cross-sectional anatomic imaging is commonly used as first-line radiographic investigation for identification of ECS, but its sensitivity for ECS detection is suboptimal, ranging from 52% to 66%.[7,8] In a systematic review, various nuclear medicine functional imaging techniques identified 79% of ECS not detected by initial conventional anatomic imaging.[8] Scintigraphy or single-photon emission computed tomography (SPECT) with [^{111}In]-pentetreotide, a somatostatin receptor (SSTR) ligand (SRL), and [^{131}I]- or [^{123}I]-metaiodobenzylguanidine (MIBG), a catecholamine analog, are commonly used for NET detection, but these studies require prolonged time (imaging at 24-48 hours after radiotracer injection) and have relatively limited sensitivity for disease detection.[9] Positron emission tomography (PET) offers significantly improved imaging quality and shorter protocols [10,11] using a variety of tracers, including [^{18}F]-fluorodeoxyglucose (FDG), [^{18}F]-dihydroxyphenylalanine (DOPA) and [^{68}Ga]-DOTATATE (DOTA-(Tyr^3)-octreotate).[7,12,13] For SRL imaging, [^{68}Ga]-DOTATATE PET/CT has proven to be more sensitive than [^{111}In]-pentetreotide SPECT in detecting various NETs.[14-18] The advantages of [^{68}Ga]-DOTATATE in patients with ECS, however, have only been described in isolated case reports or small case series.[18,19] Here we retrospectively studied the use of [^{68}Ga]-DOTATATE in localizing ECS and the resultant impact on clinical management beyond conventional imaging.

2 | PATIENTS AND METHODS

We conducted a retrospective study of all cases with ECS evaluated with [^{68}Ga]-DOTATATE imaging in three tertiary referral centres

TABLE 1 Characteristics of study participants

	University of Michigan N = 17	Mayo Clinic Rochester N = 6	MD Anderson Cancer Center N = 5	Total N = 28
Age (years)	49 [33-49]	50 [39-63]	51 [43-64]	50 [38-64]
Sex (F/M)	15/2	4/2	3/2	22/6
Clinical diagnosis of CS				
Moon face	12	4	5	21 (75%)
Dorsocervical fat pad	8	3	3	14 (50%)
Supraclavicular fat pad	8	5	2	15 (54%)
Purplish striae	9	3	0	12 (43%)
Facial plethora	11	4	1	16 (57%)
Central obesity	11	4	4	19 (68%)
Proximal muscle weakness	16	5	5	26 (93%)
Hypokalemia	13	4	3	20 (71%)
Hyperglycaemia	12	5	4	21 (75%)
Hypertension	14	5	4	23 (82%)
Biochemical diagnosis of CS				
Basal cortisol (μg/dL)	61 [41-78]	30 [19-44]	64 [24-103]	56 [28-70]
Basal ACTH (pg/mL)	160 [101-294]	112 [84-202]	123 [92-167]	127 [89-245]
Urine free cortisol (μg/24 h)	1229 [315-3234]	289 [167-3342]	441 [404-3151]	730 [225-3456]
ECS diagnosis				
Bronchial NET	5	2	1	8
Pancreatic NET	2	2	1	5
MTC	2	0	0	2
Ileal NET	1	0	0	1
Thymic NET	1	0	0	1
Non-small-cell lung cancer	1	0	0	1
NET-unknown primary[a]	5	2	3	10

Note: Age and biochemical data were expressed as medians [interquartile range].
Abbreviations: ACTH, adrenocorticotropic hormone; CS, Cushing syndrome; ECS, ectopic ACTH-secreting tumour causing Cushing syndrome; F, female; MTC, medullary thyroid carcinoma; NET, neuroendocrine tumour.
[a]NET of unknown primary origin included seven occult NETs (including one false-positive lesion) and 3 metastatic NETs with unclear primary site.

(University of Michigan, Mayo Clinic, Rochester, and The University of Texas MD Anderson Cancer Center) since FDA approval (November 2016), through October 2018. Patient demographics, clinical evaluation, imaging modalities, laboratory, histopathological results and treatment data were reviewed. The study was conducted with approval and waiver of informed consent from the Institutional Review Board at the University of Michigan, Mayo Clinic (Rochester) and MD Anderson Cancer Center.

The diagnosis of Cushing syndrome was confirmed by clinical and hormonal evaluation, in accordance with the Endocrine Society practice guidelines (Table 1).[9] Ectopic ACTH syndrome was defined by hormonal assessment compatible with ACTH-dependent Cushing syndrome, in conjunction with the absence of central gradient during bilateral inferior petrosal sinus sampling or known ECS.[3,4] All cross-sectional imaging, [^{111}In]-pentetreotide scintigraphy and SPECT, [^{68}Ga]-DOTATATE and [^{18}F]-FDG PET/CT images were reviewed by experienced radiologists and nuclear medicine physicians in each institution.

The clinical impact of [^{68}Ga]-DOTATATE was defined as the detection of primary ECS or new metastatic foci, along with consequent changes in clinical management.

3 | RESULTS

Over the study period, 28 patients (age 18-77 years, median 50, 78.6% females) with ectopic ACTH syndrome underwent [^{68}Ga]-DOTATATE scan, including 17 patients to localize the primary ECS (Table 1). Of these, the primary tumour was occult after previous imaging in 15 patients (cross-sectional imaging in all patients, [^{18}F]-FDG PET/CT scan in four patients and [^{111}In]-pentetreotide in three other patients), and in two patients, [^{68}Ga]-DOTATATE scan was the first localizing imaging study used (Figure 1). [^{68}Ga]-DOTATATE scan identified an ECS in 11/17 (65%) patients, of which seven were solitary and 4 metastatic. The diagnosis was confirmed by pathology in 8/11 patients: 5 bronchial NET, 1 thymic NET, 1 pancreatic NET and 1 metastatic NET of unknown primary origin. Surgical cure was achieved in seven of these patients (Figures 2,3), while 1 remaining patient had widely metastatic disease. In this latter patient who was not cured, [^{68}Ga]-DOTATATE identified bronchial and bone lesions but failed to identify liver metastases, which were apparent on MRI and confirmed by biopsy, illustrating false-negative metastases (Figure 4). In another patient with occult ECS, [^{68}Ga]-DOTATATE demonstrated a nodular focus of uptake in the left adrenal gland (Figure 3). Clinical cure, however, was not achieved after left adrenalectomy, and pathology showed adrenocortical hyperplasia. This case illustrates a false-positive scan, which caused a delay in contralateral adrenalectomy and cure of the hypercortisolaemia. Of the remaining two patients, one was lost to follow-up, and the second is awaiting surgery. Of the seven patients in whom the ECS source remained occult after [^{68}Ga]-DOTATATE PET/CT scan, three patients underwent bilateral adrenalectomy, two were treated with mifepristone, and two were treated with ketoconazole for management of hypercortisolaemia.

[^{68}Ga]-DOTATATE was performed to assess disease burden or recurrence in 11 patients with known ECS (Figure 1): 4 pancreatic NETs; 2 unknown primary neuroendocrine carcinomas; 2 medullary thyroid cancers (MTC); 1 ileal NET; 1 bronchial NET; and 1 non-small-cell lung cancer (NSCLC). [^{68}Ga]-DOTATATE identified 9 new metastatic foci and 3 recurrent tumours: 5 solitary bone lesions, 3 pancreatic lesions and 1 intra-abdominal lymph node. Of the 11 patients with known ECS, [^{68}Ga]-DOTATATE evaluation during follow-up period led to changes in clinical management in 7 cases: in three patients with widely metastatic cancer previously treated with chemotherapy (2 MTC and 1 pancreatic NET), [^{68}Ga]-DOTATATE uptake in numerous metastatic foci (Figure 5) led to treatment with

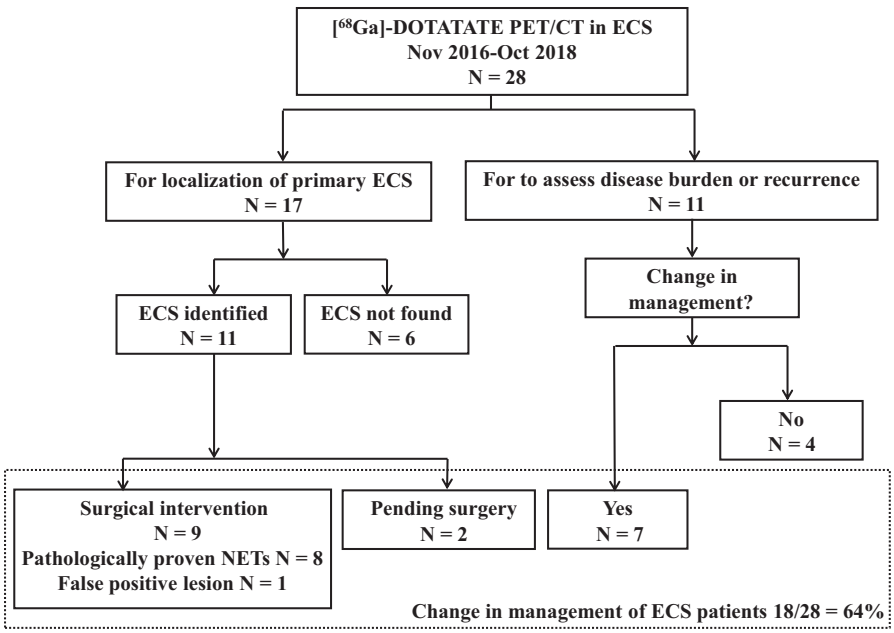

FIGURE 1 Patients with ECS evaluated at University of Michigan, Mayo Clinic Rochester and The University of Texas MD Anderson Cancer Center who underwent [^{68}Ga]-DOTATATE PET/CT between November 2016 and October 2018. The dimensions of ECS detected by [^{68}Ga]-DOTATATE PET/CT imaging ranged from 0.8 to 2.8 cm for primary tumour localization or 0.4-1.8 cm for newly found metastases. Pathology revealed poorly differentiated NET in 2 patients and well-differentiated NET in 6. ECS, ectopic ACTH-secreting tumour causing Cushing syndrome; NET, neuroendocrine tumour

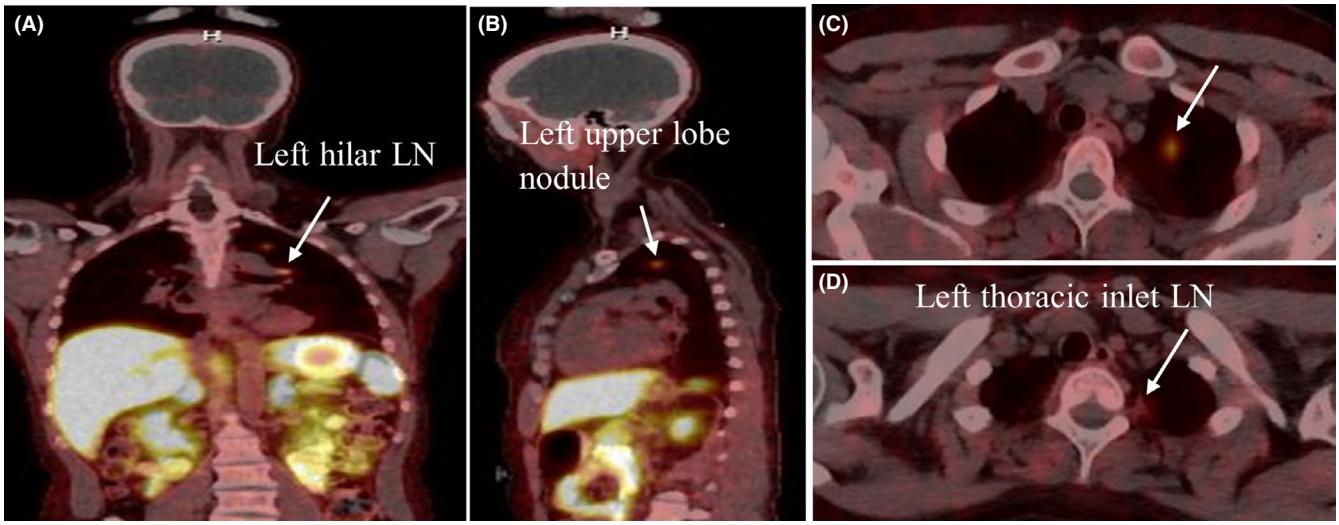

FIGURE 2 [^{68}Ga]-DOTATATE PET/CT demonstrated focal uptake in the upper lobe of the left lung (A, B, C), two foci of uptake in the left hilar region (A), and a left thoracic inlet lymph node (LN) (D) [Colour figure can be viewed at wileyonlinelibrary.com]

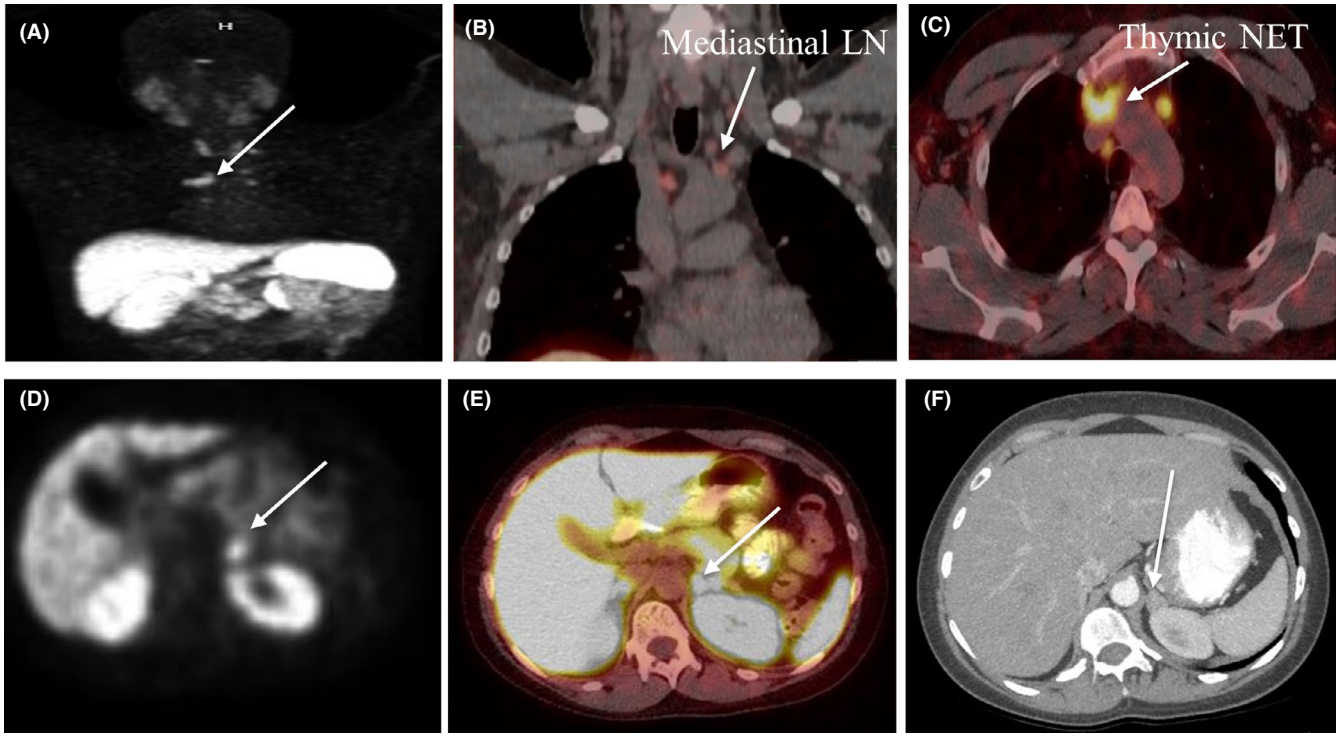

FIGURE 3 [^{68}Ga]-DOTATATE PET/CT demonstrated uptake in the thymus (A, C) and mediastinal lymph node (A, B, C). Pathology revealed high-grade thymic NET with mediastinal lymph node metastasis. [^{68}Ga]-DOTATATE PET/CT revealed focal uptake in the left adrenal gland (D, E). CT abdomen showed left adrenal thickening (F). Left adrenalectomy was performed, but pathology demonstrated adrenal cortex hyperplasia but no malignant tumour, and hypercortisolism did not resolve. NET, neuroendocrine tumour [Colour figure can be viewed at wileyonlinelibrary.com]

[^{177}Lu]- or [^{90}Y]-labelled peptide-receptor radionuclide therapy (PRRT); in two patients with prior surgical removal of primary ECS (one bronchial and one pancreatic NET), [^{68}Ga]-DOTATATE identified single recurrent left upper lung and pancreatic bed lesions, respectively, which were subsequently removed; in one patient with NET of unknown primary origin, [^{68}Ga]-DOTATATE demonstrated new focal bone lesions, which led to treatment with everolimus; and in the last patient with pancreatic NET, 2 metastatic foci were found in the pancreatic tail, which prompted treatment with a somatostatin analogue. In the remaining 4 cases (1 pancreatic NET, 1 ileal NET, 1 NSCLC and 1 NET of unclear primary origin; all metastatic), [^{68}Ga]-DOTATATE findings were concordant with conventional imaging.

The dimensions of newly detected lesions with [^{68}Ga]-DOTATATE PET/CT imaging, either primary or metastatic, ranged from 0.4 to

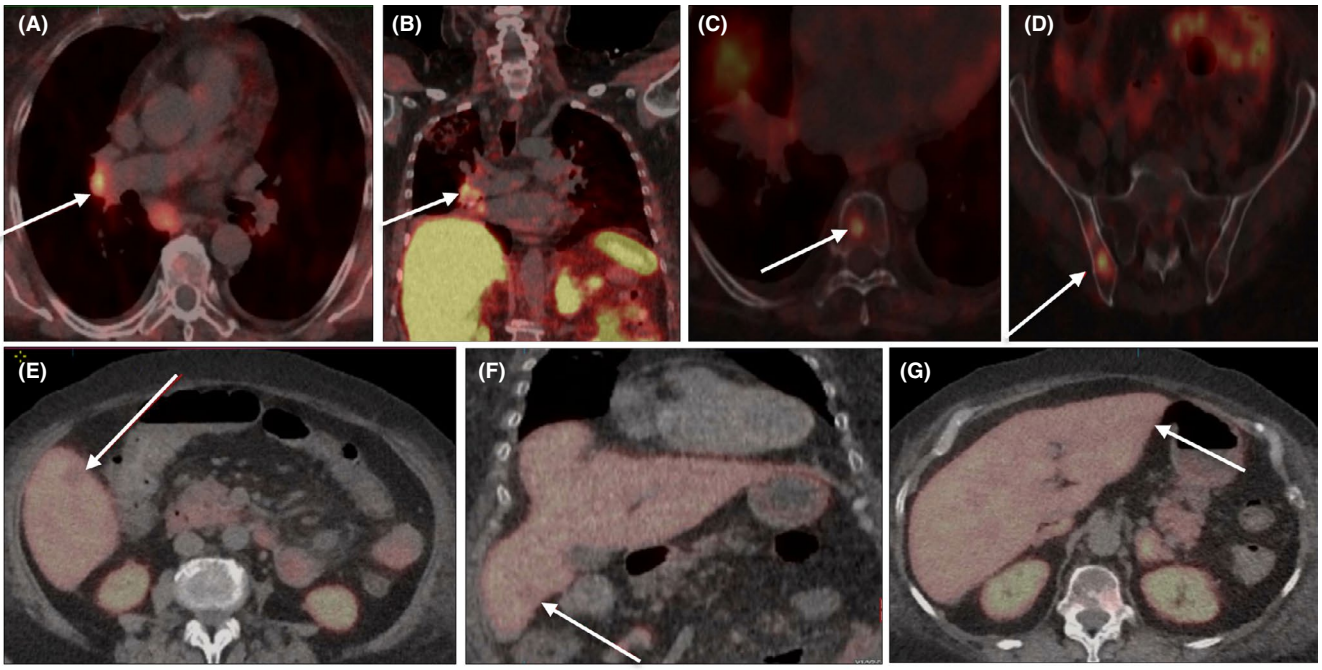

FIGURE 4 [^{68}Ga]-DOTATATE PET/CT demonstrated uptake in the right hilar area (A, B), 8th thoracic vertebra (C) and right iliac bone (D) but failed to identify three liver metastases, apparent on MRI, and confirmed by biopsy. Right liver lobe metastases (E, F) and left liver lobe metastasis (G) in a patient with NET of unclear primary origin. NET, neuroendocrine tumour [Colour figure can be viewed at wileyonlinelibrary.com]

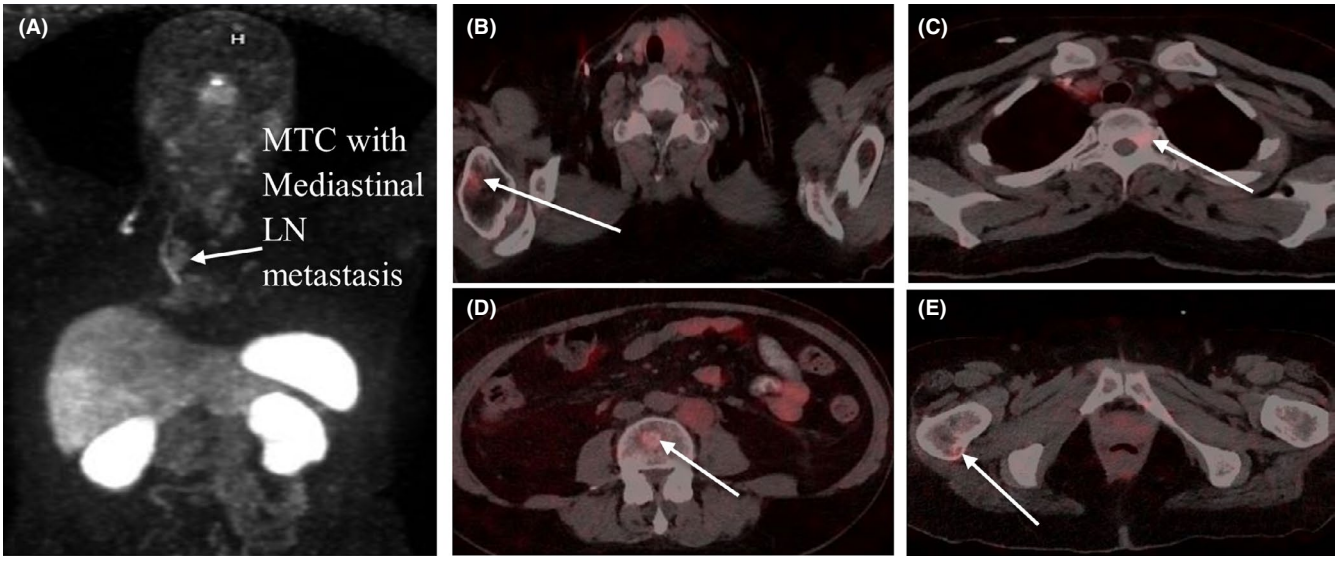

FIGURE 5 [^{68}Ga]-DOTATATE PET/CT demonstrated new bone metastatic lesions in the right humerus (B), 3rd thoracic vertebra (C), 4th lumbar vertebra (D) and right femur (E) in a patient with medullary thyroid cancer with liver and lymph node metastasis (A) [Colour figure can be viewed at wileyonlinelibrary.com]

2.8 cm. Of the eight patients with primary ECS confirmed by pathology, six were classified as well-differentiated NET (5 bronchial and 1 pancreatic) and two as poorly differentiated NET (1 thymic and 1 of unknown primary origin). The majority of primary tumours identified by [^{68}Ga]-DOTATATE PET/CT were not recognized on cross-sectional imaging, especially tumours <1 cm. In two patients, [^{68}Ga]-DOTATATE PET/CT detected tumours in the right middle lung fields that were misidentified as vascular in origin. In retrospect, however, an anatomic correlate to all DOTATATE-avid tumours except bone metastases could be identified on cross-sectional imaging (Figures 2-5).

4 | DISCUSSION

In this retrospective series of 28 patients with ectopic ACTH production leading to Cushing syndrome, [^{68}Ga]-DOTATATE localized

the primary tumour and/or metastases in the majority of study patients. [^{68}Ga]-DOTATATE is a recently approved advanced molecular imaging probe with high affinity for SSTR type 2 (0.2 ± 0.04 nmol/L, as compared to 22 ± 3.6 nmol/L for [^{111}In]-pentetreotide),[20] which, when coupled with the advanced spatial resolution of PET/CT imaging systems, can result in successful detection and accurate localization of small tumours characterized by SSTR expression. A review of the literature found that [^{68}Ga]-DOTATATE is highly sensitive (81.8%) in localization of ECS; however, only 23 of 231 patients assimilated from these studies received [^{68}Ga]-DOTATATE imaging.[8] Papadakis previously published a case of a ectopic Cushing and CRH co-secreting tumour, identified by [^{68}Ga]-DOTATATE PET/CT.[21] ECS is often highly functional and associated with a fulminant clinical course and high mortality. Thus, ECS localization is critical for managing this aggressive form of Cushing syndrome. Despite extensive conventional cross-sectional and functional imaging, up to 19% of ECS remain occult.[2-4] In our study, [^{68}Ga]-DOTATATE identified the primary ECS in 11/17 (65%) of previously occult tumours. The somewhat lower overall accuracy of [^{68}Ga]-DOTATATE PET/CT in our series might reflect a selection bias for difficult cases at our referral centres, with a high prevalence of occult ECS.

Most of these ECS were located in the thorax, and some were smaller than 1 cm, which is near the limit of detection for other imaging modalities. Furthermore, [^{68}Ga]-DOTATATE detected not only well-differentiated NET, but also a poorly differentiated ECS, which are composed of highly proliferative cells with low SSTR expression and high metabolic activity, as evidenced by [^{18}F]-FDG PET/CT.[11,22] Hypercortisolaemia can lower SSTR expression in EAS[23] and result in false-negative scintigraphy, which can be reversed with glucocorticoid antagonist therapy.[24] In our series of 10 patients with previously occult tumours that were located with [^{68}Ga]-DOTATATE scans, three and one were treated with mifepristone and ketoconazole, respectively. Similarly, of the seven patients with tumours that were not located with [^{68}Ga]-DOTATATE scans, three each were treated with mifepristone or ketoconazole prior to the scanning. Thus, six of seven false-negative scans failed to identify the source of ACTH despite concomitant treatment of hypercortisolaemia. [^{68}Ga]-DOTATATE imaging was performed only once in all patients, which precludes any conclusions about longitudinal changes or comparisons with and without treatment of hypercortisolaemia.

Of previously identified ECS, [^{68}Ga]-DOTATATE impacted clinical management in 7/11 (64%) of patients. [^{68}Ga]-DOTATATE allowed cure of recurrent disease in two patients and identified three other patients as candidates for PRRT with [^{177}Lu]- or [^{90}Y]-labelled somatostatin analogs. [10,11,25]

Physiologic uptake of [^{68}Ga]-DOTATATE in several locations such as liver, spleen, adrenal glands, thyroid, pancreas and kidneys can confound image interpretation.[26,27] A previous systematic review described one case of lung NET with a false-positive focus of uptake in the adrenal gland.[28] Similarly, in our study, an ACTH-secreting pheochromocytoma was suspected in one patient with occult tumour who had atypical peripheral [^{68}Ga]-DOTATATE uptake in the left adrenal gland and normal plasma metanephrines (Figure 3). Cushing syndrome was not resolved after left adrenalectomy, and histopathology showed adrenal cortical hyperplasia. Conversely, in another patient with metastatic NET of unknown primary origin, [^{68}Ga]-DOTATATE-avid osseous and pulmonary metastatic lesions were found, but biopsy-proven liver metastases could not be detected (Figure 4), perhaps due to the high background activity of liver and/or poor SSTR expression in certain clonal cell populations. One review of [^{68}Ga]-DOTATATE imaging for detecting ECS reported 17.4% false-negative studies.[8]

Our study demonstrates the high sensitivity of [^{68}Ga]-DOTATATE in the localization of ECS, for both occult primary tumours and metastatic lesions. Importantly, the use of [^{68}Ga]-DOTATATE impacted clinical management in 64% patients with ECS overall. High cost and limited availability of PET/CT imaging, however, might preclude the widespread use of [^{68}Ga]-DOTATATE for ECS imaging, and experience with these scans, which were FDA-approved for clinical use in the USA to localize relatively rare tumors in June 2016, is somewhat limited compared to other imaging studies. Limitations of our study include the small number of patients and the retrospective study design. In addition, the choice of imaging modalities, the management of hypercortisolaemia and the long-term plan of management were not prespecified and were subject to many subjective and circumstantial influences. Nonetheless, combining the experience of three large referral centres, our study gathers the largest number of ECS imaged with [^{68}Ga]-DOTATATE to date and provides a benchmark for the utility of this diagnostic modality for this rare but highly morbid condition. Further prospective investigations are needed to characterize the benefits and pitfalls of [^{68}Ga]-DOTATATE in diagnosis and follow-up of patients with ECS.

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CONFLICT OF INTEREST

The authors report no conflict of interest with this work.

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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