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Diagnostic utility of Gallium-68-somatostatin receptor PET/CT in ectopic ACTH-secreting tumors: a systematic literature review and single-center clinical experience

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Abstract

Purpose Tumors causing ectopic Cushing's syndrome (ECS) are often not visible with conventional imaging. Gallium-68-DOTATATE, DOTATOC, and DOTANOC positron emission tomography/computed tomography (^{68}Ga-SSTR PET/CT) reportedly exhibits greater sensitivity in identifying an ECS source, however, evidence is limited to mainly case reports and a few small retrospective studies. Previous systematic ECS imaging review has shown ^{68}Ga-SSTR PET/CT sensitivity is similar to CT (81.8%) in histologically-proven cases and is 100% in covert-cases, however, the number of patients was small and no occult cases were reported.

Methods We performed a systematic literature review of ^{68}Ga-SSTR PET/CT use in ECS patients. We also report 6 consecutive patients with confirmed active and occult ECS who underwent ^{68}Ga-DOTATATE PET/CT and were followed at our institution between 2014 and 2019.

Results We identified 33 articles (23 case-reports, 4 case-series, 5 retrospective studies and 1 prospective study) detailing ^{68}Ga-SSTR PET/CT in 69 ECS patients. Overall ^{68}Ga-SSTR PET/CT sensitivity was 64.0%, while in histologically confirmed cases (67 lesions), sensitivity was 76.1%. There were two false-positives cases, both in the adrenal glands. In covert cases, ^{68}Ga-SSTR PET/CT identified 50% of lesions. There were ten occult cases where all imaging failed to identify an adrenocorticotropic hormone source; source remains unknown. In our case series, ^{68}Ga-DOTATATE PET/CT showed decreased uptake in pancreatic neuroendocrine tumor in one patient and did not help identify an ECS source in 5 patients.

Conclusion Both this systematic literature review, the largest to date, and our single- center experience demonstrate a lower than previously reported ^{68}Ga-SSTR PET/CT sensitivity for ECS, especially in occult lesions. We suggest that the data on ^{68}Ga-SSTR PET/CT in ECS is subject to publication bias, and false-negatives are likely underreported; it's diagnostic value for ECS needs further study.

Keywords Ectopic Cushing's syndrome · Gallium · DOTATATE · DOTANOC · DOTATOC

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Introduction

Ectopic adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome (ECS) constitutes approximately 10–15% of all Cushing's syndrome (CS) and, in most severe cases, can lead to altered mental status, thromboembolism and sepsis [1, 2]. Most commonly responsible tumors are pulmonary carcinoid tumors (21–39%), followed by small cell lung carcinomas (3–21%), pancreatic neuroendocrine tumors (NET; 7–14%), carcinoid tumors in other locations (thymic, appendiceal, pancreatic), medullary thyroid carcinomas (MTCs; 2–11.6%), and pheochromocytomas (up to 5.6%) [1–3]. Identifying an ECS source is crucial as surgical removal of the offending lesion can be curative for hypercortisolism. However, approximately 12–18% of cases are occult, i.e. not identified by imaging [1, 2]. When a lesion is not found on initial imaging but subsequently observed, ECS is referred to as covert ECS [2, 4]. Conventional imaging (computed tomography; CT and/or magnetic resonance imaging; MRI) is recommended as the initial imaging modality. Functional imaging such as indium-111 (111In)−labelled pentetreotide scintigraphy with addition of single-photon emission computed tomography (SPECT), and positron emission tomography (PET) combined with CT (PET/CT) is used to characterize known lesions, assist in disease staging or to localize lesions not observed with conventional imaging. Gallium-68 labeled somatostatin receptor PET/CT (^{68}Ga-SSTR PET/CT; a collective term for 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) tracers, namely ^{68}Ga-DOTATATE, DOTATOC, and DOTANOC tracers), has been shown to be superior to other imaging modalities in identifying ECS, notably, with 100% sensitivity in covert cases, according to a previous systematic review [4]. However, the number of cases included in the review where ^{68}Ga-SSTR PET/CT was used was small (n = 23) [4]. Given the rarity of ECS and relatively recent use of ^{68}Ga-SSTR PET/CT, the literature describing the utility of this modality is scarce.

^{68}Ga-DOTATATE PET/CT has been increasingly used since approval by the US Food and Drug Administration (FDA) for neuroendocrine tumors, in 2016. A recent retrospective study reported combined data from three tertiary referral centers where detection rate of primary occult ECS tumors with ^{68}Ga-DOTATATE PET/CT was 65% (11/17) [5].

We performed a systematic review of the literature of ^{68}Ga-SSTR PET/CT use for ECS and also report that our experience with ^{68}Ga-DOTATATE PET/CT was largely not helpful in identifying ECS source in occult cases, despite previous optimistic reports.

Methods

Literature review

We performed a systematic literature review (until April 2019) in Pubmed and Scopus. Combination search terms used were; "ectopic", "ACTH", "Cushing", "gallium", "dotatate", "dotanoc", and "dotatoc".

Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were utilized (Fig. 1). Eligible publications were case reports, case series, retrospective reviews, and prospective studies that included one or more patients with confirmed ECS (clinically, biochemically and/or on pathology) in whom ^{68}Ga-SSTR PET/CT was used to localize a source. Exclusion criteria were non-English language articles, posters, reviews, commentaries, book chapters, and animal studies. A single reviewer assessed the titles, abstracts and articles' full text. Upon review of full text of qualifying publications, additional articles were excluded if they lacked evidence of ECS in described cases, did not contain individual patient clinical or biochemical data, or if ^{68}Ga-SSTR PET/CT was not performed.

Data were extracted by 3 independent reviewers. Attempt was made to account for all lesions described in each case.

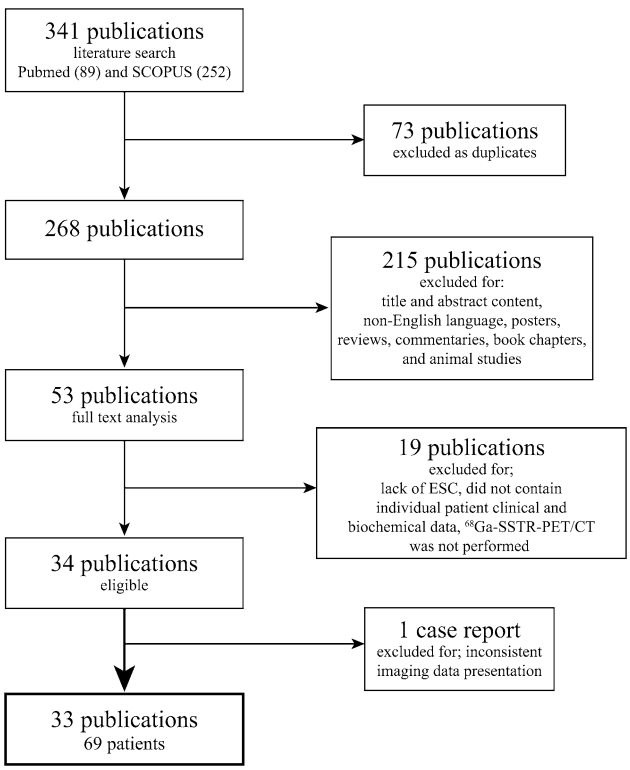

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) of publications from systematic review, updated April 2019

In the cases where the number of metastases or lymph nodes was not specified or referred to as "multiple", metastases or lymph nodes were regarded as one lesion.

Laboratory units for serum cortisol, ACTH, and urine cortisol were converted to µg/dL, pg/mL and µg/day respectively, where appropriate, if the results were expressed in other units. Due to differences in the upper limit (ULN) of normal for urine free cortisol (UFC) in different studies, the results were expressed as UFC/ULN.

An assumption was made that all reported cases had ECS. Based on this, sensitivity of ^{68}Ga-SSTR PET/CT, with confidence intervals of 95%, was calculated as the number of true positives divided by the sum of true positives and false negatives and was calculated separately for histologically confirmed lesions and for all lesions. For histologically confirmed lesions, true positives were positive lesions on ^{68}Ga-SSTR PET/CT that were confirmed on pathology, and false negatives were negative lesions on ^{68}Ga-SSTR PET/CT but were confirmed on pathology. For all lesions, true positives consisted of ^{68}Ga-SSTR PET/CT positive lesions that were histologically confirmed plus those with no pathology available but clinically consistent with a true positive, and excluding false positives. False negatives consisted of histologically confirmed lesions that were negative on ^{68}Ga-SSTR PET/CT plus occult cases, assuming one occult lesion per patient. The same strategy was applied to calculate the sensitivity of anatomic imaging.

SPSS 25 software was used for statistical analysis; unpaired *t* test was used to compare parametric variables (age and serum cortisol), Mann–Whitney test was used to compare non-parametric variables (ACTH, UFC/ULN, and lesion size), and crosstabs for categorical variables (sex and ^{68}Ga-SSTR type).

Cases at OHSU

We retrospectively reviewed records of 6 consecutive patients with confirmed ECS under an Institution Review Board approved repository with a waiver of authorization. Cushing's syndrome was diagnosed in clinically suggestive cases based on established biochemical criteria (elevated 24 h UFC, serum cortisol above 1.8 µg/dL as assessed by a 1 mg overnight dexamethasone suppression test, and elevated late-night salivary cortisol). ACTH-dependent hypercortisolism was established based on a normal or elevated random ACTH level. Combined dexamethasone-corticotropin releasing hormone (CRH) test to rule out non-tumoral hypercortisolism ("pseudo-Cushing's syndrome") was performed in selected cases using a diagnostic cutoff serum cortisol of > 2.5 µg/dL at 15 min and ACTH > 27 pg/mL as consistent with CS [6]. Inferior petrosal sinus sampling (IPSS) was performed in 4 of 6 patients using a diagnostic cutoff central-to-peripheral plasma ACTH gradient of < 2.0 before CRH administration and < 3.0 after CRH to diagnose ECS. IPSS was not performed in one patient with a previous history of surgically treated Cushing's disease (CD) who was found to have a large pancreatic tumor that was proven to be the source of ACTH. IPSS was attempted, but not completed in another patient due to technical difficulties. Pituitary MRI, body CT or MRI, and ^{68}Ga-DOTATATE PET/CT were performed at least once in all patients. ^{68}Ga-DOTATATE PET/CT was performed on a Phillips Gemini TF 16 PET/CT scanner and analyzed by experienced nuclear medicine radiologist. An ACTH ectopic source was histologically confirmed in one patient who underwent a pancreatectomy. The remaining 5 patients continue to have occult tumor. Data is presented as ± standard deviation (SD) where noted.

Results

Literature review

The final analysis included 33 publications (Fig. 1). Of those, 23 were case reports, 4 case series, 5 retrospective studies and 1 prospective study [7–37]. Individual patient data extracted from publications are presented in a Supplementary Table.

A total number of 69 patients were included; 79 lesions were identified by imaging and pathology in 59 patients, while 10 patients had occult ECS. Pathological data were reported in 57 patients; the most common finding was bronchial carcinoid tumor (49.1%), followed by thymic carcinoid tumor (10.5%), pancreatic neuroendocrine tumor; PNET (8.7%), medullary thyroid cancer; MTC (7.0%), retroperitoneal carcinoid tumor (3.5%). The remaining lesions represented 1.7% each and were thymic carcinoma, mediastinal carcinoid, prostate cancer, sphenoid sinus NET, thymic NET, bronchial paraganglioma, nasal paraganglioma, small cell lung carcinoma; SCLC, rectal small cell neuroendocrine carcinoma; diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; DIPNECH, and olfactory neuroblastoma.

The total number of ^{68}Ga-SSTR PET- positive lesions was 57 and the total number of ^{68}Ga-SSTR PET−negative lesions (including occult cases) was 32, resulting in an overall ^{68}Ga-SSTR PET/CT sensitivity of 64.0% (95% CI 53.1–73.7%). In histologically confirmed cases (67 lesions), the number of ^{68}Ga-SSTR PET/CT true positive lesions was 51 and the number of ^{68}Ga-SSTR PET/CT false negatives was 16, resulting in a sensitivity of 76.1% (95% CI 63.9–85.3%). There were two false positive lesions (both in the adrenal glands).

With regards to anatomic imaging, the total number of identified lesions was 60 and the total number of missed lesions (including occult cases) was 26, resulting in an overall sensitivity of 69.7% (95% CI 58.7–78.9%). In histologically confirmed cases, the number of true positive lesions on

anatomic imaging was 51 and the number of missed lesions was 14, for a sensitivity of 78.5% (95% CI 66.2–87.3%).

When anatomic imaging was positive (60 lesions), ^{68}Ga-SSTR PET/CT identified 70.0% (42 lesions). When anatomic imaging was negative, ^{68}Ga-SSTR PET/CT identified 50% lesions (13 of 26, assuming that the occult cases had only 1 lesion per patient). There were 10 cases that remained occult on all imaging. There were 2 patients in whom ^{68}Ga-SSTR PET/CT identified some, but not all lesions. There was one patient in whom initial ^{68}Ga-SSTR PET/CT was negative but became positive after treatment with ketoconazole.

Comparison of clinical and pathologic characteristics in patients with positive and negative ^{68}Ga-SSTR PET/CT (per lesion analysis), are presented in Table 1. There was no difference in age, sex, serum cortisol level, UFC/ULN level, or lesion size between positive and negative ^{68}Ga-SSTR PET/CT groups. ACTH level was significantly lower in ^{68}Ga-SSTR PET/CT negative group.

Cases at OHSU

Clinical, biochemical and imaging findings of the patients followed at our institution are presented in Tables 2 and 3. Average age at diagnosis was 54.6 (± 16.1) years, and 5 of 6 patients were females. The average length of follow up was 30.2 (± 22.8) months. All but one patient (patient 3) presented with a new diagnosis of CS. Patient 3 had history of CD and underwent two pituitary surgeries as well as radiation after the first surgery. She had recurrence several years after a second surgery and was treated with medical therapy for 3 years. Treatment was discontinued due to symptoms of adrenal insufficiency (AI) and low-normal UFC, however, she developed recurrence of symptoms of hypercortisolemia within 1 year and was found to have significantly elevated UFC and ACTH (Table 2). Overall, at presentation, patients' UFC was 1.7–176.8 × ULN, ACTH was 47–493 pg/dL, and random serum cortisol was 10.7–102 µg/dL. Three patients underwent combined dexamethasone-CRH testing. IPSS was performed in 4 patients who had normal MRI or pituitary adenoma < 6 mm: patient 1 had cavernous sinus sampling and IPPS 3 years apart, patient 2 had IPSS twice, 2 years apart, and patients 4 and 6 had IPSS once. In all cases, there was no central-to-peripheral gradient. Patient 3 did not undergo IPSS due to a high suspicion for an ectopic ACTH source in a new pancreatic lesion. Patient 5 did not complete the IPSS due to technical difficulties and instead had an 8 mg dexamethasone suppression test that was consistent with an ectopic source.

All patients underwent a full body CT at least once. All but patient 3 had nonspecific/non-suspicious findings on CT (Table 3). Patient 3 was found to have a new 3.2 cm pancreatic body lesion. Patients 1–4 underwent

Table 1 Literature review comparison of patient's characteristics; ^{68}Ga-SSTR PET/CT positive versus ^{68}Ga-SSTR PET/CT negative lesions

	^{68}Ga-SSTR PET/CT positive	^{68}Ga-SSTR PET/CT negative	P value
Age (years)			
Mean (SD)	46.8 (14.7)	44.0 (16.7)	0.476
n	43	25	
Sex			
Female (n; %)	23; 48	13; 52	0.931
Male (n; %)	25; 52	12; 48	
n	48	25	
Serum cortisol (µg/dL)			
Mean (SD)	40.5 (23.3)	40.7 (18.3)	0.987
n	20	12	
ACTH (pg/dL)			
Median (min–max, IQR)	240.0 (57.7–3720.0, 245.0)	72.9 (55.8–864, 78.0)	0.002
n	31	21	
24h UFC/ULN			
Median (min–max, IQR)	23.2 (1.95–167.9, 64.6)	15.8 (1.7–91.1, 86.0)	0.539
n	10	12	
Lesion size (cm)			
Median (min–max, IQR)	1.6 (0.5–10.0, 2.1)	1.2 (0.7–5.0, 0.5)	0.256
n	26	11	
^{68}Ga-SSTR type; n	DOTANOC; 18 DOTATOC; 9 DOTATATE; 26	DOTANOC; 7 DOTATOC; 5 DOTATATE; 17	0.631
Total number of lesions	57	32 (10 occult)	

IQR interquartile range

Table 2 Clinical and biochemical characteristics of patients (n = 6) in OHSU case series

Case #	Age (years)	Sex	Clinical presentation	Serum potassium (mmol/L)	Serum cortisol (μg/dL)	ACTH (pg/dL)	UFC, (μg/day)	Serum cortisol after ONDST (μg/dL)	LNSC	Dexamethasone-CRH test: Cortisol, μg/dL, Baseline → 15 min ACTH, pg/dL, Baseline → 15 min Dexamethasone, ng/dL	Ectopic source localization
1	43	F	Facial flushing, mood swings, central weight gain	3.6	10.7	47	216[a]	–	32.4, 12.0 nmol/L (nl ˂4.3 nmol/L)	Cortisol 8.4 → 8 ACTH 26 → 39 Dexamethasone 204	CSS: Max gradient before CRH 1:1 Max gradient after CRH 1:1.3 IPSS: Max gradient before CRH 1:1.3 Max gradient after CRH 1:1.2
2	56	F	Central weight gain, abdominal striae, thinning of the skin, easy bruising, worsening diabetes mellitus and hypertension	4.2	24	57	78.4[b]	14	0.05, 0.07 mcg/dL (nl < 0.09)	Cortisol 16.1 → 15.4 ACTH 42 → 40 Dexamethasone 562	IPSS: Max gradient before CRH 1:1.3 Max gradient after CRH 1:1.2 IPSS: Max gradient before CRH 1:1.2 Max gradient after CRH 1:1.2
3	67	F	Recurrence of Cushing's syndrome, generalized weakness, confusion, hypokalemia	1.9	55.7	351	3280[b]	–	–	–	Pathology of pancreatic lesion: neuroendocrine neoplasm with expression of ACTH and somatostatin 2a receptors
4	59	F	Increased abdominal girth, fat redistribution to supraclavicular area and face, plethora, hirsutism, proximal weakness, thinning of the skin and bruising	3.4	54.9	103	236[b]	–	–	Cortisol 26.7 → 26.4 ACTH 101 → 97 Dexamethasone 332	IPSS: Max gradient before CRH 1:1.2 Max gradient after CRH 1:1.5

Table 2 (continued)

Case #	Age (years)	Sex	Clinical presentation	Serum potassium (mmol/L)	Serum cortisol (μg/dL)	ACTH (pg/dL)	UFC, (μg/day)	Serum cortisol after ONDST (μg/dL)	LNSC	Dexamethasone-CRH test: Cortisol, μg/dL, Baseline → 15 min ACTH, pg/dL, Baseline → 15 min Dexamethasone, ng/dL	Ectopic source localization
5	73	F	Hospitalization for altered mental state, hypokalemia, weight gain, muscle weakness, edema	2.4	48	198	3700[b]	74.9	–	–	8 mg dexamethasone suppression test, cortisol 70.1 μg/dL
6	29	M	Progressive fatigue, weight gain, abdominal striae, edema, hypertension, diabetes mellitus	2.5	102	493	7959[b]	–	–	–	IPSS: Max gradient before CRH 1:1.2 Max gradient after CRH 1:1.4

ONDST overnight 1 mg dexamethasone suppression test, *IPSS* inferior petrosal sinus sampling, *CSS* cavernous sinus sampling

[a]Reference 21-111 μg/day

[b]Reference 4-50 μg/day

Table 3 Imaging findings and outcome in 6 patients from OHSU case series

Case #	Pituitary MRI	Body CT	^{111}In-pentetreotide SPECT/CT	^{18}F-FDG PET/CT	Ga^{68-}-DOTATATE PET/CT	Outcome
1	4 mm focus	Normal	Normal	Normal	Normal	Medical therapy with ketoconazole
2	Normal	3.5 mm lung nodule; left adrenal thickening	9 mm thyroid nodule (benign FNA) Nonfocal mild uptake in pancreatic head	Minimal focal uptake in perirectal region consistent with hemorrhoid/polyp (normal colonoscopy 2 years prior)	Normal	Medical therapy with mifepristone
3	Changes from prior TSS, 4 mm cystic lesion	3.5 cm pancreatic lesion, thickened adrenal glands	Mild uptake in adrenal glands (3 years prior to discovery of pancreatic lesion on CT)	n/a	Decreased uptake in pancreatic lesion	Distal pancreatectomy (grade 1, 2.8 cm NET, + ACTH); BLA (diffuse cortical hyperplasia)
4	Normal	Mild diffuse adrenal thickening	Normal	Normal	Normal (adrenals surgically absent)	BLA
5	3 mm focus	4 mm lung nodule; thickening of adrenal glands; 1.8 cm hepatic lesion (liver hemangioma on MRI); 7 mm cystic pancreatic body lesion (thought to be side-branch intraductal papillary mucinous neoplasm)	Normal	Mild bilateral adrenal thickening	Normal	BLA
6	4 mm lesion	4 mm nodule at the right base of the lung; 2 mm calcified nodule in the right apex; 2.4 cm left kidney cyst; thickened adrenal glands	n/a	2 mildly hypermetabolic nonenlarged subcarinal lymph nodes (favored to be reactive in the setting of surrounding inflammatory lung changes); bilaterally enlarged hypermetabolic adrenal glands	Hypermetabolic adrenal glands	BLA

FNA fine needle aspiration, *TSS* transsphenoidal surgery, *BLA* bilateral adrenalectomy

111In−pentetreotide SPECT/CT and/or ^{18}F-labeled fluoro-2-deoxyglucose (^{18}F-FDG) and CT (^{18}F-FDG-PET/CT) at least once, and all had non-specific findings.

All patients had Ga^{68}-DOTATATE PET/CT. Patients 1, 2, 3, 4 and 6 underwent Ga^{68}-DOTATATE PET/CT when they were hypercortisolemic, patient 5 after a bilateral adrenalectomy (BLA) and patient 3 also had a follow up Ga^{68}-DOTATATE PET/CT after BLA.

In patient 3, Ga^{68}-DOTATATE PET/CT showed that the new pancreatic lesion had a decreased tracer uptake compared to the surrounding pancreatic parenchyma. Biopsy of the lesion demonstrated pancreatic neuroendocrine tumor. The patient underwent distal pancreatectomy and simultaneous BLA due to severe CS. Histopathological examination of the pancreatic lesion showed a 2.8 cm well-differentiated neuroendocrine neoplasm with expression of ACTH and somatostatin 2a receptors and no metastases in the resected lymph nodes. Pathology of the adrenal glands showed diffuse cortical hyperplasia. Postoperative ACTH measured 2 weeks later was 36 pg/mL and 9 months postoperatively ACTH level was 48 pg/mL. Ga^{68}-DOTATATE PET/CT 1 year later showed no tracer uptake in the distal pancreatectomy bed and no other evidence of somatostatin receptor positive disease.

In the other patients, Ga^{68}-DOTATATE PET/CT was normal or showed non-specific findings (Table 3). Treatment for CS included medical therapy and 3 patients underwent BLA.

Discussion

^{68}Ga-SSTR PET/CT has been proposed as a highly sensitive diagnostic modality for neuroendocrine tumors in general, especially for tumors of unknown source. This is at least in part a result of superior resolution compared to traditional 111In−pentetreotide SPECT/CT. A meta-analysis of ^{68}Ga-SSTR PET/CT showed a sensitivity of 91% (95% CI 82–97%) in detection of thoracic and gastroenteropancreatic tumors [38]. A recent large prospective analysis of "^{68}Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero-Pancreatic Neuroendocrine Tumors and Unknown Primary Sites" showed superiority of ^{68}Ga-DOTATATE PET/CT with a detection rate of 95.2% versus 45.6% for standard anatomic imaging and 30.9% for 111In−pentetreotide SPECT/CT [39]. In this study, 422 of 891 lesions were identified by ^{68}Ga-DOTATATE PET/CT imaging that had been missed both by 111In−pentetreotide SPECT/CT and anatomic imaging. However, this study did not specify if there were any patients with ECS [39].

Published experience with ^{68}Ga-SSTR PET/CT for identification of ECS lesions is limited. Majority of the reports are single case reports and small case series. There are only six retrospective studies and one small prospective study (5 patients) of patients with ECS in whom ^{68}Ga-SSTR PET/CT was used [5, 17, 20, 22, 23, 26, 29].

In a retrospective study of 12 patients with ECS, Goroshi et al., found that sensitivity of ^{68}Ga-DOTANOC PET/CT was 69.2% with a positive predictive value (PPV) of 100% while CT sensitivity was 92.3% and PPV was 70.5% [20]. Wannachalee et al., reported detection rate of primary occult ECS tumors with ^{68}Ga-DOTATATE PET/CT of 65% (11/17) [5]. Contrary to this, Nakamoto, et al., reported that only 1 of 8 patients with suspected ACTH secreting NET had a primary tumor identified on ^{68}Ga-DOTATATE PET/CT, however, this study did not provide sufficient information to confirm the diagnosis of ECS in those patients [40]. Isidori et al., performed a systematic review of imaging for ECS that included case series, case reports and diagnostic studies. In their review, the overall sensitivity of ^{68}Ga-SSTR PET/CT was 81.8% (18/22), while CT detected 66.2% (137/207) and MRI 51.5% (53/103) of cases [4]. In histologically proven cases, ^{68}Ga-SSTR PET/CT sensitivity was similar to CT (81.1 vs 81.8%). Interestingly, in overt cases ^{68}Ga-SSTR PET/CT showed a lower sensitivity (70%, 9/13) compared with CT (98.3%, 113/115), while in covert cases ^{68}Ga-SSTR PET/CT had 100% sensitivity (9/9) compared with 43.6% on CT (24/55); no occult ECS cases were reported.

Our systematic review is the largest one to date and includes a larger number of ECS cases (69 patients) evaluated with ^{68}Ga-SSTR PET/CT. Additionally, we accounted for all lesions reported in the included cases, wherever possible, which allowed for more extensive assessment of ^{68}Ga-SSTR PET/CT performance. The overall sensitivity of ^{68}Ga-SSTR PET/CT was 64.0%, which is lower than reported by Isidori, et al. [4], (81.8%), while the overall sensitivity of conventional imaging was 69.7.1% compared to 66.2% reported by Isidori, et al. In histologically confirmed cases the sensitivity of ^{68}Ga-SSTR PET/CT was 76.1% and conventional imaging was 78.5%, somewhat similar to that reported by Isidori et al., (81.1% and 81.8% respectively) [4].

In our case series of confirmed ECS, ^{68}Ga-DOTATATE PET/CT was suggestive of an ECS source in 1 overt case (pancreatic tumor seen on CT) and did not help identify a culprit lesion in 5 occult cases. Adding the OHSU case series to the total pool of patients included in our systematic review would result in a ^{68}Ga-DOTATATE PET/CT sensitivity of 61%. Based on this and the literature review, we suggest that current literature on ^{68}Ga-SSTR PET/CT utility in ECS is subject to publication bias and cases of false negative scans are likely underreported.

Detection of lesions by ^{68}Ga-SSTR PET/CT relies on the presence and expression of somatostatin receptors on tumor cells. Absent or downregulated receptors can result in false negative results [41]. Glucocorticoids (GC) downregulate expression of SSTR2 and, to a milder degree, SSTR5 in vitro

[42]. High endogenous glucocorticoids are also thought to at least partially downregulate SSTR2, while control of hypercortisolism may upregulate the receptor. This was demonstrated in a report of 2 ECS cases where treatment with mifepristone resulted in a change on 111In−pentetreotide SPECT/CT from negative to positive and allowed for the bronchial carcinoid in both cases to be detected [43]. Similarly, Davi et al., demonstrated that normalization of cortisol resulted in appearance of tracer uptake in the PNET liver metastases that were previously negative on ^{68}Ga-DOTANOC PET/CT. However, in our series two ^{68}Ga-DOTATATE PET/CT scans were performed when patients were eucortisolemic; both with negative findings. In our literature review, only 3 patients were eucortisolemic at the time of ^{68}Ga-SSTR PET/CT, and all three had a positive scan. Additionally, there was no difference in median serum cortisol and median 24 h UFC/ULN between the patients with positive and negative ^{68}Ga-SSTR PET/CT.

It has been reported that ^{68}Ga-DOTATATE uptake is lower in atypical and high grade carcinoids possibly due to lower SSTR expression [44]. In our literature review, there were 9 lesions with atypical carcinoid and ^{68}Ga-SSTR PET/CT was positive in 7.

Radiotracers ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE differ in SSTR binding sites: ^{68}Ga-DOTATATE binds to SSTR2, ^{68}Ga-DOTATOC has high affinity to SSTR2 and moderate affinity to SSTR5, and ^{68}Ga-DOTANOC has high affinity to SSTR2, SSTR3, and SSTR5 [41]. In our systematic review, ^{68}Ga-DONANOC PET/CT tended to detect more lesions (72%, 18/25) compared to ^{68}Ga-DOTATOC PET/CT (64%, 9/14) and ^{68}Ga-DOTATATE PET/CT (60%, 26/43) suggesting a possibility of presence of SSTR3 or SSTR5 on the ectopic lesions.

Average size of the lesions was similar in ^{68}Ga-SSTR PET/CT—positive and negative lesions. The average size of the lesions that were detected only by ^{68}Ga-SSTR PET/CT was 0.8 cm (range 0.5–1.3 cm).

When faced with a false negative ^{68}Ga-SSTR PET/CT in ECS, one should consider a possibility of an incorrect ECS diagnosis. Once ACTH-dependent CS is established, IPSS is typically performed if the pituitary tumor is not visible or < 6 mm. However, the sensitivity of IPSS ranges between 61.7% and 100% and specificity between 50% and 100%, depending on the center, the use of CRH or desmopressin (DDAVP) for stimulation, and the expertise of the interventional radiologist [45]. Cases of false negative IPSS have also been reported, with rates of 1–10% [46, 47]. False negative IPSS results have been attributed to anomalous venous drainage, abnormal venous anatomy, lack of expertise in the procedure and/or technical problems, such as incorrect catheter placement [46]. Prolactin can be used as a marker of pituitary venous effluent and correct catheter placement [47]. In our case series, all patients who had IPSS were reported to have excellent catheter placement. One patient who had an 8 mg dexamethasone suppression test instead of IPSS had unequivocally high cortisol after dexamethasone administration, as well high clinical suspicion for ECS. The other patient who did not undergo IPSS, had ECS confirmed on pathology (pancreatic NET with ACTH staining). We followed the patients for a mean of 30.2 months and in 2 patients we did not have proof of hypercortisolemia at time of IPSS, we therefore, repeated IPSS 2–3 years later with results also indicative of ECS. Therefore, we are highly confident that all patients in our series had ECS.

Though spuriously elevated ACTH can result in a diagnostic error and extensive search for an ectopic source [48], all cases in our series had a confirmed CS based on clinical and laboratory criteria and none of the patients had adrenal nodules on imaging or adrenal pathology that would raise suspicion for ACTH-independent CS.

Our systematic review includes the largest number of patients from heterogeneous publications, thus reducing the influence of publication bias. However, the review does have some limitations. First, it is comprised mainly from case reports and case series, which are associated with publication bias where negative results tend to be not reported. However, despite this, we found a lower sensitivity of ^{68}Ga-SSTR PET/CT in identification of ECS than previously reported in a systematic review [4]. Second, many reports were missing some individual patient data, such that, in total, age and sex was available in approximately three-quarters of patients, lesion size was available in half of the patients, ACTH in half, serum cortisol in a third, and UFC only in a quarter of patients. However, pathology was available in all, except 10 occult and 2 non-occult cases. We made every attempt to account for all reported lesions rather than cases, raising the sample size and accounting for both positive and negative lesions in the same patient, unlike previous systematic review that accounted for cases and not lesions. However, we encountered an incomplete or unclear description of findings in a few reports, and we resolved questionable cases by independent review and agreement between 2 different reviewers. Lastly, we cannot exclude that some patients with occult ECS in this literature review had pituitary-dependent CS or even adrenal CS for the reasons described above.

Conclusion

Our systematic literature review, the largest to date and the case series at our institution highlight the limited utility of ^{68}Ga-DOTATATE PET/CT in ECS and suggests that literature to date may be subject to publication bias, since cases of false negative scans are likely underreported. High quality prospective studies are needed to better assess the true sensitivity and specificity of ^{68}Ga-SSTR PET/CT for ECS.

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Compliance with ethical standards

Conflict of interest Maria Fleseriu disclosures—Principal Investigator with research funding to OHSU from Novartis, Millendo, Strongbridge and has received occasional scientific consulting fee from Novartis, Strongbridge, and declares no conflict of interest. All other authors declare that they have no disclosures and no conflict of interest

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The study was institutional review board approved with a waiver of authorization.

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