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^{68}Ga-DOTATOC PET/CT in the Localization of Pituitary Tumors in Cushing's Disease

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Background: This study aimed to determine the value of ^{68}Ga-DOTATOC positron emission tomography/computed tomography (PET/CT) in localizing adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas.

Methods: In this retrospective cohort study, we enrolled 30 patients with Cushing's disease and positive ACTH immunoreactivity. All patients underwent ^{68}Ga-DOTATOC PET/CT and pituitary magnetic resonance imaging (MRI) before transsphenoidal adenomectomy.

Results: Twenty-five patients showed ^{68}Ga-DOTATOC uptake in their pituitary glands on PET/CT. Median age, pre-operative ACTH levels, pre-operative cortisol, and tumor size on MRI were comparable irrespective of DOTATOC uptake. ^{68}Ga-DOTATOC PET/CT showed a 77% success rate for localizing adenomas, which was not statistically different from that of MRI. The ACTH level in the successful localization group was significantly higher than that in the failed group (84.41 pg/mL vs. 37.26 pg/mL, P=0.001). The ACTH level was statistically significant predictor of successful localization using ^{68}Ga-DOTATOC PET/CT (P=0.013). The area under the curve was 0.932 with a cutoff of 53.86 pg/mL for ACTH levels to determine successful localization. Pre-operative ACTH levels above 53.86 pg/mL showed the best diagnostic accuracy in predicting the success of localizing adenomas (sensitivity, 91.3%; specificity, 85.7%). Mean and maximum standardized uptake value of adenoma negatively correlated to pre-operative ACTH level.

Conclusion: Plasma ACTH level is a favorable predictor for the successful localization and negative correlation with ^{68}Ga-DOTATOC uptake of corticotroph adenomas in ^{68}Ga-DOTATOC PET/CT. ^{68}Ga-DOTATOC PET/CT did not improve tumor localization for Cushing's disease compared with MRI alone.

Keywords: Adrenocorticotropic hormone; Pituitary ACTH hypersecretion; Pituitary neoplasms; Positron-emission tomography; Ga(III)-DOTATOC

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INTRODUCTION

Cushing's disease (CD), the most common cause of endogenous Cushing's syndrome, is caused by adrenocorticotropic hormone (ACTH)-secreting pituitary tumors [1,2]. To achieve the best results for patients, precise diagnosis, appropriate treatment, and careful management of the disease and its related comorbidities are required [3]. The localization of ACTH-secreting pituitary tumors is paramount as definitive management mainly involves surgical resection of the tumors. Most of these tumors are microadenomas, and their diagnosis relies on specialized imaging of the sellar and parasellar regions. Although magnetic resonance imaging (MRI) remains the investigation of choice, approximately 50% of microadenomas in CD are clearly visible on standard 1.5 Tesla (T) MRI and most lesions are very small [4]. Although higher resolution techniques can increase the chances of detecting very tiny lesions, they are not available in most clinics and the protocol is not standardized yet. In this context, functional imaging can help confirm the presence or location of suspected lesions.

Positron emission tomography/computed tomography (PET/CT) has been explored as an alternative to or modality to be combined with MRI for the localization of corticotroph adenomas. ^{18}Fluoro-deoxy-glucose PET/CT has a limited role in the diagnosis of CD, but corticotropin-releasing hormone (CRH) stimulation can increase its success rate [5]. ^{11}C-methionine can permit more accurate localization of primary lesions [6]. PET/CT using the somatostatin analog ^{68}gallium-DOTATOC (^{68}Ga-DOTATOC) has shown good efficacy in the accurate localization and assessment of the functional status of neuroendocrine tumors (NETs), providing good resolution and spatial orientation. Although corticotropic adenomas express somatostatin receptors (SSTRs), the performance of ^{68}Ga-DOTATOC PET/CT in assessing CD is not well-known [7].

In this study, we focused on the performance of ^{68}Ga-DOTATOC PET/CT as a tool for localizing ACTH-secreting pituitary tumors and tried to determine the patients with CD who would be suitable candidates for the adjunctive use of ^{68}Ga-DOTATOC PET scans.

METHODS

Subjects

Thirty patients were enrolled in this retrospective study. The patients underwent surgical resection of the pituitary tumor through transsphenoidal adenomectomy (TSA) at Severance Hospital between 2015 and 2019 and had histologically proven CD with positive ACTH immunoreactivity. All patients underwent ^{68}Ga-DOTATOC PET/CT and pituitary MRI before surgery. Bilateral inferior petrosal sinus sampling (BIPSS) was also attempted for all patients, but catheterization was failed in five cases.

The disease diagnosis was based on international criteria [4]. None of the patients were taking glucocorticoids. Moreover, the final diagnosis was confirmed using surgical pathology and clinical follow-up.

The data were collected under the conditions of regular clinical care with the approval of the Institutional Review Board of Yonsei University Health System, Severance Hospital, and the requirement for written informed consent was waived owing to our study's retrospective design (IRB No. 4-2020-0414).

Hormonal assessment

Basal plasma cortisol and ACTH levels were measured at 8:00 AM before surgery. The ACTH levels were measured using an electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). Cortisol levels and 24-hour urine free cortisol (UFC) were measured by chemiluminescence immunoassay (Beckman Coulter Inc., Brea, CA, USA).

An 8:00 AM plasma cortisol concentration higher than 1.8 μg/dL, after 1 mg dexamethasone had been administered at midnight, was considered a positive result in the overnight dexamethasone suppression test (ON DST) [4,8]. Moreover, a plasma cortisol level reduced by less than 50% of the original level after 6-hourly 2 mg dexamethasone had been administered for 2 days was considered as suppression in the high-dose dexamethasone suppression test (HD DST) [8].

^{68}Ga-DOTATOC PET/CT protocol

Approximately 122 MBq (3.3 mCi) of ^{68}Ga-DOTATOC was administered intravenously. Sixty minutes after intravenous injection of ^{68}Ga-DOTATOC, scanning was performed using a dedicated PET/CT scanner (Discovery 600, General Electric Medical Systems, Milwaukee, WI, USA) with a spiral CT scan for attenuation correction with a 0.5 second rotation time at 60 mA, 120 kVp, and 5.0 mm section thickness. PET scan of the head were then acquired for 3 minutes per bed position in the three-dimensional mode. The PET images were reconstructed using an ordered-subset expectation-maximization algorithm (two iterations and 16 subsets) with attenuation, random, scatter, and decay corrections. The PET/CT images were reviewed and analyzed by two nuclear medicine physicians based on a consensus.

^{68}Ga-DOTATOC PET/CT interpretation

The PET/CT images were visually evaluated by two experienced specialists independently in the Department of Nuclear Medicine (Dongwoo Kim, with 5 years of experience; Eung-Hyuck Cho with over 10 years of experience). Each specialist independently interpreted the ^{68}Ga-DOTATOC PET images twice, with a 2-week interval between readings to minimize recall bias. The images were presented in a randomized order, and specialists were blinded to clinical and other imaging data. The interpretation was based on a visual assessment of uptake patterns, where regions of increased or decreased tracer uptake relative to the surrounding background tissue were considered abnormal. In case of disagreement, the two readers reached a consensus again and presented the result.

The region of interest (ROI) was delineated using MIM software version 6.5 (Software Inc., Cleveland, OH, USA). The pituitary gland was identified, and a circular ROI with a fixed diameter of 3 mm was drawn for all patients. This ROI was placed over the suspected lesion. For normal pituitary glands, the same 3 mm ROI was used. The mean standardized uptake value (SUV_{mean}) and maximum standardized uptake value (SUV_{max}) for both pituitary adenomas and normal pituitary glands were automatically measured using MIM version 6.5. The SUV for the volume of interest was calculated as follows: [decay-corrected activity (kBq)/volume (mL)]/[injected dose (kBq)/body weight (g)].

MRI evaluation

All patients underwent pre-operative dynamic MRI of the sellar region using 3.0T MR units (Achieva, Philips Medical Systems, Best, the Netherlands). Axial T2-weighted, high-resolution coronal T2-weighted image, and delayed gadolinium-enhanced coronal T1-weighted MRI were performed. All MRI images were reviewed using a Picture Archive Communication System (PACS). The extent, location, and size of the pituitary tumors were reviewed by two radiologists. Two skilled radiologists (Yae Won Park and Sung Soo Ahn; both with over 10 years of experience) independently assessed the MRI images visually. Their objective was to evaluate whether the MRI images exhibited a 'negative' or 'positive' result for pituitary adenoma, along with the precise location, if present.

The maximal diameter of the adenoma was defined on the coronal and sagittal planes and measured manually. Pituitary adenomas were classified as microadenomas (<10 mm) or macroadenomas (≥10 mm) based on their maximal diameters. Tumoral invasions were evaluated by the modified Knosp classification based on MRI images [9,10].

BIPSS protocol

All the BIPSS procedures were conducted prior to TSAs. Catheterization was performed via a unilateral femoral venous approach [11]. After correct catheter placement, simultaneous blood samplings of 3 mL were obtained from the periphery (P) as well as the left and right inferior petrosal sinus (IPS). After sampling, CRH at a dose of 1 μg/kg was administered and further P and IPS samples were drawn after 5 and 10 minutes. Before each sample was drawn, the catheters were aspirated, and saline-diluted blood was discarded. All the samples were delivered on ice for ACTH and prolactin measurement.

A ratio of IPS:P prolactin ≥1.8 was determined as an indicator of successful catheterization. We interpreted that a prolactin-normalized ACTH IPS:P ratio: (1) <0.8 suggested ectopic cushing syndrome and (2) ≥1.3 indicated CD [12]. An intersinus ACTH ratio of ≥1.4 was used for the lateralization of pituitary adenomas [12,13].

Statistical analysis

Values were expressed as medians (range). The Mann–Whitney *U* test was used to evaluate the differences between the groups for clinical indicators without normal distribution. Fisher's exact test was used to compare categorical data.

Interobserver agreement regarding image analysis was evaluated with kappa (κ) statistics and intraclass correlation coefficients (ICCs). Kappa values were indicated as follows: less than 0.20, poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; and greater than 0.81, excellent agreement. ICC results were interpreted according to the following criteria: poor (ICC <0.50), moderate (ICC=0.50–0.74), good (ICC=0.75–0.90), and excellent (ICC >0.90) [14].

To evaluate the independent predictors of success rates for tumor localization, we used binary logistic regression analysis. We measured the receiver operating characteristic (ROC) curve to evaluate the accuracy of pre-operative ACTH as a tool for determining the success of localization. The Youden index, a function of sensitivity and specificity, was calculated to identify the optimal cutoff point. The index ranges from 0 to 1, where a value closer to 1 indicates better performance of the test in distinguishing between conditions. Statistical analyses were performed using SPSS software version 18 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $P<0.05$.

RESUTS

Patients' characteristics

The baseline characteristics of the patients included in this study are shown in Table 1. The median age of the 30 patients at diagnosis was 34 years (range, 15 to 68). Most patients were women (77%). The median adenoma size measured by MRI was 8.50 mm (range, 3.00 to 72.00). Eleven adenomas were macroadenomas and 19 were microadenomas. Moreover, 20 tumors showed no cavernous sinus invasion.

We classified the patients into two groups depending on focal pituitary DOTATOC uptake on ^{68}Ga-DOTATOC PET/CT and

Table 1. Imaging and Clinical Characteristics of Patients with Cushing's Disease

Characteristic	Total	DOTATOC uptake	No-uptake	*P* value
Number	30	25	5	
Age at diagnosis, yr	34.00 (15.00–68.00)	30.00 (15.00–68.00)	51.00 (19.00–63.00)	0.090
Sex				0.304
Male	7 (23.33)	7 (28.00)	0	
Female	23 (76.67)	18 (72.00)	5 (100.00)	
24-hr UFC, μg/day	683.00 (184.70–2,661.80)	694.60 (233.80–2,661.80)	456.20 (184.70–1,983.40)	0.597
Pre-op ACTH, pg/mL	78.89 (19.90–286.40)	84.30 (19.90–286.40)	50.87 (34.30–77.58)	0.080
Pre-op cortisol, μg/dL	20.55 (5.20–112.70)	20.60 (8.10–112.70)	17.90 (5.20–24.30)	0.522
Size on MRI, mm	8.50 (3.00–72.00)	8.75 (3.00–72.00)	5.00 (4.00–10.00)	0.977
Suppression on ON DST	0	0	0	1.000
Suppression on HD DST	14/21 (66.67)	11/17 (64.71)	3/4 (75.00)	1.000
Knosp classification				0.891
0	20 (66.67)	16 (64.00)	4 (80.00)	
1	3 (10.00)	2 (8.00)	1 (20.00)	
2	2 (6.67)	2 (8.00)	0	
3a	1 (3.33)	1 (4.00)	0	
3b	1 (3.33)	1 (4.00)	0	
4	3 (10.00)	3 (12.00)	0	

Values are expressed as median (range) or number (%).
UFC, urine free cortisol; op, operative; ACTH, adrenocorticotropic hormone; MRI, magnetic resonance imaging; ON DST, overnight dexamethasone suppression test; HD DST, high-dose dexamethasone suppression test.

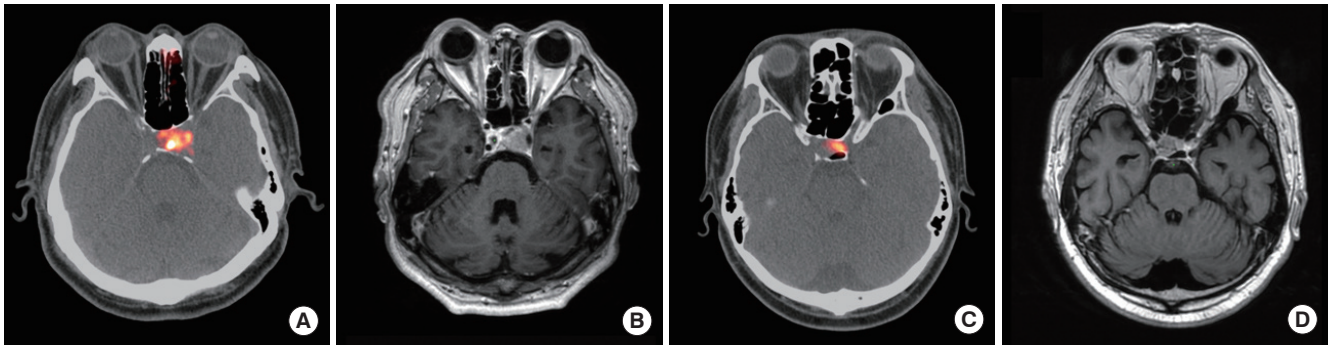

Fig. 1. Images of ^{68}gallium-DOTATOC (^{68}Ga-DOTATOC) positron emission tomography/computed tomography (PET/CT) and magnetic resonance imaging (MRI). (A) ^{68}Ga-DOTATOC PET/CT image. It showed increased ^{68}Ga-DOTATOC uptake in the left sellar region. (B) MRI. A 2.9 cm-sized solid cystic lesion with left cavernous sinus invasion. (C) ^{68}Ga-DOTATOC PET/CT image. Focal ^{68}Ga-DOTATOC uptake was observed in left lateral wing of sellar area on ^{68}Ga-DOTATOC PET/CT. (D) MRI. A 1.4 cm enhancing lesion with hemorrhage was located in the right lateral wing on MRI.

compared their baseline characteristics (Table 1). We defined the DOTATOC uptake group as those who showed focal difference of DOTATOC uptake compared to adjacent tissues on ^{68}Ga-DOTATOC PET/CT and the no-uptake group as those who did not. We presented DOTATOC images in Fig. 1. Five patients had no DOTATOC uptake on PET/CT images, although their tumors were pathologically confirmed. All members of the no-uptake group were female. The 24-hour UFC, pre-operative ACTH, and pre-operative cortisol levels were higher in the DOTATOC uptake group compared with the no-uptake group, but this difference was not statistically significant (694.60 μg/day vs. 456.20 μg/day, 84.30 pg/mL vs. 50.87 pg/mL, and 20.60 μg/dL vs. 17.90 μg/dL, respectively).

Comparison of ^{68}Ga-DOTATOC PET/CT, MRI, and BIPSS in CD

We compared the success rates of localizing adenomas using ^{68}Ga-DOTATOC PET/CT, MRI, and BIPSS, based on the location of adenomas identified by surgeons following TSA. All surgically identified adenomas were positive for ACTH immunoreactivity.

The interobserver agreement for localizing adenomas was 0.903 (95% confidence interval [CI], 0.776 to 1.030) for DOTATOC PET/CT and 0.946 (95% CI, 0.842 to 1.050) for sellar MRI, confirming excellent interobserver agreement. The intraobserver agreement was also confirmed to be above 0.9, and the results were judged reliable. MRI, which is the standard for diagnosis, successfully localized pituitary tumors in 90.00% of patients with CD. In comparison, 77% of PET and 68% of BIPSS were successful in localizing tumors. The success rates of these three methods were not statistically different for the localization of ACTH-secreting pituitary tumors (P=0.127). For microadenomas, MRI showed a success rate of 84% for localization compared to 74% with ^{68}Ga-DOTATOC PET/CT and 63% with BIPSS (P=0.401).

Regarding MRI, the success rate of localization was 100% for macroadenomas but decreased to 84% for microadenomas. This difference was not statistically significant (P=0.239) (Table 2). ^{68}Ga-DOTATOC PET/CT and BIPSS did not show differences in the success rates of localizing macroadenomas and microadenomas.

False-positive cases for localizing corticotroph adenomas on ^{68}Ga-DOTATOC PET/CT

The qualitative analysis of tumor localization for CD is presented in Table 3. There were two cases with false-positive DOTATOC uptake for pituitary adenoma localization in our study.

The first case (case 29) had a T2 hyperintense adenoma suspicious lesion on the left wing of the pituitary gland on MRI, and DOTATOC uptake was shown in the left side of the pituitary gland. BIPSS revealed a central tumor, lateralized to the right side of the pituitary. The surgeon identified a solid tumor on the right side of the pituitary gland and successfully removed it. Results of pathology and ACTH immunohistochemistry identified an ACTH-secreting pituitary tumor.

The second case (case 28) was diagnosed with ACTH-dependent CD. The basal ACTH level was 37.76 pg/mL and cortisol secretion was suppressed on the HD DST; however, sellar MRI did not reveal any suspicious lesions. DOTATOC uptake was identified on the left side of the pituitary gland. BIPSS identified a central tumor but failed to lateralize the tumor. Surgery revealed an ACTH-secreting pituitary adenoma in the middle of the pituitary gland.

Comparison of imaging and clinical characteristics depending on successful localization of corticotroph adenomas on ^{68}Ga-DOTATOC PET/CT

Twenty-three adenomas were successfully localized using ^{68}Ga-

Table 2. Comparisons Regarding Localizing Adrenocorticotropic Hormone-Secreting Adenomas on ^{68}Ga-DOTATOC PET/CT, MRI, and BIPSS in Cushing's Disease

Variable	Total	Successful localization		*P* value
		Macroadenoma	Microadenoma	
^{68}Ga-DOTATOC PET/CT	23/30 (76.67)	9/11 (81.81)	14/19 (73.68)	0.485
MRI	27/30 (90.00)	11/11 (100.00)	16/19 (84.21)	0.239
BIPSS	17/25 (68.00)	7/9 (77.78)	10/16 (62.50)	0.374

Values are expressed as number/total number (%).
^{68}Ga-DOTATOC, ^{68}gallium-DOTATOC; PET/CT, positron emission tomography/computed tomography; MRI, magnetic resonance imaging; BIPSS, bilateral inferior petrosal sinus sampling.

Table 3. Qualitative Analysis for Localizing Pituitary Adenomas by Diagnostic Modalities for Cushing's Disease

Subject number	Sex, age, yr	^{68}Ga-DOTATOC PET/CT	MRI	Size, mm	BIPSS
1	F, 64	+	+	3.0	–
2	F, 24	+	+	3.5	+
3	F, 44	+	+	4.0	+
4	F, 19	–	+	4.0	+
5	M, 25	+	+	5.0	
6	F, 63	–	+	5.0	–
7	F, 15	+	+	5.5	+
8	F, 58	+	+	6.0	+
9	F, 28	+	+	6.0	
10	M, 25	+	+	6.0	+
11	F, 39	+	+	6.0	
12	F, 18	+	+	6.0	+
13	F, 68	+	+	8.0	–
14	F, 17	+	+	8.5	+
15	F, 30	+	+	9.0	+
16	M, 23	+	+	9.0	–
17	F, 51	–	+	10.0	+
18	F, 46	+	+	10.0	
19	F, 34	+	+	10.0	
20	F, 20	+	+	10.0	–
21	M, 20	+	+	13.0	+
22	F, 40	+	+	14.0	+
23	F, 38	+	+	14.0	–
24	F, 34	+	+	16.0	+
25	M, 65	+	+	17.0	+
26	M, 49	+	+	29.0	+
27	M, 42	–	+	72.0	+
28	F, 24	–	–		–
29	F, 28	–	–		+
30	F, 50	–	–		–

Subjects are numbered according to the study convention. Successful or failed localization was denoted by '+' and '–' compared to the final location of the ACTH-secreting pituitary adenoma. Subjects 28 and 29 were false-positive cases for ^{68}Ga-DOTATOC PET/CT, as they showed suspicious ^{68}Ga-DOTATOC uptake, but the uptake location ultimately differed from the final location identified via surgery.
^{68}Ga-DOTATOC, ^{68}gallium-DOTATOC; PET/CT, positron emission tomography/computed tomography; MRI, magnetic resonance imaging; BIPSS, bilateral inferior petrosal sinus sampling.

DOTATOC PET/CT, while seven were not. We compared several parameters between the successful and failed tumor localization groups using ^{68}Ga-DOTATOC PET/CT (Table 4).

Between the two groups, there was no difference in median age at diagnosis (34 years vs. 42 years), female proportion (74% vs. 86%), 24-hour UFC level (712.50 μg/day vs. 456.20 μg/day), and pre-operative cortisol level (20.60 μg/dL vs. 18.80 μg/dL) (all $P>0.05$). The only difference between the two groups was the pre-operative ACTH level. The pre-operative ACTH level in the group with successful localization (84.41 pg/mL [range, 39.24 to 286.40]) was significantly higher than that in the group without localization (37.26 pg/mL [range, 19.99 to 77.58], $P=0.001$). Further, the success rate for localization was not affected by the tumor size when using ^{68}Ga-DOTATOC PET/CT (8.50

Table 4. Comparison of the Characteristics Depending on the Successful Localization of ACTH-Secreting Pituitary Adenomas on ^{68}Ga-DOTATOC PET/CT

Characteristic	Localization		*P* value
	Success (*n*=23)	Fail (*n*=7)	
Age at diagnosis, yr	34.00 (15.00–68.00)	42.00 (19.00–63.00)	0.462
Female sex	17 (73.91)	6 (85.71)	0.468
24-hr UFC, μg/day	712.50 (184.70–2,661.80)	456.20 (233.80–1,983.40)	0.292
Plasma ACTH, pg/mL	84.41 (39.24–286.40)	37.26 (19.99–77.58)	0.001
Plasma cortisol, μg/dL	20.60 (5.20–112.70)	18.80 (15.60–27.90)	0.848
Adenoma size, mm	8.50 (3.00–29.00)	6.00 (4.00–72.00)	1.000

Values are expressed as median (range) or number (%).
ACTH, adrenocorticotropic hormone; ^{68}Ga-DOTATOC, ^{68}gallium-DOTATOC; PET/CT, positron emission tomography/computed tomography; UFC, urine free cortisol.

mm [range, 3.00 to 29.00] vs. 6.0 mm [range, 4.00 to 72.00], *P*=1.000).

Prediction for successful localization of ACTH-secreting pituitary adenomas using ^{68}Ga-DOTATOC PET/CT

A binary logistic regression model predicting the successful localization using ^{68}Ga-DOTATOC PET/CT with pre-operative ACTH levels was found to be statistically significant (chi-square value 1=16.24, *P*=0.001), with a Nagelkerke *R*-squared value of 0.631. The pre-operative ACTH level was statistically significant in predicting the odds of successful localization using ^{68}Ga-DOTATOC PET/CT (odds ratio, 1.096; 95% CI, 1.020 to 1.178; *P*=0.013). For every 10 pg/mL increase in ACTH levels, the localizing success rate using ^{68}Ga-DOTATOC PET/CT increased by 96%, according to this model.

The ROC curve for the pre-operative ACTH level to predict the localization of corticotroph tumors is shown in Fig. 2. The area under the curve was 0.932, with a cutoff value of 53.86 pg/mL (Youden index: 0.770). ACTH levels higher than 53.86 pg/mL showed the best diagnostic accuracy for the successful localization of primary lesions in CD, with a sensitivity and specificity of 91.3% and 85.7%, respectively.

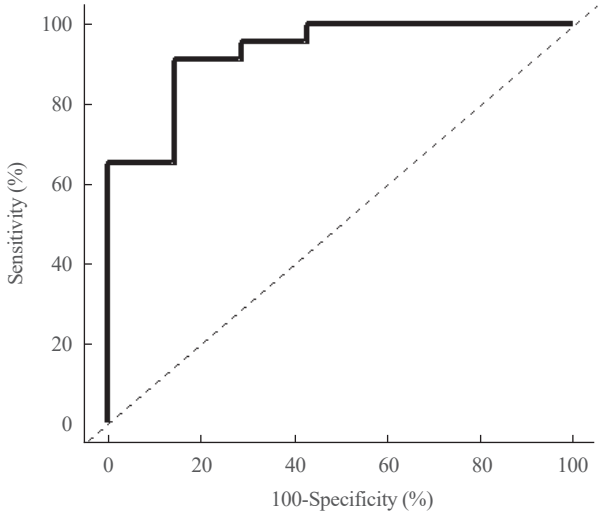

Fig. 2. A receiver operating characteristic curve was used to assess the accuracy of plasma adrenocorticotropic hormone (ACTH) as a tool to determine the successful localization of ACTH-secreting pituitary adenomas using ^{68}gallium-DOTATOC positron emission tomography/computed tomography. The area under the curve was 0.932, with a cutoff of 53.86 pg/mL. An 8:00 AM plasma ACTH level higher than 53.86 pg/mL showed the best diagnostic accuracy for the successful localization of the primary lesions (sensitivity, 91.3%; specificity, 85.7%).

^{68}Ga-DOTATOC uptake in the patients with Cushing's disease

We included 23 pituitary adenomas which were successfully localized in ^{68}Ga-DOTATOC PET scan, and evaluated SUV_{mean} and SUV_{max}. All ICCs for SUV measurements were above 0.75, and the results were reliable. The results are presented in Fig. 3. The SUV_{mean} of adenoma was lower than that of the surrounding normal tissue, but this difference was not statistically significant (4.86 [range, 1.84 to 11.25] vs. 6.26 [range, 1.69 to 25.56], Z=–0.824, *P*=0.410). There was no significant difference in SUV_{max} either (6.39 [range, 2.57 to 12.52] vs. 7.50 [range, 2.98 to 27.90], Z=–1.048, *P*=0.295). Additionally, we found that both SUV of adenoma correlated to pre-operative ACTH level (SUV_{mean} Spearman rho=–0.415, *P*=0.049; SUV_{max} Spearman rho=–0.415, *P*=0.049).

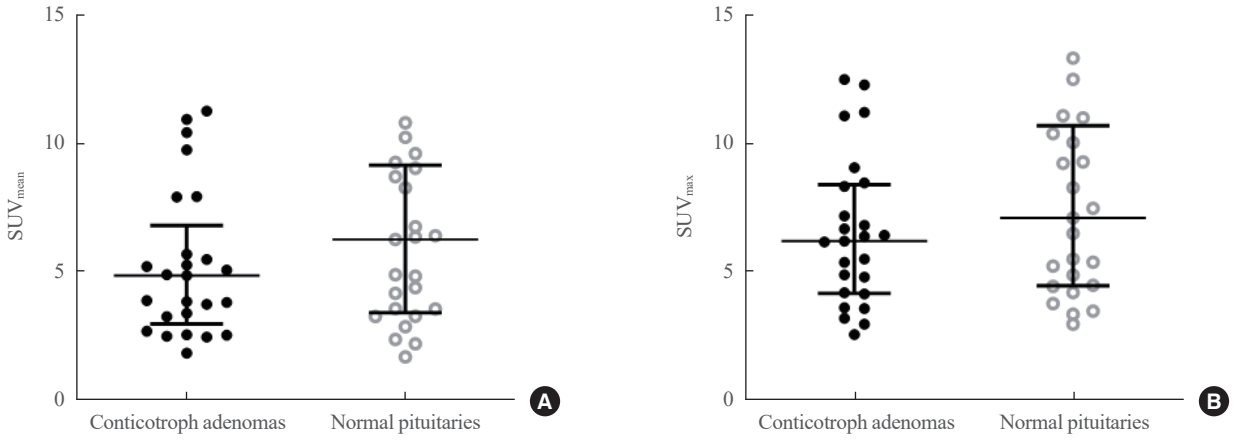

Fig. 3. Standardized uptake values (SUVs) of the patients with Cushing's disease. The mean standardized uptake value (SUV_{mean}) (A) and maximum standardized uptake value (SUV_{max}) (B) of corticotroph adenomas and normal pituitaries are shown. The SUVs between corticotroph adenoma and the surrounding normal tissue was not significantly different. Bars presented median and interquartile range of this figure.

DISCUSSION

In this study, 83.33% of the patients with surgically proven ACTH-producing pituitary tumors showed focal DOTATOC uptake at their pituitary glands on ^{68}Ga-DOTATOC PET/CT. There were no differences in the imaging or clinical characteristics between patients with and without DOTATOC uptake. Of the 25 patients, 23 showed DOTATOC uptake at a location consistent with that identified during surgery. Patients with successful localization had higher pre-operative ACTH levels than those with failed localization. The success rate of localization was not statistically different among ^{68}Ga-DOTATOC PET/CT, MRI, and BIPSS. Tumor size did not influence the success of tumor localization by ^{68}Ga-DOTATOC PET/CT. We identified that pre-operative ACTH level was a predictive factor for successful localization of the primary lesion, with a threshold of 53.86 pg/mL. Moreover, patients with higher plasma ACTH levels were more likely to have the primary lesion successfully located on ^{68}Ga-DOTATOC PET/CT than those with lower plasma ACTH levels.

MRI is the imaging modality of choice for the detection of ACTH-secreting pituitary adenomas [4]. Prior studies have shown that ACTH-producing pituitary microadenomas are undetectable on 1.5T MRI in 36%–64% of cases [15-17]. In our study, three out of 18 adenomas (20%) confirmed by surgery failed to localize on MRI.

We found that the diagnostic success of ^{68}Ga-DOTATOC PET/CT was determined by the hormonal activity of the corticotroph adenomas, but not by size. However, previous studies have reported that the localization of corticotroph adenomas using MRI is affected by the size of the adenomas rather than by hormonal activity [16,18]. Adenoma size does not necessarily correlate with the degree of hypercortisolism in CD [19]. Patients with smaller adenomas may present with higher hypercortisolism. Thus, ^{68}Ga-DOTATOC PET/CT could be a promising approach to improving diagnostic success compared to MRI alone for certain patients with smaller adenomas but higher ACTH secretion.

We believe that in such instances, ^{68}Ga-DOTATOC PET/CT may help clinicians localize corticotroph adenomas before surgical removal, especially in patients with high ACTH secretions. However, in our study, there were no cases with negative MRI findings identified on ^{68}Ga-DOTATOC PET imaging. In our research, the focus was on a small group, and there were only a few instances of negative MRI cases. The initial factor behind this is the enhanced MRI detection rate attributed to the advanced scanning technology used at our institution. We performed 3.0T MRI with dynamic contrast-enhanced, half-dose contrast, and spoiled gradient recalled acquisition; these sequences were reported to enhance the MRI detection rate for CD [20-23]. Moreover, we included the subjects who underwent TSA and had confirmed pathologically-positive ACTH-secreting pituitary adenomas. This meant that cases without surgery were excluded because the ACTH source was not clearly identified. We expect further studies on the role of ^{68}Ga-DOTATOC PET/CT in CD to confirm the possibilities we have suggested.

Corticotropic pituitary tumors have been reported to exhibit lower DOTATOC uptake compared to normal pituitary tissue in healthy subjects [24]. Similarly, another study found that functioning pituitary microadenomas, including 89.1% of adreno-

corticotropic adenomas, demonstrated decreased DOTA-octreotate (DOTATATE) uptake relative to surrounding normal tissue [25]. These findings suggest that hypercortisolism may downregulate SSTR2 expression, reducing DOTATOC uptake [24, 26].

Our data showed that ACTH hypersecretion was associated with lower DOTATOC uptake and served as a favorable predictor for successful tumor localization. This may be explained by the reduced SSTR2 expression in both adenomas and surrounding normal tissue due to hypercortisolism, improving visual discrimination. Plasma ACTH levels, as a direct indicator of tumor activity, may better reflect receptor expression compared to systemic cortisol levels, which are influenced by metabolic and circadian factors. Although SSTR5 expression in corticotropic adenomas can theoretically bind ^{68}Ga-DOTATOC, tumor size or tracer kinetics may also contribute to localization success. Further studies with larger cohorts are needed to clarify the mechanisms linking ACTH secretion, SSTR expression, and ^{68}Ga-DOTATOC uptake in CD.

Radiolabeled somatostatin analogs, such as ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC, are valuable tools for diagnosing and treating NETs by targeting overexpressed SSTR. While both compounds exhibit similar binding profiles, ^{68}Ga-DOTATATE has approximately 10-fold higher *in vitro* affinity for SSTR2 compared to ^{68}Ga-DOTATOC [27]. This difference may influence their effectiveness in detecting NETs, which frequently overexpress SSTR2. However, clinical data comparing their uptake in NETs remain inconsistent, with some studies favoring ^{68}Ga-DOTATATE PET/CT and others suggesting better diagnostic outcomes with ^{68}Ga-DOTATOC PET [28-30]. Currently, no direct comparisons exist for these two compounds regarding the localization of ACTH-secreting pituitary adenomas. Future research should directly compare the diagnostic utility of ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC PET/CT in patients with CD.

In this study, we evaluated the successful localization of corticotroph adenomas, but not their detection, using diagnostic modalities. This meant that we defined failed localization as adenomas that were identified on the left side of the pituitary gland on imaging but that were confirmed to be located on the right side upon surgery. In these cases, there may be opinions claiming that tumor detection was successful because imaging predicted the presence of tumors in the pituitary gland, especially considering the low resolution of PET/CT. However, we determined that these cases failed to localize the adenomas to avoid potential false positives. In addition, it is important to evaluate the ability of imaging to determine the location within the pituitary gland rather than the presence of the tumor alone. Evidence of localization before surgery can convince surgeons to perform guided hemi-hypophysectomies.

Our study has several limitations. This study has the inherent limitations of a retrospective study design. Because the primary aim of our study was to evaluate the efficacy of ^{68}Ga-DOTATOC PET/CT in the localization of pituitary tumors, we recruited only pathologically positive samples. However, future studies might investigate the possible role of ^{68}Ga-DOTATOC PET/CT in the detection of pituitary tumors by including both pathologically negative and positive samples. Furthermore, even if the tumors identified via the imaging modalities were real corticotroph adenomas, we may have missed subjects with negative immunohistochemistry results. This study did not use a quantitative definition of pituitary adenoma on ^{68}Ga-DOTATOC PET/CT, though SUV values were used to describe DOTATOC uptake in corticotropic pituitary adenomas. While some studies defined adenomas quantitatively using SUVs, these definitions vary due to differing reference regions and cutoff values, resulting in no consensus [31-33]. In this study, adenomas were identified based on a visual assessment of increased or decreased uptake relative to background tissue, considering clinical context and prior imaging. This method aligns with previous studies where experienced specialists visually identified tumor characteristics [24,34,35]. We also know that the definition by experienced specialists shows a high degree of concordance and that statistics are available to evaluate its reliability, variability may still occur. This limitation is acknowledged, and future studies should aim to establish standardized criteria, including potential SUV-based thresholds, to improve reproducibility [14].

Timely and accurate localization of ACTH-secreting pituitary adenomas is associated with prognosis and quality of life; however, this is clinically challenging. This study showed that the plasma ACTH level before surgery was a favorable predictor for the successful localization of primary lesions by ^{68}Ga-DOTATOC PET/CT, with a 53.86 pg/mL threshold. However, the use of ^{68}Ga-DOTATOC PET/CT as adjuvant imaging did not improve localization success compared to using MRI alone.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

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