Improved surgical outcome in patients with ACTH- and GH-secreting adenomas diagnosed by a MET-PET fusion 3T-MRI method

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Abstract

Object. Early diagnosis and treatment is important for Cushing's disease and acromegaly. The aim of this study was to improve surgical results by early diagnosis using the new sensitive method of [^{11}C] methionine-positron emission tomography (MET-PET) fusion 3T-magnetic resonance imaging (3T-MRI).

Methods. Endocrinological examination suggested abnormal secretion of adrenocorticotropic hormone (ACTH) or growth hormone (GH) in all cases. The pituitary tumors were investigated by composite 3T-MRI and MET-PET imaging. High MET uptakes in the pituitary region were regarded as pituitary adenoma. Forty-nine patients with Cushing's disease were examined with MET-PET. Thirty-five cases of Cushing's adenomas that were not detected by conventional MRI, but detected by MET-PET were also evaluated.. One hundred and thirty GH-secreting adenomas, including 97 patients with typical acromegaly and 33 patients with no apparent clinical features of acromegaly (pre-acro), were evaluated. The surgical cure rate was compared between patients with acromegaly and pre-acromegaly.

Results. The diagnostic accuracy of the localization of Cushing's disease was 100%. The overall cure rate of 35 Cushing's disease patients who were not diagnosed by 3T-MRI but were diagnosed by MET-PET fusion 3T-MRI was 94%. This result surpasses the reported surgical cure rate of 50–70% in Cushing's adenomas that were not detected by MRI. The surgical cure rates for acromegaly and pre-acromegaly were 67% and 100%, respectively. Patients with pre-acromegaly had a better surgical cure rate relative to patients with typical acromegaly.

Conclusions. Early detection of ACTH- and GH-secreting adenomas is important because early surgical intervention can achieve a better cure rate.

Introduction

Cushing's disease is a serious endocrinopathy that, if left untreated, greatly increases morbidity and carries a four-fold increased risk of mortality,[1] which is largely

associated with cardiovascular complications and abnormal glucose metabolism.[2] The duration of Cushing's disease is a significant predictor of cardiovascular risk,[3] and the risk of cardiovascular disease remains even after effective treatment.[4] Furthermore, the standard mortality ratio has been attributed to an increased mortality rate within the first year after diagnosis.

Conversely, acromegaly is associated with a two- or three-fold increase in patient mortality, and a reduced life expectancy of 10–15 years relative to the general population. This reduced life expectancy is because of the presence of other diseases, such as diabetes mellitus, high blood pressure, hyperlipidemia, cardiovascular disease, respiratory disease, and neoplastic complications.[5-8] The duration of disease is a prognostic factor, hence, early diagnosis and treatment for Cushing's disease and acromegaly is highly desirable. The typical first-line treatment for these conditions is transsphenoidal surgery. This means that improving the surgical cure rate is more important than finding alternative treatments. Regardless of the mode of resection (microscopic or endoscopic),[9] patients with large adenomas[10,11] and adenomas with cavernous sinus invasion (i.e., high Knosp scores) are less likely to achieve remission.[12,13]

The basic approach for improving the surgical cure rate is to diagnose adrenocorticotropic hormone (ACTH)- or growth hormone (GH)-secreting adenomas early enough before they become large adenomas, invade cavernous sinuses, or have clinical features such as Cushing's syndrome and acromegaly.

In the current study, we retrospectively surveyed the surgical results of patients diagnosed with ACTH- or GH-secreting adenomas, paying special

attention to the relationship between the early detection of ACTH- or GH-secreting adenoma and surgical outcome.

Methods

Patient Population

Fifty-eight patients who were examined with [^{11}C] methionine-positron emission tomography (MET-PET) underwent transsphenoidal microscopic surgery (TS) for ACTH secreting adenoma by a single skilled pituitary surgeon (H.I.) between 2008 and 2013 at the Southern Tohoku General Hospital. Among these patients we excluded two patients who were lost to follow-up, five patients who were recurrent cases who underwent TS surgery in another hospital, and two patients who were cured of Cushing's disease but not proven to have ACTH secreting adenoma by pathological study, probably because of sampling error. Therefore we included 49 patients with ACTH secreting adenoma in this study. Of the 49 patients, 15 were male and 34 were female. The patients' mean age was 47 years (range 11–77 years). Of the 49 patients with Cushing's disease, 15 cases consisted of 'overt' Cushing's disease and 34 cases had 'preclinical' Cushing's disease. All patients underwent transsphenoidal exploration of the pituitary gland by a skilled pituitary neurosurgeon (H.I.). The follow-up period was longer than 2 years. An ACTH-secreting adenoma was histologically confirmed in all of these patients. Our prerequisites for surgery were that the preclinical diagnostic criteria for Cushing's disease or overt Cushing's disease were fulfilled. The surgical cure rate of Cushing's adenomas, which was not detected by conventional magnetic resonance imaging (MRI) but detected by MET-PET, was evaluated (Table 1), and the results were compared with previous reports.[14,15,16]

Table 1; Summary of the pre- and post-operative clinical data in patients with Cushing's disease.

No.	sex	age	Diagnosis of 3T-MRI	pathology	post OP Dexa. 0.5mg supp.	post OP Dexa. 1mg supp.
1	F	74	positive	Cushing's disease	suppressed	suppressed
2	F	63	positive	Cushing's disease	suppressed	suppressed
3	F	45	positive	Cushing's disease	suppressed	suppressed
4	F	60	positive	Cushing's disease	suppressed	suppressed
5	F	26	positive	Cushing's disease	suppressed	suppressed
6	F	49	positive	Cushing's disease	suppressed	suppressed
7	F	75	positive	Cushing's disease	suppressed	suppressed
8	M	32	positive	pre-clinical Cushing	suppressed	suppressed
9	F	55	positive	pre-clinical Cushing	suppressed	suppressed
10	M	67	positive	pre-clinical Cushing	not suppressed	suppressed
11	M	42	positive	pre-clinical Cushing	not suppressed	suppressed
12	M	66	positive	pre-clinical Cushing	not suppressed	suppressed
13	F	35	negative	Cushing's disease	suppressed	suppressed
14	M	30	negative	Cushing's disease	suppressed	suppressed
15	F	53	negative	Cushing's disease	suppressed	suppressed
16	F	53	negative	Cushing's disease	suppressed	suppressed
17	F	58	negative	Cushing's disease	suppressed	suppressed
18	F	11	negative	Cushing's disease	suppressed	suppressed
19	F	39	negative	Cushing's disease	suppressed	suppressed
20	F	38	negative	Cushing's disease	suppressed	suppressed
21	M	26	negative	pre-clinical Cushing	suppressed	suppressed
22	F	21	negative	pre-clinical Cushing	suppressed	suppressed
23	F	26	negative	pre-clinical Cushing	suppressed	suppressed
24	F	62	negative	pre-clinical Cushing	suppressed	suppressed
25	M	39	negative	pre-clinical Cushing	suppressed	suppressed
26	F	19	negative	pre-clinical Cushing	suppressed	suppressed
27	M	35	negative	pre-clinical Cushing	suppressed	suppressed
28	M	44	negative	pre-clinical Cushing	suppressed	suppressed
29	F	66	negative	pre-clinical Cushing	suppressed	suppressed
30	F	27	negative	pre-clinical Cushing	suppressed	suppressed
31	M	48	negative	pre-clinical Cushing	suppressed	suppressed
32	F	27	negative	pre-clinical Cushing	suppressed	suppressed
33	F	57	negative	pre-clinical Cushing	suppressed	suppressed
34	F	66	negative	pre-clinical Cushing	suppressed	suppressed
35	M	65	negative	pre-clinical Cushing	suppressed	suppressed
36	M	51	negative	pre-clinical Cushing	not suppressed	suppressed
37	F	77	negative	pre-clinical Cushing	not suppressed	not suppressed
38	F	58	negative	pre-clinical Cushing	suppressed	suppressed
39	F	38	negative	pre-clinical Cushing	suppressed	suppressed
40	F	35	negative	pre-clinical Cushing	suppressed	suppressed
41	F	46	negative	pre-clinical Cushing	suppressed	suppressed
42	F	42	negative	pre-clinical Cushing	suppressed	suppressed
43	F	65	negative	pre-clinical Cushing	suppressed	suppressed
44	M	59	negative	pre-clinical Cushing	suppressed	suppressed
45	F	53	negative	pre-clinical Cushing	suppressed	suppressed
46	M	53	negative	pre-clinical Cushing	suppressed	suppressed
47	F	46	negative	pre-clinical Cushing	suppressed	suppressed
48	M	46	negative	pre-clinical Cushing	suppressed	suppressed
49	F	46	negative	pre-clinical Cushing	suppressed	suppressed

A total of 139 patients underwent transsphenoidal microscopic surgery

(TS) for GH secreting adenoma that was initially performed by one of the authors (H.I.) between 2002 and 2012 at Ohara General Hospital and Southern Tohoku General Hospital. All patients had undergone 3T-MRI examination; in addition, 57 patients had undergone MET-PET examination. The follow up period was longer than 2 years. Nine of the 139 patients missed follow-up; therefore we included 130 cases in this study. Of these patients, 54 were male and 76 were female. The patients' mean age was 48.1 years (range 11–73 years). Of the 130 patients, 97 were cases of 'overt' acromegaly. The remaining 33 patients had no apparent clinical characteristics of acromegaly (i.e., pre-clinical acromegaly), such as large cheekbones, bulging forehead, enlarged jaw, and soft tissue swelling resulting in enlargement of the hands, feet, nose, or lips.[6,17] Patients with pre-Acromegaly had high value of normal sex- and age-adjusted IGF-1 level and/or GH value, and had not suppressed a glucose-suppressed (nadir) GH level of less than 0.4 ng/ml. The surgical cure rate was compared between patients with acromegaly and pre-acromegaly.

The present study was conducted in accordance with the declaration of Helsinki (1964). Informed consent was obtained from all patients.

Magnetic Resonance Imaging

The size and extent of the tumors were determined using magnetic resonance (MR) images obtained with a 3.0-T MR unit (Signa HDx; General Electric, Fairfield, CT, USA). T1- and T2-weighted thick sagittal and coronal spin-echo MR images were obtained as 2-mm-thick slices. Additional T1-weighted axial, sagittal, and coronal MR images (500/15 ms) were obtained immediately after injection of 0.1 mmol/kg gadolinium-diethylenetriaminepenta-acetic acid (Schering, Berlin, Germany). The images were reconstructed by means of a two-dimensional Fourier transformation on a 256 × 256 image matrix. The tumor size and cavernous sinus invasion were evaluated on axial, sagittal, and coronal

images of MET-PET fusion 3T-MRI with gadolinium enhancement. The tumor volume was measured using a reliable empirical formula for volume estimation published by Petersen et al.[18] Follow-up MRI and hormonal examinations were performed to detect the recurrence of the tumor every 6 months after surgery.

Positron Emission Tomography Imaging

As of 2008, the PET-computerized tomography (PET-CT) studies were undertaken using the Discovery LS (General Electric) for all cases. The PET machine uses bismuth germanium oxide crystals. All patients fasted before the procedure and received intravenous injections of [^{11}C] methionine (MET; 5.6 mBq × body weight [dose range, 225.7–558.3 mBq, i.e., 6.1–15.1 mCi]). PET scans of 10 min duration were obtained starting 20 min after injection. At 1 h after the MET injection, all patients received intravenous injection of fludeoxyglucose (FDG; 3.7 mBq × body weight [dose range, 155–269.5 mBq, i.e. 4.2–7.3 mCi]). PET scans of 10 min duration were obtained starting 60 min after injection. The MET-/FDG-PET procedure was performed in a three-dimensional mode, which provided a set of 35 planes with a section thickness of about 4.1 mm. The uptake of FDG and MET during PET scanning was evaluated using a standardized uptake value (SUV) max.

Image Post-Processing

The MR and PET images were co-registered to Gd-enhanced, T1-weighted axial, coronal, and sagittal images using the software workstation (Advantage Windows, General Electric). For co-registration between MR images and PET images, MRI data were first reconstructed based on the CT skull shape ascertained using PET-CT. This procedure was performed based on anatomical landmarks, such as optic nerves, the internal occipital protuberance, and the vestibular cochlear nerve. Then, the

MR images were fused to the PET scan. Thereafter, the PET scans that had been overlaid onto the MR images were automatically viewed.[19,20]

The presence of pituitary adenomas was evaluated by composite 3T-MRI and MET-PET imaging. Using a MET SUVmax value, we set up a threshold of adenomatous “high” uptake of MET for a normal-appearing pituitary gland in a volunteer. Background activity in normal pituitary tissue in this study showed a mean (± SD) MET SUVmax of 1.3 ± 0.23, and a mean FDG SUVmax of 3.19 ± 0.74. The background activity of normal pituitary tissue from PET examination in the 10 individuals who did not seem to have pituitary disease was 0.74 ± 0.18 (range 0.50–1.0) for MET SUVmax and 2.72 ± 0.96 (range 1.3–4.5) for FDG SUVmax[19,20]. Thus, background noise in proposed adenoma cases was higher than that in cases with normally functioning pituitary glands, probably because of tumor uptake artifacts.

In light of the above findings, we felt that SUVmax of 1.0 was reasonable to define as a critical value to differentiate normal pituitary tissue and hormone active adenomatous tissue. The FDG uptake was not detected in adenomas with low activity most likely because the background activity of FDG was greater than that of MET.

Laboratory Evaluation

1) The diagnostic criteria of preclinical Cushing’s disease are as follows:

a) An uncertain existence of pituitary tumor following diagnostic imaging (MRI)

b) Normal or high morning serum ACTH values and normal serum cortisol values

c) The lack of specific cushingoid features

If all three criteria were met and it was still unclear whether Cushing disease was present, additional screening was performed in which the

abnormality of cortisol secretion, which originates from autonomous ACTH secretion, was examined. Diagnostic factors from the screening inspection included the following:

i) A serum cortisol value of ≥2.5 μg/dl when sleeping (measured at midnight)

ii) A morning serum cortisol value of ≥3 μg/dl after 0.5 mg dexamethasone suppression at night

iii) Paradoxical reaction of ACTH (≥1.5 times the former value) on a 1-deamino-8-d-arginine vasopressin test

If two or more of these three items met the criteria, then this was evidence of cortisol secretion abnormalities due to autonomous ACTH secretion. To discriminate between ectopic ACTH syndrome, it was assumed that no abnormal findings following FDG/MET-PET scanning were observed in the entire body. Endocrinological examination suggested abnormal secretion of ACTH or GH in all cases.

(2) The endocrine status of the patients with GH-secreting adenomas was evaluated before and after surgery by measurement of serum levels of GH and insulin-like growth factor-1 (IGF-1), prolactin, ACTH, cortisol, thyroid-stimulating hormone, free-T3 and free-T4, follicle-stimulating hormone, luteinizing hormone, estradiol, and testosterone.[21] The secretory status of the tumor and preoperative evaluation of the baseline pituitary function were established. Precise endocrinological tests were performed using the GH suppression test, as determined using the 75-g oGTT loading test and the TRH/LHRH loading test, to examine the paradoxical response to GH. These stimulatory and inhibitory tests were not indicated in patients with severe diabetes mellitus or with large pituitary adenoma for fear of pituitary apoplexy.

Surgical Technique

The general approach to surgery was to remove the adenoma completely

and to prevent damage to normal pituitary function. MET-PET can visualize the localization of the suspected microadenomas. Clues to finding an adenoma were by the presence of a different color and softness of the tissue in the area of high uptake area of MET. Usually Cushing adenoma is easy to find by experienced surgeons because it is whitish in color and very fragile.

Since microadenomas show a poorly formed reticulum network (so-called pseudocapsule), it is difficult and unnecessary to take out the adenoma by extracapsular extraction. Therefore, in the area of high uptake MET-PET, we observed discolored pituitary tissue and sometimes removed it along with a small part of adjacent tissue to assess for clear histological margins. The MET-high uptake area is usually larger than the adenoma because of the poor resolution of the PET images, but the suspected area of the adenoma can be defined by a MET-PET image, and is enough to find the target area to treat Cushing disease, and therefore the conventional method of full exploration of the gland and hemi-hypophysectomy is not necessary. For macroadenomas invading the cavernous sinus, we used endoscopy in addition to microscopy to ascertain the presence of residual adenoma. To avoid any complications such as carotid injury, we always used Doppler sonography before making dural incisions to the sellar floor.

Remission Criteria

Postoperative remission or cure of ACTH-secreting adenomas was defined by the disappearance of hypercortisolism and serum cortisol levels under 3.0 ug/dl at 8:00 a.m. after administration of 0.5 or 1 mg oral dexamethasone at 23:00.

Those patients with GH-secreting adenomas who had glucose-suppressed (nadir) GH level of less than 1.0 ng/ml, and a normal sex- and age-adjusted IGF-1 level were defined as being in remission using the 2000 criteria[22]. Likewise, those patients with GH-secreting adenomas who had a

glucose-suppressed (nadir) GH level of less than 0.4 ng/ml, a normal sex- and age-adjusted IGF-1 level, and postoperative random GH levels of 1 ng/ml or less were defined as being in remission based on the 2010 criteria[23]. To identify remission, we examined these criteria at 1, 6, and 12 months after surgery.

Pathological Examination

Surgical specimens were fixed in 10% neutral buffered formalin and embedded in paraffin. Tissue sections (3 um thickness) were prepared and stained with hematoxylin and eosin. Immunohistochemical staining was performed using the avidin-biotin complex method with the following antibodies: polyclonal adrenocorticotropic hormone (Dako, Glostrup, Denmark); polyclonal growth hormone (Dako); polyclonal prolactin (Dako); monoclonal thyroid-stimulating hormone-β (Neo markers, Fremont, CA, USA); monoclonal luteinizing hormone-β (Cosmo Bio Co. Ltd, Tokyo, Japan); monoclonal follicle-stimulating hormone-β (Cosmo Bio Co. Ltd); polyclonal α-subunit (Dako), and monoclonal Ki-67 (Dako).

Statistical Analysis

Because none of the parameters showed a normal distribution, Spearman's rank correlation test was used. A P-value of <0.05 was considered statistically significant.

To compare the differences between two independent groups, where each group showed a normal distribution, Welch's t-test was used.

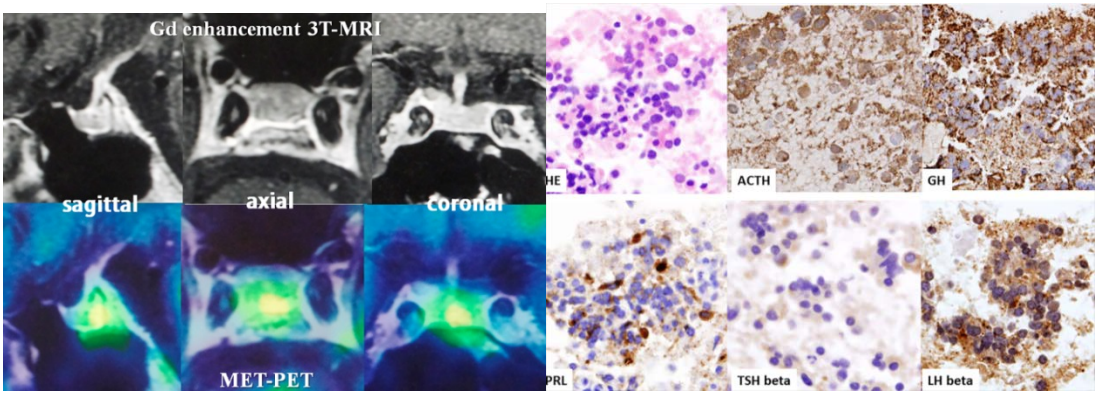
Results

Diagnostic Sensitivity of MRI and MET-PET

The diagnostic accuracy of MET-PET fusion MRI on the localization of Cushing's disease was 100%, and that of 3T-MRI was 29% (Table 2). Patients who had high MET uptake observed in the pituitary region

underwent the operation, and all of their adenomas were identified as ACTH-secreting adenomas by histopathology (Fig. 1). Among the 35 patients in which adenoma was not visualized by 3T-MRI, eight patients with overt Cushing's disease (23%) and 27 with subclinical Cushing's disease (77%) were included (Table 1).

Fig. 1. Pre-clinical Cushing's disease in a 53-year-old man. a) sagittal, axial, and coronal images of Gd-enhanced MRI, and MET-PET. b) Pathological findings of resected adenoma. Immuno-positive cells for ACTH , GH, PRL, TSH beta, and LH beta were observed.



a) **b)**

Table 2. Diagnostic sensitivity of MRI and MET-PET in the diagnosis of Cushing's disease.

	No. of Patients	Diagnostic rate
3T-MRI	49	14 (29%)
MET-PET	49	49 (100%)

Conversely, the diagnostic sensitivities of 3T-MRI and MET-PET fusion 3T-MRI in patients with GH-secreting adenomas are shown in Table 3.

Table 3 Diagnostic sensitivity of 3T-MRI and MET-PET in the diagnosis of acromegaly and pre-acromegaly.

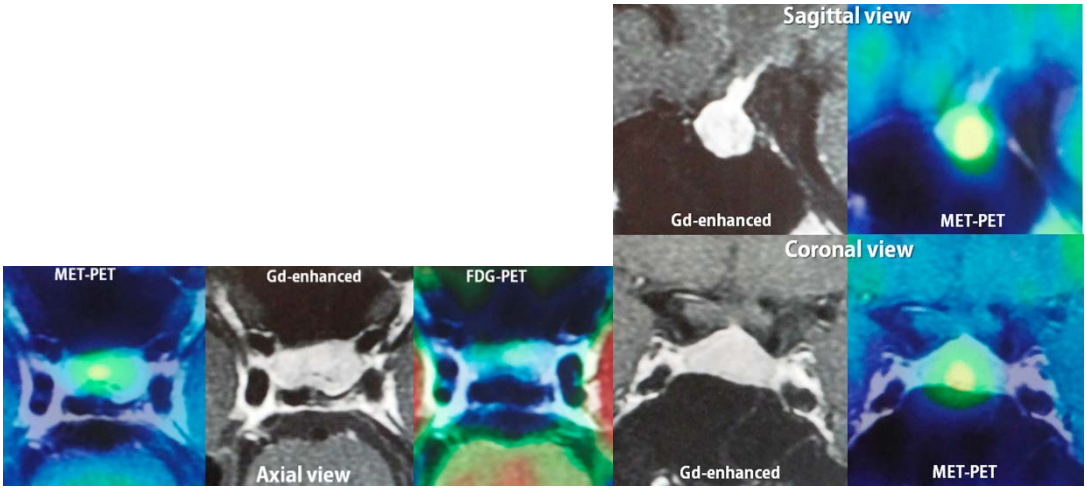
Patients (N=130)	Diagnostic methods	No. of patients	Detectability (cases)	Detectability (%)
Pre-clinical acromegaly	3T-MRI	33	11/33	33
	MET-PET	26	26/26	100
Acromegaly	3T-MRI	97	96/97	99
	MET-PET	31	31/31	100

The diagnostic sensitivity of 3T-MRI was 33% in pre-clinical acromegaly. In contrast, the diagnostic sensitivity of MET-PET fusion 3T-MRI was 100% for pre-clinical acromegaly and 99% for overt acromegaly (Fig 2).

Fig. 2. Pre-acromegaly in a 25-year-old woman.

a) Axial, coronal, and sagittal images of MET-PET, FDG-PET, and Gd-enhanced MRI.

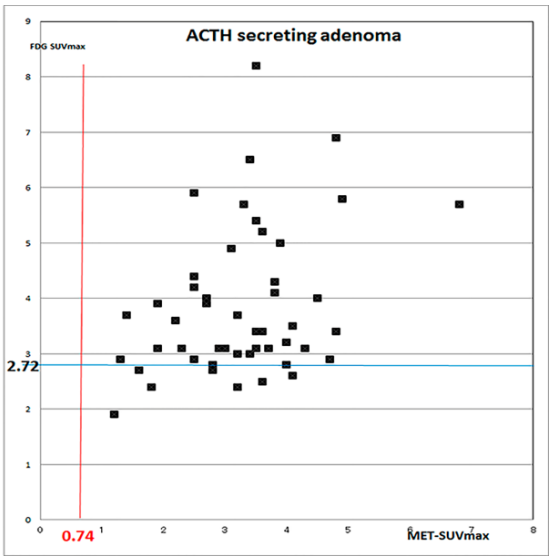
b) Sagittal and coronal images of Gd-enhanced MRI and MET-PET.



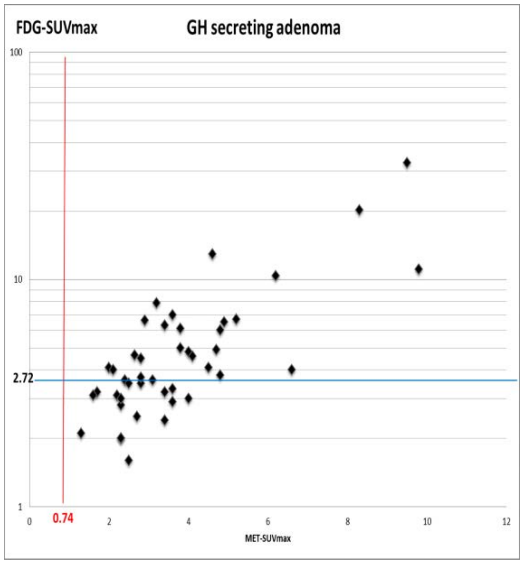
a) b)

Thus, the diagnostic accuracy of MET-PET was perfect and far superior to the diagnostic accuracy of 3T-MRI. Those patients with GH-secreting adenomas who were diagnosed by MET-PET fusion MRI and not diagnosed by 3T-MRI had significantly higher values (P = 0.01) of tumor SUV max. Relationship between MET-SUVmax and FDG-SUVmax in patients with ACTH secreting adenomas and GH secreting adenomas revealed that all the patients with ACTH and GH secreting adenomas showed MET-SUVmax values more than 1.3 (Fig. 3).

Fig. 3. Relationship between MET-SUVmax and FDG-SUVmax in patients with ACTH secreting adenomas (a) and GH secreting adenomas (b). Vertical line (0.74) indicates mean MET-SUVmax in a normal pituitary gland. Horizontal line (2.72) indicates mean FDG-SUVmax in a normal pituitary gland. Note that all the patients with ACTH and GH secreting adenomas showed MET-SUVmax values more than 1.3.



a)



b)

Surgical Outcome

The overall cure rate of 49 patients with Cushing's disease was 98% using the criterion of a morning serum cortisol level of less than 3 ug/dl after oral administration of 1 mg dexamethasone. Using the criterion of a morning cortisol level of less than 3 ug/dl after oral administration of 0.5 mg dexamethasone, the overall cure rate of the 49 Cushing's disease patients was 92%. The cure rate of the 35 Cushing's disease patients that were not detected by 3T-MRI but were diagnosed by MET-PET fusion 3T-MRI was 94%.

The overall surgical cure rate for acromegaly using the 2000 cure criteria and 2010 cure criteria was 75% and 72%, respectively. Using the 2000 cure criteria, the surgical cure rate for acromegaly patients was 67%, while the surgical cure rate for patients without obvious clinical features of acromegaly (pre-clinical acromegaly) was 100%. Using the 2010 cure criteria, the surgical cure rate for acromegaly patients was 62%, and the surgical cure rate for pre-clinical acromegaly was 100% (Table 4). The over all surgical cure rate using subgroups of Knosp grading were 100% in Grade 0 (N=24), 100% in Grade 1 (N=22), 86% in Grade 2 (N=35), 56% in

Grade 3(N=33), and 31% in Grade 4 (N=16).

Thus, the early detection of ACTH- or GH-secreting adenoma with MET-PET fusion 3T-MRI dramatically improved surgical outcome.

Complications of Surgical Management

None of the patients experienced permanent diabetes insipidus. No mortality and morbidity occurred, and none of the patients had a cerebrospinal fluid fistula. Hypopituitarism after surgery occurred in only one patient with GH-secreting adenomas.

Discussion

Transsphenoidal microsurgical removal of GH- or ACTH-secreting pituitary adenoma is a first-line treatment. Our data revealed that it is important to diagnose GH- and ACTH-secreting adenomas as early as possible, because this contributes to an improved surgical cure rate that results in the prevention of progressive organ failure. Adverse effects caused by the surgical procedures were minimal because most of the early-stage adenomas corresponded to Knosp grade 0–1. Therefore, there was no need for manipulation in the cavernous sinus, resulting in a reduced risk factor for surgery.[12] Patients with pre-clinical acromegaly had a tendency to have smaller-sized adenomas, be of younger age, have lower GH and IGF-1 levels, and a better surgical cure rate relative to patients with typical acromegaly.[24,25]

For the detection and delineation of tumor location, especially in the case of microadenoma, the diagnostic accuracy of superconductive MRI has been reported to be only 10–40%, with 33% false-negatives and 20% false-positives.[19,26] In general, the use of dynamic MRI improves diagnostic accuracy. However, no significant difference between the diagnostic accuracy of these two imaging techniques has been shown.[19] Conventional imaging has failed to diagnose early-stage GH-secreting adenoma.

However, MET-PET fusion MRI has enabled the detection of adenoma in all patients with abnormal GH dynamics that have been examined.[25,27] Pre-clinical Cushing's adenoma was efficiently detected using MET-PET fusion MRI,[19,20] and similarly, pre-clinical acromegaly was also detected by MET-PET fusion MRI.[24,25]

The reason why we could set up a threshold of MET uptake between adenoma cells and normal pituitary cells was as follows. Our *in vitro* ultrastructural experimental data show that the pituitary cells are undergoing active protein synthesis, regardless of whether the adenoma is functional. The amount of protein synthesis within corticotroph or somatotroph cell adenomas greatly exceeded that in normal pituitary tissue[20]. It has been established that, as a rule, one pituitary cell produces one pituitary hormone. On the other hand, all the early cases of ACTH and GH producing adenomas had plurihormonal adenoma.[28] Thus high incidence of multihormone producing cells in pre-Cushing's adenoma and pre-acromegalic patients may play a significant role in high protein synthesis.[29] For these reasons, MET uptake by the adenoma provides a good contrast to normal pituitary tissue.

The criteria of "high" uptake of MET were defined as follows. Background activity in normal pituitary tissue in this study showed a mean MET SUVmax of 1.3 ± 0.23, and a mean FDG SUVmax of 3.19 ± 0.74. In contrast, the background activity of normal pituitary tissue by PET examination in the 10 volunteer individuals who did not seem to have pituitary disease was 0.74 ± 0.18 (range 0.50–1.0) for MET SUVmax. Therefore we considered SUVmax 1.0 as a reasonable critical value to differentiate normal pituitary tissue and hormone active adenomatous tissue. We suspect adenoma to exist when SUVmax of MET-PET exceeds 1.0.

The high sensitivity of MET-PET in the detection of microadenoma is attributed to the following factors: (1) GH adenoma and ACTH adenoma have high cellularity relative to normal anterior pituitary tissue; (2) almost

all of the cells in these two types of adenomas show strong positive immunoreactivity for either GH or ACTH; (3) electron microscopic studies have shown that ACTH adenoma and GH adenoma have densely packed secretary granules in their cytoplasm; (4) adenomas from pre-clinical Cushing's disease and pre-clinical acromegaly produce many hormones.[28] In light of these findings, it is clear that amino acid metabolism in ACTH and GH adenomas is extremely active, and accounts for the high accumulation of methionine during MET-PET.

The overall cure rates obtained in studies involving several large series of patients with acromegaly treated by transsphenoidal surgery using modern cure criteria were reported as follows: 67% (N = 117, Kreutzer et al.[30]), 57% (N = 506, Nomikos et al.[31]), 52% (N = 103, Beauregard et al.[32]), and 64% (N = 160, Gittoes et al.[33]) (Table 5).

Table 5. Summary of the reported series of surgical cure rate operated more than 100 cases of GH-secreting adenomas. (The remission criteria used was the 2000 cure criteria.)

	Reporter	Year of publication	No. of patients	Cure rate (2000 criteria)
1	Kreutzer J.	2001	117	67%
2	Nomikos P.	2005	506	57%
3	Beauregard C.	2003	103	52%
4	Giustina A.	2000	160	64%
5	Ikeda H. (present report)	2015	130	75%

The overall cure rate for GH-secreting adenoma in our study was 73% using the 2010 modern cure criteria[23] and 81% using the previously reported 2000 cure rate.[22] Our surgical cure rate was much higher than

those reported in previous studies, probably because early detection and early surgical intervention contributed to an improvement in the cure rate.

There is still no widespread agreement regarding the definition of an apparent cure for Cushing's disease, and remission rates after surgery vary according to the criterion used at the time of assessment. Urinary free cortisol is no longer useful for diagnosing Cushing' disease or to evaluate remission, except in special conditions.[14,34]

We adopted strict remission criteria, including adrenal insufficiency and cortisol suppression after 0.5 or 1 mg overnight dexamethasone suppression test. Even with these strict remission criteria, we detected a very good remission rate of 90% (criteria of 0.5 mg suppression) and 98% (criteria of 1 mg suppression). The overall cure rate of Cushing's disease is between 72.3% and 100%, if a positive MRI finding with clear visualization of the adenoma was obtained.[9] However, the remission rate in patients with negative or inconclusive MRI drops to only 50–71.4%.[14-16] Our surgical cure rate of 35 Cushing's disease patients who were not detected by 3T-MRI but were diagnosed by MET-PET fusion 3T-MRI was 94%. This result surpasses the reported surgical cure rate in Cushing's disease adenomas that was negative by MRI (Table 6). Thus, it is important to visualize the location of the adenoma to improve surgical results. The goal of managing acromegaly and Cushing's disease is to provide patients with the most effective means of long-term control of these benign but potentially disabling diseases. For this purpose, early diagnosis and early surgical treatment of acromegaly and Cushing's disease promises to provide a high cure rate and minimal adverse surgical effects.

Conclusions

Early-stage GH-secreting adenomas and Cushing's disease adenomas are inevitably microadenomas, and as a result, the rate of detection of these tumors using superconductive MRI is unsatisfactory. However, the

MET-PET fusion 3T-MRI method provides a far higher sensitivity (100%) in delineating GH- and ACTH-secreting adenomas and determining their location. We emphasize the usefulness of MET-PET fusion 3T-MRI in diagnosing GH- and ACTH-secreting adenomas, if the presence of a GH- or ACTH-producing tumor is suspected from an endocrinological point of view. This in turn contributes to the early diagnosis and high surgical cure rate of GH- and ACTH-secreting adenomas.

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