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Composite MET-PET Fusion MRI is a Novel Method to Determine Adjuvant Therapy for Growth Hormone Secreting Adenomas

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Abstract

Background: Normalization of abnormal Growth Hormone (GH) and Insulin-like Growth Factor (IGF)-1 secretion is essential for the treatment of acromegaly. Although the diagnostic accuracy of magnetic resonance imaging (MRI) has increased in recent years, MRI may fail to detect residual adenoma, even in patients with high IGF-1 levels. The recently developed composite methionine (MET)-PET fusion 3 Tesla (3T)-MRI technique has helped us to determine the location of adenomas that could not be detected by conventional MRI. Regions with high MET uptake are suggestive of residual adenomas. In this study, we sought to confirm the positional relationship between regions of high MET uptake and the sites of viable residual adenoma cells.

Methods: We analyzed the results of six patients who underwent gamma knife radiosurgery or re-operation as adjuvant therapy with the aid of composite MET-PET fusion MRI.

Results: Based on our experiences in these six patients, composite MET-PET fusion 3T-MRI is useful to plan surgery, and to plan the dose and area of radiation required for gamma knife radiosurgery of an active lesion.

Conclusion: The use of composite MET-PET fusion 3T-MRI and subsequent dose planning enabled us to achieve a high remission rate with adjuvant therapy for patients with acromegaly, because MET-PET could clearly detect and delineate the residual tumor.

Keywords: GH adenoma; Transsphenoidal surgery; MET-PET; 3T-MRI; Gamma knife; Residual tumor

Introduction

Acromegaly is associated with a 2–3-fold increase in patient mortality, and a reduction in life expectancy of 10–15 years relative to the general population [1-5]. Therefore, normalization of abnormal Growth Hormone (GH) and Insulin-like Growth Factor (IGF)-1 secretion is essential for the treatment of acromegaly.

Although the diagnostic accuracy of Magnetic Resonance Imaging (MRI) has increased in recent years, MRI may fail to detect residual adenoma, even in patients with high IGF-1 levels. Although Dynamic MRI is generally thought to improve diagnostic accuracy, in a report examining the diagnostic rates of MRI using 1.0T-MRI and Dynamic MRI, true positivity of MRI was 11/21 (52%), and true positivity of Dynamic MRI was 14/21 (67%). A significant difference between the diagnosis rates of MRI and Dynamic MRI was not observed [6]. Dynamic MRI could indicate the existence of abnormal findings; it was ineffective in the diagnosis regarding the range of the abnormal findings. Due to taking many small ROI (Region of Interest), mapping is virtually impossible.

We recently developed a composite methionine (MET)-Positron Emission Tomography (PET) fusion 3 Tesla (3T)-MRI imaging modality. This modality showed excellent accuracy for detecting Cushing's microadenomas and recurrent Cushing's adenomas, which could not be detected or delineated by conventional MRI [7,8].

Adenomas may also be difficult to detect in patients with acromegaly using conventional MRI, as the detection rate of adenomas was 87% using MRI but increased to 100% in the same patients when using MET-PET fusion MRI [9]. Therefore, treating patients with acromegaly whose adenoma could not identified by MRI is a major clinical issue. In this context, composite MET-PET fusion 3T-MRI has helped us to determine the location of adenomas that could not be detected by MRI.

Regions with high MET uptake are suggestive of residual adenomas. To examine whether these regions fulfill the necessary and sufficient criteria to indicate the location of the residual tumor, we compared the abnormal GH dynamics between gamma knife radiosurgery and re-operation as adjuvant therapy. In other words, we sought to confirm the positional relationship between regions of high MET uptake and the sites of viable residual adenoma cells.

Materials and Methods

As of 2008, positron emission tomography-computerized tomography (PET-CT) studies had been performed using the Discovery LS (GE Medical Systems, Fairfield, CT, USA) in 50 patients with a GH secreting adenoma. MET-PET was performed in six patients to define the residual adenoma after initial surgery. Five of the six patients underwent gamma knife radiosurgery as adjuvant therapy, while the other patient underwent re-operation (Table 1).

The PET machine used bismuth germanium oxide crystals. The patients fasted before the procedure and received intravenous injections of [11C]-MET (5.6 MBq×body weight [dose range, 225.7–558.3 MBq; 6.1–15.1 mCi]). PET scans of 10 min duration were obtained starting at 20 min after MET injection. At 1 h after MET injection, all of the patients received an intravenous injection of fluorodeoxyglucose (FDG) (3.7 MBq×body weight [dose range, 155–269.5 MBq; 4.2–7.3

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Case	Age	SUVmax: MET	SUVmax: FDG	GH (mg/ml)	IGF-1 (ng/ml)	residual tumor volume (cm^3)	Kno-sp's Grade	Aju-vant Treat.
1	49	1.9	8.1	4.8	431	negligible	G4	gamma knife
2	57	2.8	4.5	1.97	178	negligible	G3	gamma knife
3	71	3	0	0.27	279	negligible	G3	gamma knife
4	59	3.4	6.3	1.94	382	negligible	G3	gamma knife
5	27	4.3	7.5	5.9	885	negligible	G4	gamma knife
6	40	1.4, 1.6	0	4.85	443	negligible	G4	re-ope

Table 1: Clinical and radiological data of the patients with acromegaly.

mCi]). PET scans of 10 min duration were obtained starting at 60 min after FDG injection. The MET/FDG-PET procedure was performed in the three-dimensional mode, which provided a set of 35 planes with ~4.1 mm thick sections. The uptake of FDG and MET during the PET scan was evaluated based on the maximum standardized uptake value (SUVmax).

The MRI and PET scans were co-registered to gadolinium (Gd)-enhanced T1-weighted images and T2-weighted images using Advantage Windows software (GE Medical Systems). For co-registration of MRI and PET scans, the MRI data were first reconstructed using the skull shape determined by PET-CT. This procedure was performed based on anatomical landmarks, such as optic nerves, the internal occipital protuberance, and the vestibular cochlear nerve. The MRI and PET scans were then fused together. The PET scans that had been overlaid onto the MRI scans were then automatically viewed [7,8].

Endocrine assessments

The basal GH and IGF-1 levels were measured before gamma knife radiosurgery or before re-operation. The hormone levels were then measured every 3–6 months after adjuvant therapy.

Pathologic examinations

Surgical specimens were fixed in 10% neutral-buffered formalin and embedded in paraffin. Tissue slices (3 μm thick) 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.), and polyclonal α-subunit (DAKO).

Radiosurgery technique

Radiosurgery was performed using the gamma knife unit model C (Elekta, Stockholum, Sweden). A stereotactic frame was fixed to the patient's head, and then MRI (1 mm thick slices, axial direction, T1-weighted with contrast enhancement and T2-weighted images) and CT (1.25 mm thick slices without contrast) were performed. The treatment was planned using the GammaPlan system (Ver. 9, Elekta). The standard marginal dose applied to GH secreting adenomas was 25 Gy at ≥ 50% of the isodose line. The dose applied to the visual pathway was limited to <10 Gy.

Follow-up assessments

The follow-up assessments included serial MRI and endocrine tests performed at 3 month intervals. The duration of follow-up after adjuvant therapy ranged from 6 to 30 months.

Results

The location of the residual tumor after surgery could not be determined by 3T-MRI in any of the six patients. However, MET-PET fusion MRI revealed high accumulation of MET in all six patients. Five of the patients underwent gamma knife radiosurgery and the changes in their serum IGF-1 levels are shown in figure 1. IGF-1 levels normalized within 1 year after radiosurgery in these five patients. These results indicate that regions of high MET uptake are likely to indicate the presence of viable tumor cells. In other words, the regions of high MET uptake satisfied the necessary and sufficient criteria for localization of adenoma.

In the patient who underwent re-operation (case 1) four small foci with high MET uptake were observed on preoperative MET-PET fusion MRI (Figures 2a and 2b). These foci could not be detected after re-operation (Figures 2c and 2d) and the previously elevated IGF-1 levels had reverted to the normal range. Therefore, in this patient, the regions of high MET uptake satisfied the necessary and sufficient criteria for residual adenoma.

Representative case 1

The patient was a 31-year-old male with acromegaly. At the age of 31 years, a pituitary adenoma was detected on MRI and a transsphenoidal operation was performed at a local hospital. However, only partial resection of the tumor was achieved. For the residual adenoma, the patient was treated with gamma knife radiosurgery with a marginal dose of 18 Gy at the age of 33 years. As the patient's serum IGF-1 level remained elevated 3 years after radiosurgery (656 ng/ml), he was treated with various drugs, including cabergoline, long-acting release somatostatin, and pegvisomant. Despite these treatments, the serum IGF-1 level remained high (500 ng/ml) at 5 years after radiotherapy. Therefore, the patient was admitted to our clinic for surgical treatment (Figure 3a).

MET-PET revealed high MET uptake by the residual adenoma

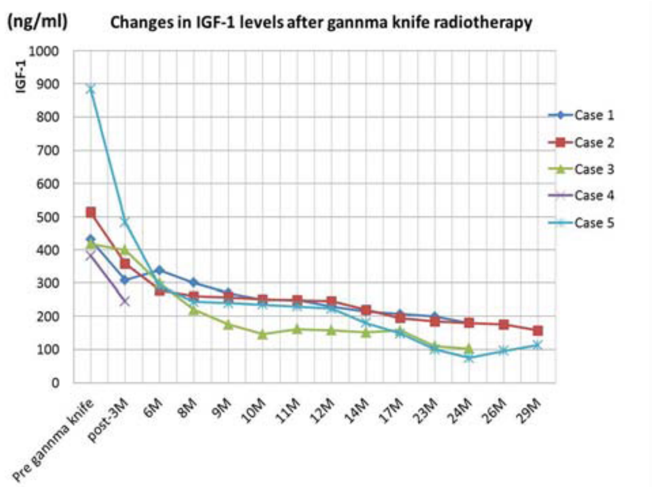

Figure 1: Changes in IGF-1 levels after gamma knife radiosurgery.

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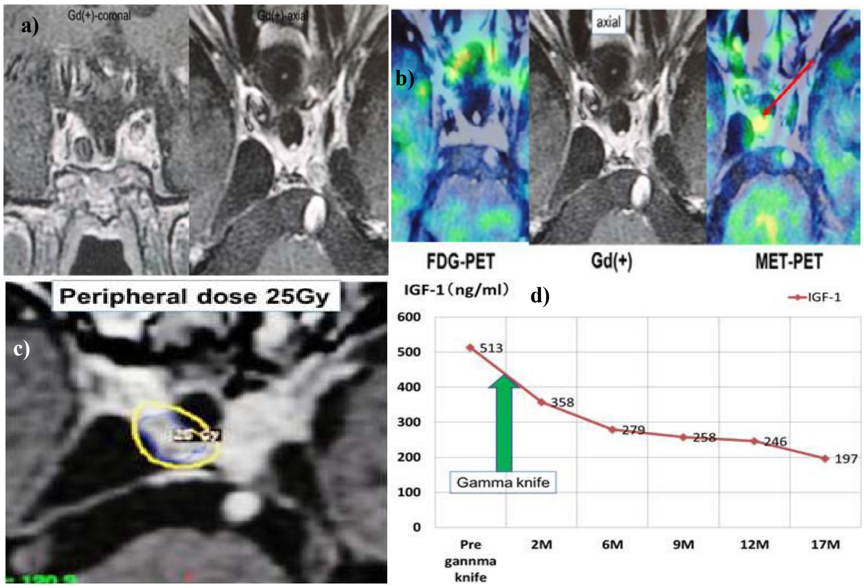

Figure 2: Features of patient #2. a) Post-operative MRI, b) Post-operative MET-PET fusion MRI. The red arrow indicates the region of high MET uptake in the sellar region. c) Gamma knife dose planning, axial MRI scan. (d) Changes in IGF-1 levels after gamma knife radiosurgery.

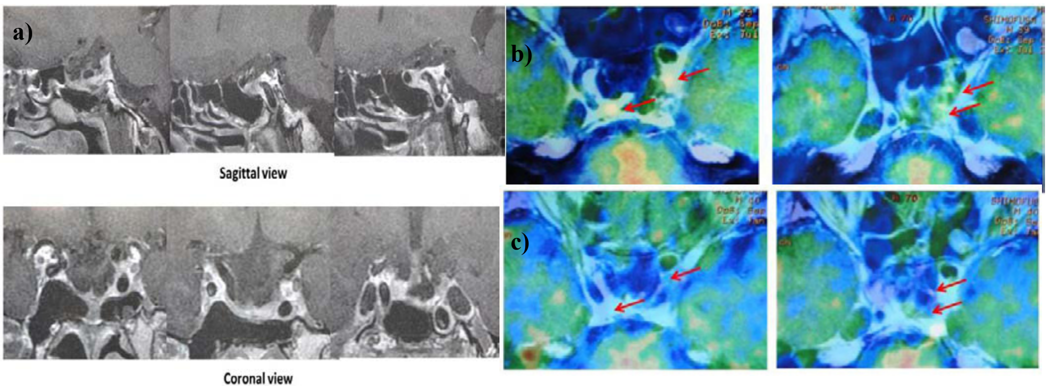

Figure 3: Features of patient #1, a) MRI on admission. T1WI-Gd enhancement, b) Pre-operative MET-PET, Arrows indicate MET high uptake within the adenoma, c) Post-operative MET-PET. MET high uptake was completely disappeared.

(Figure 3b), suggesting that the adenoma was actively proliferating. Therefore, a second transsphenoidal operation was performed. In this procedure, the region of high MET uptake was completely removed (Figure 3c). The patient's serum IGF-1 was normalized after the re-operation (231 ng/ml), and the patient is now being followed up as an outpatient.

Representative case 2

The patient was a 71-year-old male with acromegaly. This patient underwent a transsphenoidal operation 15 years ago and was followed up as an outpatient. His IGF-1 level gradually increased, and reached 765 mg/ml at the age of 71 years. However, MRI did not detect a recurrent adenoma (Figure 2a). Therefore, MET-PET was performed and a region of high MET uptake area was detected, as shown in figure 2b. FGD-PET showed no FDG uptake in the pituitary. Based on these findings, we irradiated the region of high MET uptake by gamma knife radiosurgery with a peripheral dose of 25 Gy (Figure 2c). The sequential changes in IGF-1 levels are shown in figure 2d. The patient's IGF-1 levels were normalized within 6 months after radiosurgery.

Based on our experience in these two representative cases, MET-PET fusion 3T-MRI is useful to plan surgery and to plan the dose and area of radiation required for gamma knife radiosurgery of an active lesion.

Discussion

Identification of the residual tumor after surgery is important to aid the selection of adjuvant therapy. Adjuvant treatments, such as re-operation and gamma knife radiosurgery, are currently indicated for residual tumor, based on postoperative MRI findings. However, it is often difficult to detect an adenoma using MRI. Additionally, the granulation tissue that forms after a surgical procedure increases the difficulty of identifying a residual tumor [10]. Considering these limiting factors, the adjuvant therapy that was selected based on MRI findings may prove to be ineffective.

In terms of gamma knife adjuvant therapy, the sequential changes in IGF-1 after gamma knife radiosurgery differ between MRI-based dose planning (Figure 4) [11-13] and MET-PET-based dose planning (Figure 1). Notably, the remission rate following gamma knife radiosurgery

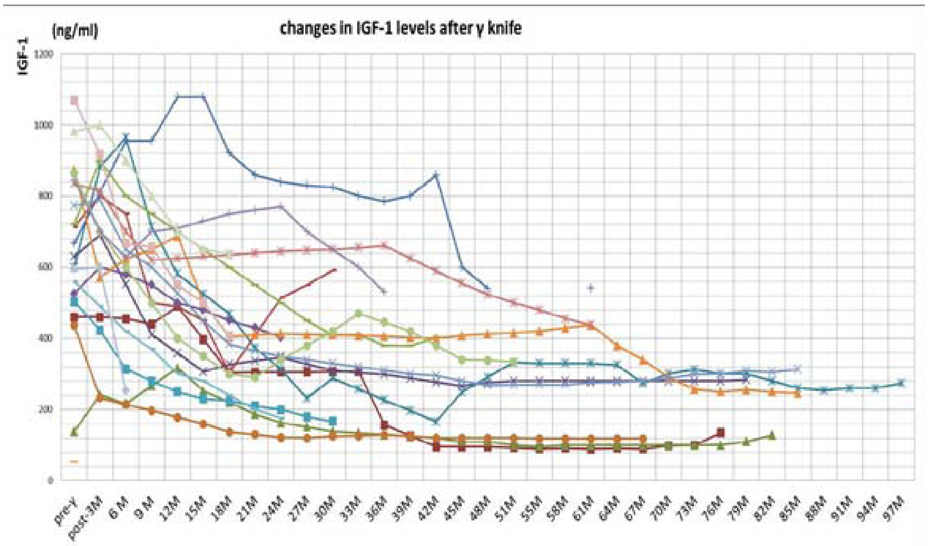

Figure 4: Changes in IGF-1 levels after gamma knife radiosurgery.

based on MET-PET findings tended to be higher than that based on MRI findings. Furthermore, the time to remission is shorter with MET-PET-based dose planning for radiosurgery compared with MRI-based dose planning [11-14]. Because of the small number of patients and the size of the residual tumor [15] differed between patients, we cannot reach a conclusion on the superiority of either method. Nevertheless, for the five patients who underwent gamma knife radiosurgery based on MET-PET findings, dose planning based on MET-PET findings was superior to that based on MRI alone.

For the patient who underwent re-operation, this procedure was the last treatment option, because he had previously received radiotherapy and pharmacotherapy. However MET-PET revealed foci corresponding to a residual tumor in a surgically accessible location, the sellar region. Therefore, we decided to resect the residual tumor. After surgery, the region with high MET uptake had disappeared and the patient's IGF-1 levels reverted to normal levels. Therefore, the region of high MET uptake on MET-PET fulfilled the necessary and sufficient criteria for a residual tumor.

Conclusion

In conclusion, the use of MET-PET and subsequent dose planning enabled us to achieve a high remission rate with adjuvant therapy for patients with acromegaly because MET-PET could clearly detect and delineate the residual tumor.

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