

**Peel-off resection of the pituitary gland for functional pituitary adenomas: pathological significance and impact on pituitary function**

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## **ABSTRACT**

**Purpose:** Functional pituitary adenomas (FPAs) lacking a well-defined pseudocapsule can invade the adjacent pituitary gland. In such situations, peel-off resection of the adjacent pituitary gland after selective adenomectomy might lead to complete tumor removal, resulting in optimal endocrinological outcomes. Here, we present the significance of peel-off resection of the pituitary gland in patients with FPA in whom complete extracapsular tumor removal cannot be achieved.

**Methods:** We performed a retrospective review of 21 patients with FPA who underwent transsphenoidal surgery (TSS). After selective adenomectomy, peel-off resection of the adjacent pituitary gland was performed in 13 patients because complete extracapsular resection could not be achieved, while peel-off resection was not performed in the remaining 8 patients because complete extracapsular resection was accomplished. The clinical outcomes of these groups were compared. The pituitary tissues obtained by peel-off resection were pathologically examined for tumor cells.

**Results:** Early postoperative biochemical remission was achieved in 20 patients (95.2%). Anterior pituitary functions were not aggravated postoperatively in any patient; however, transient diabetes insipidus (DI) occurred in 2 patients. There were no statistically significant differences in the clinical outcomes of the two groups. A pseudocapsule was pathologically detected in the adjacent anterior pituitary even in patients in whom no pseudocapsule was intraoperatively detected. Tumor cells were pathologically detected in 7 (58.3%) of 12 pituitary tissues examined.

**Conclusions:** Peel-off resection of the pituitary gland, which can remove a small tumor cell remnant in the adjacent pituitary, might maximize the effectiveness of TSS with minimal impact on postoperative pituitary function.

**Keywords:** pituitary resection, transsphenoidal surgery, pseudocapsule, pituitary adenoma, acromegaly, Cushing disease

## INTRODUCTION

Transsphenoidal surgery (TSS) has become the first-line treatment for almost all functional pituitary adenomas (FPAs), except for prolactinomas. Studies have reported that many FPAs are effectively resected by TSS with minimal postoperative morbidity [1-4]. From a technical surgical standpoint, complete tumor resection with the extracapsular resection technique has been reported to maximize the effectiveness of TSS for FPAs [5, 6]. However, there are some pituitary adenomas that intraoperatively lack a well-defined pseudocapsule, and complete extracapsular resection cannot be achieved for these adenomas [5, 7-9]. In this situation, clusters of tumor cells can spread into the adjacent normal tissues [5, 9-11]; therefore, supra-total resection of the adenoma that includes the surrounding normal tissues might contribute to improving postoperative biochemical remission and long-term recurrence rates. Studies have shown a high invasion rate into the surrounding dura mater by invasive adenomas [12-15]; thus, it is assumed that similar tumor invasion can also be detected in the adjacent pituitary gland. However, there have been no studies detailing pituitary involvement in patients with FPA in whom complete extracapsular resection could not be achieved.

We performed peel-off resection of the adjacent pituitary gland after selective adenectomy in patients with FPA in whom complete extracapsular resection could not be achieved because no pseudocapsule (or an incomplete pseudocapsule) was intraoperatively detected between the tumor and the adjacent pituitary gland. In this article, we present the clinical and pathological outcomes of patients who underwent peel-off resection of the pituitary gland for FPAs. In addition, we evaluated the impact of this maneuver on postoperative pituitary functions.

## **METHODS**

### **Patients**

We retrospectively reviewed the data of 21 patients with FPA who had been treated by endoscopic endonasal transsphenoidal surgery (eTSS) at Nagoya University Hospital (Aichi, Japan) during the study period between January 2017 and October 2018. All patients preoperatively received a clinical diagnosis of FPA by both endocrinological examination and magnetic resonance imaging. After selective adenomectomy, peel-off resection of the adjacent pituitary gland was performed in 13 patients (Group A) because complete extracapsular resection was not achieved between the tumor and the pituitary gland due to the existence of an incomplete pseudocapsule or the absence of a pseudocapsule according to the intraoperative findings. In the remaining 8 patients, however, peel-off resection was not performed; complete extracapsular resection had been achieved in the majority of the patients (Group B). We compared the clinical characteristics, endocrinological outcomes, and postoperative morbidities of the two groups. Informed consent for publication of our article was obtained from each patient.

### **Endocrinological evaluations**

The basal hormonal status was preoperatively assessed in all patients. The dynamic hormonal status was also assessed not only to confirm the preoperative clinical diagnoses but also to evaluate preoperative anterior

pituitary functions. Growth hormone deficiency (GHD) was diagnosed upon observation of low serum levels of insulin-like growth factor-1 (IGF-1) adjusted for sex and age and low response in the GH-releasing hormone (GRH) test or GH-releasing peptide-2 (GHRP-2) test: a peak serum GH level of  $<3$  ng/ml in the GRH test or  $<15$  ng/ml in the GHRP-2 test. Secondary hypothyroidism was diagnosed when serum-free thyroxine (FT4) levels were low while thyroid-stimulating hormone (TSH) levels were suppressed or normal. Secondary hypoadrenalism was diagnosed upon observation of low morning serum cortisol levels accompanied by clinical symptoms of hypoadrenalism that responded to glucocorticoid replacement therapy. Hypogonadotropic hypogonadism was diagnosed when serum testosterone levels were low in men and when menstrual irregularity was observed in premenopausal women with low serum gonadotropin levels. Diabetes insipidus (DI) was diagnosed when hypotonic polyuria was  $>3000$  mL/day. Basal hormonal status was evaluated at one week and 3 months after surgery and twice per year thereafter. Dynamic hormonal status was also assessed one week and 3 months after surgery to evaluate postoperative anterior pituitary functions.

Postoperative biochemical remission was defined as a nadir serum GH level of  $<0.4$  ng/ml after an oral 75-g glucose load and/or a subsequently normal IGF-1 level adjusted for sex and age for acromegaly; morning serum cortisol level that was  $<5$   $\mu$ g/dl within 7 days postoperatively and thereafter indicating no evidence of hypercortisolism for Cushing disease; normalized morning serum TSH, free triiodothyronine (FT3), and FT4 levels for thyrotroph adenoma; and a serum prolactin (PRL) level of  $<15$  ng/ml for prolactinoma.

## **Surgical procedure**

Under general anesthesia by endotracheal intubation, the patient was placed in a supine position with the upper body raised by 15 degrees, and the patient's head was fixed in a Sugita four-point head holder® (Mizuho Medical Innovation, Tokyo, Japan). eTSS was performed via the right transseptal approach using an Endo Arm® (Olympus, Tokyo, Japan). After a wide sphenoidotomy, sufficient sellar bone was removed. Then, the anterior sellar dura was incised based on the tumor shape. First, all patients were thoroughly examined for the presence of a pseudocapsule. When a pseudocapsule was intraoperatively detected, complete extracapsular tumor resection was attempted. Once complete extracapsular resection was achieved, peel-off resection of the pituitary gland was not performed. However, in patients in whom it was not possible to achieve complete extracapsular resection because the pseudocapsule was incomplete or was not detected intraoperatively (Fig. 1a), gross total removal of the adenoma was attempted in a piecemeal fashion. Then peel-off resection of the pituitary gland was performed to remove any small tumor cell remnant on the surface of the adjacent pituitary. In practice, a sharp incision was made by using a surgical knife at the anterior edge of the adjacent pituitary gland that was in direct contact with the tumor (Fig. 1b); subsequently, the tumor bed was circumferentially peeled off. We paid particular attention to the peeling process so that the slice of the adjacent pituitary gland that was peeled off was as thin as possible (thickness less than 1 mm) to minimize the impact on pituitary functions (Fig. 1c and d). We did not resect the posterior pituitary gland, even when the tumor was in direct contact with it. After tumor removal with or without peel-off resection of the pituitary gland, the anterior sellar dura was reconstructed by dural suturing. The details of dural reconstruction are described



in our previous article [16].

### **Pathological examinations**

Surgically resected tumor tissues were evaluated by routine pathological and immunohistochemical examination. Anterior pituitary tissues obtained by peel-off resection of the pituitary gland were also pathologically examined not only to evaluate whether they contained tumor cells but also to evaluate whether they contained histological evidence of a pseudocapsule. In immunohistochemical studies, specimens were incubated with antibodies against the following proteins: GH (Dako, Carpinteria, CA, USA; A0570), PRL (Dako, Carpinteria, CA, USA; A0569), the beta subunit of TSH (Dako, Carpinteria, CA, USA; M3503), adrenocorticotrophic hormone (ACTH) (Dako, Carpinteria, CA, USA; M3501), follicle-stimulating hormone (FSH) (Dako, Carpinteria, CA, USA; M3504), and luteinizing hormone (LH) (Dako, Carpinteria, CA, USA; M3502).

### **Statistical analysis**

Statistical analyses were performed using the chi-square test and the Mann-Whitney U test. Differences of  $p < 0.05$  were considered statistically significant.

## **RESULTS**

## **Patients and tumor characteristics**

The patients included 10 males and 11 females, with an overall mean age of 56.5 years (range 29-82 years) at the time of surgery. The mean age of Group A (51 years) was lower than that of Group B (65.5 years); however, the difference was not significantly different ( $p=0.052$ ). The clinical diagnosis was acromegaly in 15 patients (9 patients in Group A; 6 in Group B), Cushing disease in 4 patients (2 patients in Group A; 2 in Group B), prolactinoma in one patient (Group A), and thyrotroph adenoma in one patient (Group A). Only one patient with acromegaly in Group A was a recurrent case. The tumors consisted of 6 microadenomas ( $<10$  mm maximal tumor diameter) and 15 macroadenomas ( $\geq 10$  mm); the overall mean maximum tumor diameter was 14.4 mm (range, 5.1-30.9 mm; Group A: 14.7 mm, range 5.1-30.9 mm; Group B: 13.8 mm, range 8.7-17.7 mm). Six adenomas (28.6%) were grade 0, 7 (33.3%) were grade 1, 6 (28.6%) were grade 2, and 2 (9.5%) were grade 3 on the Knosp classification scale. Two patients (9.5%) preoperatively showed partial anterior pituitary dysfunction; one patient presented with isolated GHD, and the other presented with isolated secondary hypoadrenalism. Both patients were included in Group A. No patient preoperatively showed DI. The overall mean follow-up period was 14 months (range, 5-25 months). There were no statistically significant differences in the patient demographics or tumor characteristics between the two groups (Table 1).

## **Intraoperative findings**

Among the 13 patients in Group A, 9 patients (69.2%) could not achieve complete extracapsular resection

between the tumor and the surrounding pituitary gland due to an incomplete pseudocapsule, while the remaining 4 patients (30.8%) could not undergo complete extracapsular resection because a pseudocapsule was not detected intraoperatively. On the other hand, 7 (87.5%) of 8 patients in Group B had a well-defined pseudocapsule between the tumor and the adjacent pituitary gland and achieved complete extracapsular resection. The remaining patient in Group B intraoperatively lacked a pseudocapsule; however, the majority of the tumor existed in the cavernous sinus, and the area in which the tumor was in direct contact with the pituitary gland was quite narrow. Therefore, we coagulated the surface of the adjacent pituitary gland after selective adenomectomy, and peel-off resection of the pituitary gland was not performed. The mean tumor diameter of the 5 FPAs in which no pseudocapsule was intraoperatively detected (10.3 mm, range 5.1-15.6 mm) was smaller than that of the 16 FPAs in which a pseudocapsule (well-defined or incomplete) was intraoperatively detected (15.6 mm, range 6.2-30.9 mm); however, the difference was not significantly different ( $p=0.064$ ). The posterior pituitary was exposed in 3 patients; all of these patients were included in Group A.

### **Endocrinological outcomes**

Early biochemical remission by eTSS alone was achieved in 20 patients (95.2%): 12 of 13 patients (92.3%) in Group A and 8 of 8 patients (100%) in Group B. Only one patient with acromegaly in Group A in whom diffuse tumor invasion to the surrounding dura mater was intraoperatively detected failed to achieve biochemical remission. Although the patient could not achieve a nadir serum GH level of  $<0.4$  ng/ml after an oral 75-g glucose load, the

subsequent IGF-1 levels were around the upper limit when adjusted for sex and age during the follow-up period.

Therefore, the patient was under close observation without any postoperative medication. On the other hand, one acromegalic patient in Group B, who had achieved early biochemical remission by eTSS alone, showed elevated serum IGF-1 levels adjusted for sex and age at 9 months postoperatively. The patient underwent oral cabergoline therapy (0.25 mg/week) and achieved endocrinological control. Thus, biochemical remission by eTSS alone at the time of last follow-up was achieved in 19 patients (90.5%): 12 of 13 patients (92.3%) in Group A and 7 of 8 patients (87.5%) in Group B (Table 1).

Anterior pituitary functions were not aggravated after eTSS in any patient. Conversely, preoperative GHD, detected in one patient in Group A, was improved after eTSS. Two patients (15.4%) in Group A presented postoperative transient DI; however, no patient showed permanent DI in either group. Of the 3 patients in whom the posterior pituitary was intraoperatively exposed, one patient (33.3%) developed postoperative transient DI. There were no statistically significant differences in the endocrinological outcomes of the two groups (Table 1). There was no postoperative CSF leakage in either group.

## **Pathology**

Preoperative clinical diagnosis was confirmed by pathological examination in all patients. In only one patient in Group A, the anterior pituitary tissue obtained by peel-off resection was mixed with the tumor specimens and could not be subjected to pathological examination. Therefore, a total of 12 anterior pituitary tissues underwent

pathological examination, and tumor cells were detected in 7 patients (58.3%) (Fig. 2). All anterior pituitary specimens obtained by peel-off resection were pathologically confirmed to belong to the anterior pituitary; however, reticulin staining demonstrated that histological evidence of a pseudocapsule existed in the adjacent pituitary even in patients in whom no pseudocapsule was intraoperatively detected (Fig. 2).

## **DISCUSSION**

### **The pathological significance of peel-off resection of the pituitary gland**

The existence of a pseudocapsule that surrounds a pituitary adenoma was first reported by Costello [17] in 1936. Recently, the pseudocapsule was used as a surgical dissection plane to achieve complete tumor removal for pituitary adenomas (extracapsular resection). However, this surgical technique is not always available because some pituitary adenomas lack a pseudocapsule detectable by intraoperative findings alone or possess an incomplete pseudocapsule. Studies have demonstrated that the possession rate of a pseudocapsule varies depending on the characteristics of the pituitary adenoma, including the pathological type and tumor size [5, 7]. Furthermore, clusters of tumor cells can spread into adjacent normal tissues at the cellular level from adenomas lacking a well-defined pseudocapsule [5, 7-9]. In our previous article, we demonstrated a high invasion rate to the medial wall of the cavernous sinus in cases in which an FPA lacking a well-defined pseudocapsule was in direct contact with the medial wall [14]. Thus, it is assumed that similar tumor invasion can also be detected pathologically in the adjacent

pituitary gland. Indeed, Kuwayama [18] demonstrated that radical tumor resection, which extended excision to include the surrounding pituitary gland within 1.5 mm of the interface, could improve the biochemical remission rates and long-term recurrence rates of FPAs.

In this study, we performed peel-off resection of the pituitary gland after selective adenectomy in patients with FPAs in whom complete extracapsular tumor resection was not possible between the tumor and the adjacent pituitary gland. In such situations, an impalpable pseudocapsule, which could not be detected intraoperatively, might remain attached to the adjacent pituitary and a small tumor cell remnant might exist in the adjacent pituitary at a cellular level. Indeed, histological evidence of a pseudocapsule was pathologically detected in the anterior pituitary specimens obtained by peel-off resection even in patients in whom no pseudocapsule was intraoperatively detected (Fig. 2). Oldfield [3] suggested that all pituitary adenomas with a maximal diameter more than 2 mm possessed a pseudocapsule. Furthermore, tumor cells were pathologically detected in more than half of the pituitary specimens examined in the current study. This tumor remnant in the surrounding pituitary gland, if it was not removed, might be an obstacle to postoperative biochemical remission or might be the beginning of tumor recurrence. Therefore, peel-off resection of the adjacent pituitary gland after selective adenectomy can be an effective surgical option to achieve complete tumor removal of FPAs in which complete extracapsular resection cannot be achieved.

#### **The impact of peel-off resection of the pituitary gland on endocrinological outcomes**

The greatest concern in performing peel-off resection of the pituitary gland is its impact on pituitary functions. However, pituitary gland incision or partial pituitary gland resection is often performed to access a pituitary lesion in TSS, and this maneuver was reported to not aggravate postoperative pituitary functions [19]. We believe that some surgical technical recommendation should be implemented to prevent deterioration of pituitary functions when performing peel-off resection of the pituitary gland. First, the surface of the anterior pituitary gland, which is in direct contact with the tumor, should be peeled off as thin as possible (thickness less than 1 mm). Rees et al. [20] demonstrated a clear association between the extent of surgery and postoperative hypopituitarism, although only 33% of patients who underwent hemihypophysectomy for Cushing disease showed postoperative anterior pituitary deficiency. Moreover, peeling as thin a slice as possible off the anterior pituitary gland can minimize injury and exposure of the posterior pituitary, which might result in a minimal impact on postoperative posterior pituitary function. Second, the posterior pituitary gland is never resected, even when the tumor is in direct contact with the posterior pituitary. Indeed, no patients showed postoperative deterioration of anterior pituitary functions or permanent DI in the current study. Postoperative transient DI has been reported to occur in 4.6-16.6% of patients who undergo TSS for pituitary adenoma [21-24]. In this study, 2 of 13 patients (15.4%) with peel-off resection of the pituitary gland showed postoperative transient DI; the incidence did not appear to be higher than that of previous studies. Furthermore, the incidence of postoperative transient DI did not show any statistically significant difference between the peel-off group and the non-peel-off group in this study.

On the other hand, previous studies have reported that the biochemical remission rate of patients with FPA

who undergo extracapsular resection is higher than that of patients without extracapsulectomy [5, 6]. In the current study, however, no statistically significant difference in the biochemical remission rates of the two groups was detected. Therefore, peel-off resection of the adjacent pituitary gland might improve endocrinological outcomes in patients with FPA in whom complete extracapsular resection cannot be achieved. We suggest that peel-off resection of the pituitary gland is an effective surgical option to achieve optimal endocrinological outcomes for patients with FPAs who cannot undergo complete extracapsular resection due to the intraoperative absence of a pseudocapsule (or the presence of an incomplete pseudocapsule).

The limitations of this work are the relatively small sample size and the short follow-up period, which was insufficient to establish the true advantages of the maneuver. Further outcome data, including long-term biochemical remission and recurrence rates in surgical cases with or without peel-off resection of the pituitary gland, are needed to justify the proposed technique.

## **CONCLUSIONS**

Peel-off resection of the adjacent pituitary gland after selective adenomectomy is one of the most effective surgical techniques to achieve complete tumor removal for FPAs in which complete extracapsular resection cannot be achieved, because a histological pseudocapsule can be present in the adjacent pituitary even in patients in whom no pseudocapsule is intraoperatively detected. Indeed, tumor cells were pathologically detected in the adjacent pituitary gland in more than half of patients with FPAs in whom complete extracapsular resection could not be



achieved in the current study. Furthermore, the incidence of postoperative morbidities was not aggravated in patients who were subject to this surgical technique. Although further outcome data are needed to justify the proposed technique, peel-off resection of the pituitary gland can maximize the effectiveness of TSS with minimal postoperative endocrinological morbidities in patients with FPAs in whom complete extracapsular resection cannot be achieved.

## **COMPLIANCE WITH ETHICAL STANDARDS**

### **Funding**

None

### **Conflict of interests**

The authors declare that they have no conflicts of interest.

### **Ethical approval**

All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with either the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent was not required.

**Informed consent**

Informed consent was obtained from all individual participants who were included in the study.

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## FIGURE CAPTIONS

**Fig. 1** Intraoperative images during the endoscopic transsphenoidal surgery in an acromegalic patient. **a)** During selective adenomectomy, no pseudocapsule was detected between the tumor (white arrow) and the adjacent pituitary gland. Gross tumor removal was attempted in a piecemeal fashion. **b)** After selective adenomectomy, a sharp incision (black arrow) was made at the anterior edge of the pituitary gland that was in direct contact with the tumor. **c)** As thin a slice as possible of the surface of the pituitary gland was peeled off, and the tumor bed was circumferentially resected. **d)** After the peel-off resection of the adjacent pituitary gland, the medial wall of the left cavernous sinus was exposed; however, the majority of the pituitary gland was preserved. MW: medial wall of the cavernous sinus, Pit: pituitary gland

**Fig. 2** Pathology of anterior pituitary tissues obtained by peel-off resection of the pituitary gland. **a-d)** A case presentation of a patient with Cushing disease in whom an incomplete pseudocapsule was intraoperatively detected. A tumor cell mass (black circle) was detected in the anterior pituitary gland by hematoxylin-eosin staining (**a**). By using anti-follicle-stimulating hormone (FSH) staining, the anterior pituitary was detected as the immunopositive area (black arrows), while the tumor mass was detected as the immunonegative area (black asterisk) (**b**). The tumor mass was detected as the immunopositive area using anti-adrenocorticotrophic hormone (ACTH) staining (white asterisk), which indicated that the pathology of the tumor was corticotroph adenoma (**c**). According to reticulin staining, the anterior pituitary tissue consisted of several layers of reticulin (pseudocapsule) (**d**). **e-h)** A case presentation of a patient with Cushing disease in whom no pseudocapsule was intraoperatively detected. A tumor

cell mass (white circle) was detected in the anterior pituitary by hematoxylin-eosin staining **(e)**. The tumor mass was detected as the immunonegative area by anti-luteinizing hormone (LH) staining (black asterisk) **(f)**, while it was detected as the immunopositive area by anti-ACTH staining (white asterisk) **(g)**. According to reticulin staining, the anterior pituitary tissue partially maintained normal palisading of the anterior pituitary lobe (white arrow), while it partially contained a pseudocapsule (black arrow) and tumor cell mass (white asterisk) **(h)**. **i-l** A case presentation of a patient with acromegaly in whom no pseudocapsule was intraoperatively detected. No tumor cells were detected in the anterior pituitary by hematoxylin-eosin staining **(i)**, anti-prolactin (PRL) staining **(j)**, and anti-growth hormone (GH) staining **(k)**. According to reticulin staining, the majority of the anterior pituitary tissue maintained normal palisading of anterior pituitary lobe, while it partially contained a pseudocapsule (white asterisk) **(l)**