A survey of surgically resected pituitary incidentalomas and a comparison of the clinical features and surgical outcomes of non-functioning pituitary adenomas discovered incidentally versus symptomatically

Mayo Ono1), Izumi Fukuda1), Akimi Soga1), Shigeyuki Tahara2), Akio Morita2) and Hitoshi Sugihara1)

1) Dept. of Endocrinology, Diabetes and Metabolism, Graduate School of Medicine, Nippon Medical School, Tokyo 113-8603, Japan
2) Dept. of Neurosurgery, Graduate School of Medicine, Nippon Medical School, Tokyo 113-8603, Japan

Abstract. Pituitary tumors are discovered either incidentally by imaging studies (incidentalomas) or via evaluation of certain clinical symptoms (symptomatic tumors). In this study, we first surveyed patients with incidentalomas who underwent surgery. Cases included 62.3% non-functioning adenomas (NFPAs), 14.5% functioning adenomas, and 13.8% Rathke’s cleft cysts. Next, we compared the clinical features and surgical outcomes of 145 patients whose preoperative diagnosis was NFPA (incidentalomas [n = 79] vs. symptomatic tumors [n = 66]). The patients with incidentalomas were older (59.9 vs. 55.3 years, \( p < 0.05 \)) and had smaller tumors compared with the patients with symptomatic tumors (mean maximum diameter: 23.1 vs. 27.5 mm, \( p < 0.01 \)). The main reason for undergoing imaging studies was headache (\( n = 25 \)) in the incidentaloma group and visual disturbance (\( n = 46 \)) in the symptomatic tumor group. The incidence of preoperative pituitary hormone deficiencies was lower in the incidentaloma than symptomatic tumor group (growth hormone deficiency: 37.7% vs. 66.7%, \( p < 0.01 \); gonadotropin deficiency: 19.0% vs. 39.4%, \( p < 0.01 \); adrenocorticotropic hormone deficiency: 3.8% vs. 18.2%, \( p < 0.01 \); thyroid stimulating hormone deficiency: 6.3% vs. 12.1%, \( p = 0.25 \)). Postoperative pituitary function was better preserved in the incidentaloma than symptomatic tumor group (no deficiency: 58.2% vs. 38.9%, \( p < 0.01 \)). The difference in postoperative complications between groups was not statistically significant (incidentalomas vs. symptomatic tumors: 21.5% vs. 19.7%, \( p = 0.84 \)). In conclusion, incidentalomas were detected while smaller size and lower incidence of hormone deficiency than symptomatic tumors, and the pituitary hormones were also preserved after surgery. It is important to observe incidentalomas carefully and to judge whether to operate appropriately before they become symptomatic tumors.

Key words: Pituitary adenoma, Incidentaloma, Symptomatic tumor, Transsphenoidal surgery, Pituitary hormone

PITUITARY TUMORS are often not diagnosed until they have grown large enough to compress the optic nerve, causing visual disturbances and altering pituitary hormone levels. Recently, however, pituitary tumors have been detected more frequently due to the widespread use of computed tomography (CT) and magnetic resonance imaging (MRI). In Japan, since the implementation in 1988 of brain imaging as part of health check-ups for the general public (Brain Dock), asymptomatic pituitary tumors have been detected more frequently. The annual incidence of pituitary tumors is 1–6 per 100,000 of the population [1, 2], whereas its prevalence is 2.5–22.5% on autopsy [3, 4]. The prevalence of pituitary adenomas is 80–100 per 100,000 of the population, with non-functioning pituitary adenomas accounting for 15–30% of these tumors [5, 6].

Pituitary tumors are discovered either incidentally by imaging studies conducted for unrelated reasons (incidentalomas) or based on certain clinical symptoms caused by the tumor (symptomatic tumors). Therapeutic intervention is required for most symptomatic tumors. On the other hand, surgery is indicated for non-functioning incidentalomas that cause visual field abnormalities or hypopituitarism, according to clinical practice guidelines [7].

Few studies have compared the clinical characteristics and surgical outcomes of pituitary incidentalomas with those of symptomatic tumors. In this study, we first investigated the etiology of incidentalomas in patients...
who underwent surgery. Next, we compared the differences in clinical features of patients whose preoperative diagnosis was non-functioning pituitary adenoma (NFPA), discovered as either an incidentaloma or symptomatic tumor, who underwent endoscopic transsphenoidal surgery (eTSS). In particular, pre- and postoperative pituitary functions, including hormone stimulation test results, were evaluated.

**Subjects and Methods**

**Patients**

The study was approved by the Nippon Medical School and Faculty of Medicine Ethics Committee (no. 30-05-927), registered at UMIN-CTR (UMIN000040299), and was conducted in accordance with the principles of the Declaration of Helsinki. We obtained patient data retrospectively and disclosed the present study information, giving participants an opportunity to opt out in accordance with the guidelines of the Nippon Medical School and Faculty of Medicine Ethics Committee.

Incidentaloma was defined as a “previously unsuspected pituitary lesion that was found incidentally by imaging studies performed for unrelated reasons” [7]. The indications for surgical treatment of incidentalomas were determined according to the clinical practice guidelines proposed by The Japan Brain Dock Society (2014 in Japanese, created based on [8]).

**Study 1: An investigation of the etiology of surgically resected incidentalomas**

Among 412 patients who underwent pituitary surgery for the first time between 2011 and 2017 at our institution, 159 patients were considered to have incidentalomas. The etiology of these lesions was analyzed.

**Study 2: A comparison of the clinical features and surgical outcomes between incidentalomas and symptomatic tumors that were preoperatively diagnosed as NFPA**

Pituitary incidentalomas are both clinically and etiologically heterogeneous. To compare the pituitary function and surgical outcomes between incidentalomas and homogenous symptomatic tumors, we focused on tumors that were pre-operatively diagnosed as NFPA, which was the most frequent etiology among surgically resected incidentalomas in Study 2. Preoperative diagnosis of NFPA was considered clinically after exclusion of hormone-producing adenomas by appropriate endocrinological tests.

Among 206 patients diagnosed with NFPA who underwent eTSS between 2011 and 2017 at our institution, 61 were excluded from Study 2 for the following reasons: re-operation (n = 23), unknown medical history (n = 3), no baseline hormone data (n = 6), no growth hormone (GH) stimulation test without an appropriate reason such as emergency surgery (n = 29) (Fig. 1). Incidentalomas were defined as pituitary masses that were found incidentally by imaging studies. Accordingly, the remaining 145 patients were classified into either the incidentaloma group (n = 79) or symptomatic tumor group (n = 66).

Age, sex, body mass index (BMI), reasons for undergoing imaging studies, maximum tumor diameter,
pituitary function, postoperative complications and the final pathological diagnosis were obtained and compared between the two groups.

**Pituitary hormone evaluation**

Functioning adenomas were diagnosed as follows. GH-producing tumors were suspected based on characteristic clinical manifestations; diagnoses was confirmed following detection of elevated insulin-like growth factor-1 (IGF-1) and a lack of GH suppression below 0.4 ng/mL following an oral glucose tolerance test. Adrenocorticotropic hormone (ACTH)-producing tumors were suspected based on characteristic clinical manifestations and comorbidities; diagnoses were confirmed by elevated 24-hour urinary free cortisol (UFC), a lack of cortisol diurnal rhythm, and a lack of serum cortisol suppression following a dexamethasone 0.5 mg suppression overnight test. In addition, ACTH response on a corticotropin-releasing hormone (CRH) 100 μg test, cortisol response on a dexamethasone 8 mg overnight test, and the results of cavernous sinus sampling were confirmed as needed. Prolactin-producing tumors were suspected based on irregular menstruation or infertility in women and hyperactive sexual desire disorder or gynecomastia in men, and diagnosed by the presence of pituitary tumors with hyperprolactinemia for which other causes were ruled out. Thyroid-stimulating hormone (TSH)-producing tumors were diagnosed based on inappropriate secretion of TSH and the existence of macro-pituitary adenomas.

NFPA were clinically diagnosed after excluding the hormone-producing tumors described above. Pituitary hormone deficiencies were primarily evaluated in accordance with clinical guidelines [9]. Patients underwent baseline hormone evaluation both before and after surgery. Patients were considered to have overt central adrenal insufficiency if their morning cortisol level was below 4 μg/dL or peak cortisol level below 10 μg/dL, according to a CRH test (100 μg administration). Central hypothyroidism was diagnosed based on a low free thyroxine level with a normal or low TSH level. Hypogonadotropic hypogonadism was diagnosed as follows. Hypogonadotropic hypogonadism was diagnosed in premenopausal women with irregular menstruation or amenorrhea, after confirming serum gonadotropin (Gn), estradiol and prolactin levels to exclude hyperprolactinemia or ovarian disease. Postmenopausal women with a low estradiol level without a sufficiently elevated Gn level were regarded as having hypogonadotropic hypogonadism. In men, hypogonadotropic hypogonadism was diagnosed based on a low serum testosterone level without an elevated Gn level. TSH response on a thyrotropin-releasing hormone (TRH) test, and luteinizing hormone (LH) and follicle-stimulating hormone (FSH) responses on a luteinizing hormone-releasing hormone (LH-RH) test were also referenced if available. Severe GH deficiency was defined as a peak GH level below 9 ng/mL, determined by a growth hormone releasing peptide-2 test [10]. Arginine vasopressin (AVP) deficiency was defined as postoperative polyuria and low urine specific gravity that required more than 1 year of desmopressin treatment.

**Diagnosis of pituitary tumors**

All pituitary tumors were confirmed pathologically. Classification of functioning or non-functioning adenomas was based on clinical diagnosis. Pathological findings of NFPA were classified according to the World Health Organization classification of tumors of the pituitary gland [11].

**Statistical analysis**

The values of the clinical and tumor characteristics are expressed as means ± standard deviation. Differences between groups were assessed using the two-tailed Student’s t-test or nonparametric Wilcoxon rank sum test for continuous data and Fisher’s exact test for categorical data, and differences were considered significant at \( p < 0.05 \). Statistical analyses were performed using JMP, version 13.2 (SAS Institute, Cary, NC, USA). We performed a multiple logistic regression analyses to investigate the factors related to the post-operative severe pituitary hormone deficiencies using SPSS version 25.

**Results**

**Study 1: An investigation of the etiology of surgically resected incidentalomas**

Details regarding final pathological diagnosis of incidentalomas from 159 patients who underwent surgery are shown in Table 1. A total of 99 patients had NFPA (62.3%), 23 patients had functioning adenomas (14.5%), 22 patients had Rathke’s cleft cysts (13.8%), and 6 patients had meningiomas (3.8%). Patients with NFPA had no symptoms related to excessive hormone levels. Among the 99 NFPA, there were 74 gonadotroph adenomas (74.7%), 10 corticotroph adenomas (10.1%), 5 somatotroph adenomas (5.1%), 1 thyrotrroph adenoma (1.0%), 1 adenoma with unusual immunohistochemical combination (1.0%), and 8 null cell adenomas (8.1%).

**Study 2: A comparison of the clinical features and surgical outcomes between incidentalomas and symptomatic tumors that were preoperatively diagnosed as NFPA**

To compare pituitary function and surgical outcomes between incidentalomas and homogenous symptomatic
tumors, we focused on 145 patients with a pre-operative diagnosis of NFPA. Of the 145 total patients, 79 had pituitary incidentalomas and 66 symptomatic pituitary tumors. In Study 2, “incidentalomas” and “symptomatic tumors” indicate NFPAs (pre-operative estimated diagnosis) discovered either incidentally or symptomatically. The clinical characteristic of the patients in the incidentaloma and symptomatic tumor groups are summarized in Table 2. Patients with incidentalomas were older than those with symptomatic tumors (59.9 ± 3.0 vs. 55.3 ± 3.3 years, p < 0.05), but the sex ratio (males/females: 44/35 vs. 39/27, p = 0.74) and BMI (24.3 ± 4.7 vs. 28.6 ± 5.2, p = 0.22) did not differ between the two groups. Among the patients with incidentalomas, 65 underwent surgery immediately after diagnosis for the following reasons: unrecognized visual field abnormality revealed by Goldmann visual examination (n = 28), optic nerve compression identified by MRI (n = 29), invasion of the cavernous sinus that was expected to be difficult to remove completely during follow-up (n = 4) and the patient’s request (n = 4). Optic nerve compression was detected by MRI in 57 of the 65 patients with incidentalomas who underwent surgery shortly after diagnosis; none of these patients was aware of any visual disturbances. Preoperative Goldmann visual field tests were performed in 38 of these 57 patients, of whom visual field defects were detected in 28.

The remaining 14 patients with incidentalomas underwent surgery during follow up. The reasons for surgery in these patients were tumor growth (n = 6), occurrence of a visual field abnormality confirmed by visual field tests (n = 2), optic nerve compression newly revealed by MRI (n = 2), pituitary apoplexy (n = 2), the patient’s request (n = 1) and hydrocephalus (n = 1).

**Reasons for undergoing brain imaging studies**

The main reasons for undergoing brain imaging studies, which are summarized in Fig. 2A and B, were headache (n = 25), medical checkup (n = 17), dizziness (n = 14) and head trauma (n = 8) in the incidentaloma group. In the symptomatic tumor group, the reasons were visual disturbance (n = 46), acute onset headache due to pituitary apoplexy (n = 8), irregular menstruation (n = 2) and hyponatremia (n = 4). Two patients in the symptomatic tumor group experienced hyponatremia due to ACTH deficiency, and the remaining two patients underwent surgery because they had optic nerve compression in addition to hyponatremia. Tumors discovered because of headaches that were not considered a symptom of a pituitary mass by the patient’s attending physician were classified as incidentalomas, whereas tumors discovered because of acute onset headache due to pituitary apoplexy were considered symptomatic tumors. Tumors discovered by whole-brain imaging during a medical checkup were also considered incidentalomas.

**Tumor characteristics**

The tumor characteristics are shown in Table 3. The mean maximum diameter of the incidentalomas was significantly smaller than that of the symptomatic tumors (23.1 ± 1.9 mm vs. 27.5 ± 2.1 mm, p < 0.01). The preoperative diagnosis of all subjects was NFPA (n = 145).

| Tumor characteristics | Incidentaloma group (n = 79) | Symptomatic tumor group (n = 66) | p-value |
|-----------------------|-----------------------------|---------------------------------|---------|
| Male/female           | 44/35                       | 39/27                           | 0.74    |
| Age (years)*          | 59.9 ± 3.0                  | 55.3 ± 3.3                      | <0.05   |
| BMI*                  | 24.3 ± 4.7                  | 28.6 ± 5.2                      | 0.11    |

*Age and BMI are expressed as means ± standard deviation.

---

**Table 1** Final diagnosis of surgically resected incidentalomas

| Diagnosis                           | N (%)  |
|-------------------------------------|--------|
| Total                               | 159    |
| Non-functioning pituitary adenoma   | 99 (62.3%) |
| Gonadotroph adenoma                 | 74/99 (74.7%) |
| Corticotroph adenoma                | 10/99 (10.1%) |
| Somatotroph adenoma                 | 5/99 (5.1%) |
| Thyrotroph adenoma                  | 1/99 (1.0%) |
| Adenaoma with UIC*                  | 1/99 (1.0%) |
| Null cell adenoma                   | 8/99 (8.1%) |
| Functioning pituitary adenoma       | 23 (14.5%) |
| PRL*-producing adenoma              | 11 (6.9%) |
| GH*-producing adenoma               | 8 (5.0%) |
| TSH*-producing adenoma              | 2 (1.3%) |
| ACTH*-producing adenoma             | 2 (1.3%) |
| Rathke’s cleft cyst                 | 22 (13.8%) |
| Meningioma                          | 6 (3.8%) |
| Chordoma                            | 3 (1.9%) |
| Arachnoid cyst                      | 3 (1.9%) |
| Pituicytoma                         | 2 (1.3%) |
| Craniopharyngioma                   | 1 (0.6%) |

*1. Adenaoma with unusual immunochemical combination, 2. Prolactin, 3. Growth hormone, 4. Thyroid stimulating hormone, 5. Adrenocorticotropic hormone

---

**Table 2** Clinical characteristics of patients

|                         | Incidentaloma group (n = 79) | Symptomatic tumor group (n = 66) | p-value |
|-------------------------|-----------------------------|---------------------------------|---------|
| Male/female             | 44/35                       | 39/27                           | 0.74    |
| Age (years)*            | 59.9 ± 3.0                  | 55.3 ± 3.3                      | <0.05   |
| BMI*                    | 24.3 ± 4.7                  | 28.6 ± 5.2                      | 0.11    |

*Age and BMI are expressed as means ± standard deviation.
Fig. 2  Reasons for undergoing brain imaging studies in patients with pituitary tumors

A: Reasons for undergoing brain imaging studies in patients with incidentalomas.

The reasons for undergoing imaging studies were mainly headache (n = 25), a medical checkup (n = 17), dizziness (n = 14) or head trauma (n = 8) in the incidentaloma group. * Headache in this group was not considered a symptom of the pituitary mass by the patient’s attending physician and was evaluated by whole brain imaging during a medical checkup.

B: Reasons for undergoing brain imaging studies in patients with symptomatic tumors.

Visual disturbance (n = 46), acute onset headache due to pituitary apoplexy (n = 8) and hyponatremia (n = 4) were the main reasons for undergoing imaging studies in the symptomatic tumor group. ** All headaches in this group were acute onset headaches due to pituitary apoplexy.

Table 3  Tumor characteristics

|                      | Incidentaloma group (n = 79) | Symptomatic tumor group (n = 66) | p-value |
|----------------------|------------------------------|---------------------------------|---------|
| Maximum tumor diameter (mm) | 23.1 ± 1.9                  | 27.5 ± 2.1                      | <0.01   |
| Diagnosis            | Pre-TSS*                     | Post-TSS                        |         |
|                      | 79                           | 77                              | 66      | 60      |
| NFPA (clinical diagnosis)*1 | 60 (77.9%)                   | 48 (80.0%)                      | 0.99    |
| Gonadotroph adenoma  | 60 (77.9%)                   | 66                              | 48 (80.0%) |
| Corticotroph adenoma | 6 (7.8%)                     | 5 (8.3%)                        |         |
| Somatotroph adenoma  | 5 (6.5%)                     | 3 (5.0%)                        |         |
| Thyrotroph adenoma   | 1 (1.3%)                     | 0                               |         |
| Adenoma with UIC*2   | 1 (1.3%)                     | 0                               |         |
| Null cell adenoma    | 4 (5.2%)                     | 4 (6.7%)                        |         |
| NFPA + RCC*3         | —                            | 0                               | —       | 1*      |
| FPA*4                | —                            | 0                               | 0       | 4       |
| Prolactinoma*5       | —                            | 2                               | 4       |         |
| Pituicytoma          | —                            | 2                               | —       | 1       |

*1 Non-functioning pituitary adenoma. *2 Adenoma with unusual immunochemical combination, *3 Rathke’s cleft cyst, *4 Functioning pituitary adenoma, *5 Prolactinoma was histologically classified as sparsely granulated lactotroph adenoma based on World Health Organization classification of tumors of the pituitary gland. * Transsphenoidal surgery.  

Maximum tumor diameter (mm) is expressed as means ± standard deviation.
changed from NFPA to pituicytoma in 2 patients in the incidentaloma group. The preoperative mean serum prolactin levels in these 4 patients with prolactinomas was $95.2 \pm 49.1$ ng/mL, and the levels were lower for their tumor sizes. Therefore, preoperative estimated diagnosis of these patients was NFPA with hyperprolactinemia due to stalk effect. Postoperatively, they were confirmed as prolactinomas (histologically as sparsely granulated lactotroph adenomas), which were distinguished from silent lactotroph adenomas in NFPA group, based on the characteristic findings of Golgi-pattern staining for prolactin [11].

NFPA (incidentalomas vs. symptomatic tumors) included gonadotroph adenomas (77.9% vs. 80.0%), corticotroph adenomas (7.8% vs. 8.3%), somatotroph adenomas (6.5% vs. 5.0%), thyrotroph adenomas (1.3% vs. 0%), adenomas with unusual immune chemical combination (1.3% vs. 0%), and null cell adenomas (5.2% vs. 6.7%). No significant difference in the proportion of NFPA was observed between groups ($p = 0.99$).

**Pituitary hormone deficiencies in each group**

The incidence of a preoperative pituitary hormone deficiency in each group (incidentalomas vs. symptomatic tumors) was 37.7% vs. 66.7% for GH deficiency ($p < 0.01$), 19.0% vs. 39.4% for hypogonadism ($p < 0.01$), 3.8% vs. 18.2% for ACTH deficiency ($p < 0.01$) and 6.3% vs. 12.1% for TSH deficiency ($p = 0.25$). Postoperatively, both new deficiencies and recovery from preoperative deficiencies were seen for each hormone, as shown in Table 4. The rate of a new deficiency or hormone level recovery did not differ between the groups. The net incidence of postoperative pituitary hormone deficiencies in each group (incidentalomas vs. symptomatic tumors) was as follows: 30.4% vs. 57.6% for GH deficiency ($p < 0.01$), 24.1% vs. 48.4% for hypogonadism ($p < 0.01$), 5.1% vs. 19.7% for ACTH deficiency ($p < 0.01$), 7.6% vs. 13.6% for TSH deficiency ($p = 0.28$) and 2.5% vs. 16.7% for AVP deficiency ($p < 0.01$).

As shown in Table 5, pituitary function was preserved better in the incidentaloma than symptomatic tumor group.

### Table 4 Pituitary hormone deficiencies

| Deficient hormone | Time of evaluation | Incidentaloma group ($n = 79$) | Symptomatic tumor group ($n = 66$) | $p$-value |
|-------------------|-------------------|-------------------------------|-----------------------------------|----------|
| GH (severe)       | Pre-TSS           | 37.7% (29/77)                 | 66.7% (40/60)                     | <0.01    |
|                   | Post-TSS*         | 30.4% (24)                    | 57.6% (38)                        | <0.01    |
|                   | New deficitb      | 5/48 (+1/2)*                  | 4/20 (+5/6)*                      | 0.43     |
|                   | Recoveryc         | 11/29                         | 11/40                             | 0.44     |
| Gonadotropin      | Pre-TSS           | 19.0% (15)                    | 39.4% (26)                        | <0.01    |
|                   | Post-TSS          | 24.1% (19)                    | 48.4% (32)                        | <0.01    |
|                   | New deficit       | 8/64                          | 10/40                             | 0.12     |
|                   | Recovery          | 4/15                          | 4/26                              | 0.43     |
| ACTH              | Pre-TSS           | 3.8% (3)                      | 18.2% (12)                        | <0.01    |
|                   | Post-TSS          | 5.1% (4)                      | 19.7% (13)                        | <0.01    |
|                   | New deficit       | 4/75                          | 5/55                              | 0.49     |
|                   | Recovery          | 3/3                           | 4/12                              | 0.08     |
| TSH               | Pre-TSS           | 6.3% (5)                      | 12.1% (8)                         | 0.25     |
|                   | Post-TSS          | 7.6% (6)                      | 13.6% (9)                         | 0.28     |
|                   | New deficit       | 2/74                          | 3/59                              | 0.65     |
|                   | Recovery          | 1/5                           | 1/7                               | 1.00     |
| AVP               | Pre-TSS           | none                          | none                              |          |
|                   | Post-TSS          | 2.5% (2)                      | 16.7% (11)                        | <0.01    |

Pre-TSS, before transsphenoidal surgery
Post-TSS, after transsphenoidal surgery
*: Postoperative evaluation of GH stimulation test was conducted on 2 patients in the incidentaloma group and 6 patients in the symptomatic tumor group whose preoperative test was lacking because of emergency surgery due to pituitary apoplexy or hydrocephalus.
a: Net incidence of post-surgical hormone deficiency
b: Number of patients who had a new deficit/Number of patients preoperatively normal
c: Number of patients postoperative recovered/Number of patients who had preoperative hormone deficient
group both preoperatively (no deficiency: 57.1% vs. 28.3%, \( p < 0.01 \)) and postoperatively (no deficiency: 58.2% vs. 28.8%, \( p < 0.01 \)). Similarly, compared with the incidentaloma group, the presence of two or more pituitary hormone deficiencies was more common in the symptomatic tumor both preoperatively (18.2% vs. 40.0%, \( p < 0.01 \)) and postoperatively (20.1% vs. 47.0%, \( p < 0.05 \)). The rates of increased or decreased pituitary hormone deficiencies after surgery did not differ between groups. (Table 5). The factors related to the postoperative severe hypopituitarism in a multivariable model which included age, sex, BMI, maximum tumor diameter and the tumor group whether the symptomatic tumor or incidentaloma were shown in Table 6. “Severe hypopituitarism” was defined as more than 3 pituitary hormone deficiencies in this article. The symptomatic tumor was the most significant related factor (OR 5.037 [95% CI, 1.543–16.444]) among the other significant factors including male sex (OR 4.152 [95%CI, 1.270–13.577]) and maximum tumor diameter (OR 1.077 [95%CI, 1.011–1.147]).

### Postoperative complications

Major and minor postoperative complications occurred in 20 cases (17 patients) with incidentalomas and 16 cases (13 patients) with symptomatic tumors (Table 7). The incidences did not differ between the incidentaloma and symptomatic tumor groups (21.5% vs. 19.7%, \( p = 0.84 \)). Two patients in the incidentaloma tumor group experienced the major complication of postoperative meningitis, which was treated with intravenous administration of antibiotics; one of these cases was complicated with cerebrospinal fluid leakage requiring closure operation and subarachnoid hemorrhage, which did not require surgery. In the symptomatic tumor group, six patients experienced major complications: meningitis treated with intravenous administration of antibiotics (\( n = 3 \)), cerebrospinal fluid leakage requiring closure operation (\( n = 1 \)), subarachnoid hemorrhage requiring re-operation (\( n = 1 \)) and hydrocephalus (\( n = 2 \)). Two of three cases of meningitis were complicated with hydrocephalus (\( n = 2 \) ) and symptomatic hyponatremia (\( n = 1 \)), respectively.

Minor complications occurred in 16 patients with

| Table 5  | Pituitary hormone deficiencies before and after transsphenoidal surgery |
|----------|-------------------------------------------------------------------------|
|          | Incidentaloma group | Symptomatic tumor group | \( p \)-value |
| Preoperative (\( n \)) | 77* | 60* | <0.01 |
| None | 57.1% (\( n = 44 \)) | 28.3% (\( n = 17 \)) | <0.01 |
| 1 | 24.7% (\( n = 19 \)) | 31.7% (\( n = 19 \)) | 0.44 |
| \( \geq 2 \) | 18.2% (\( n = 14 \)) | 40.0% (\( n = 24 \)) | <0.01 |
| Postoperative (\( n \)) | 79 | 66 | |
| None | 58.2% (\( n = 45 \)) | 28.8% (\( n = 19 \)) | <0.01 |
| 1 | 22.8% (\( n = 18 \)) | 24.3% (\( n = 16 \)) | 0.85 |
| \( \geq 2 \) | 20.1% (\( n = 16 \)) | 47.0% (\( n = 31 \)) | <0.05 |
| Deteriorated** | 24.1% (\( n = 19 \)) | 28.8% (\( n = 19 \)) | 0.57 |
| Improved*** | 19.0% (\( n = 15 \)) | 15.2% (\( n = 10 \)) | 0.66 |

*: Preoperative evaluation of GH stimulation test was lacking in 2 patients in the incidentaloma group and 6 patients in the symptomatic tumor group because of emergence surgery due to pituitary apoplexy or hydrocephalus.

**: Number of deficient axis increased post-operatively

***: Number of deficient axis decreased post-operatively

| Table 6  | Factors related to the post-operative severe hypopituitarism |
|----------|---------------------------------------------------------------|
| Factor | Odds ratio | 95% Confidence interval | \( p \)-value |
| Age | 1.027 | 0.989–1.066 | 0.17 |
| Male Sex | 4.152 | 1.270–13.577 | <0.05 |
| BMI | 0.880 | 0.746–1.038 | 0.13 |
| Maximum tumor diameter | 1.077 | 1.011–1.147 | <0.05 |
| Symptomatic tumor | 5.037 | 1.543–16.444 | <0.01 |
incidentalomas and 8 patients with symptomatic tumors. As shown in Table 7, the most common minor complications were symptomatic hyponatremia (10 in the incidentaloma group and 4 in the symptomatic tumor group) and epistaxis (3 in the incidentaloma group and 2 in the symptomatic tumor group).

**Table 7  Postoperative complications**

|                          | Incidentaloma group | Symptomatic group | p-value |
|--------------------------|---------------------|-------------------|---------|
| **Total complications (Number of patients)** | 20 (17) | 16 (13) | 0.84 |
| **Incidence**            | 21.5% (17/79)       | 19.7% (13/66)     |         |
| **Major complications**  |                     |                   | 0.14    |
| Meningitis               | 3 (2) (2.5%)        | 7 (6) (9.1%)      |         |
| CFS leak                 | 2 (2.5%)            | 3 (4.5%)          |         |
| SAH* (operation required)| 1 (1.3%)            | 1 (1.5%)          |         |
| Hydrocephalus            | 0                   | 2 (3.0%)          |         |
| **Minor complications**  |                     |                   | 0.26    |
| Symptomatic hyponatremia| 10 (12.7%)          | 4 (6.1%)          |         |
| Epistaxis                | 3 (3.8%)            | 2 (3.0%)          |         |
| SAH* (operation not required) | 1 (1.3%) | 2 (3.0%) |         |
| Hematoma                 | 1 (1.3%)            | 0                 |         |
| Dysosmia                 | 1 (1.3%)            | 0                 |         |
| Anemia                   | 1 (1.3%)            | 0                 |         |
| Oculomotor paralysis     | 0                   | 1 (1.5%)          |         |

* SAH, Subarachnoid hemorrhage

**Discussion**

Considering the high prevalence of pituitary incidentalomas, understanding their management is important. Of all incidentalomas that were surgically resected in our institution, there were 62.3% NFPAs, 14.5% functioning adenomas, and 13.8% Rathke’s cleft cysts. Oyama et al. reported that among 550 patients with incidentalomas, 261 (47.4%) patients underwent surgery, and the etiology varied greatly between those who did and did not undergo surgery. According to their study, incidentalomas that were surgically resected included 81% NFPAs and 16% Rathke’s cleft cysts, while observed incidentalomas included 44% NFPAs and 40% Rathke’s cleft cysts. However, with respect to patients with incidentalomas who did not undergo surgery, diagnoses were based on imaging studies and endocrinological findings [12].

Another study reported that among their incidentaloma cases, 51% were NFPAs, 17% were Rathke’s cleft cysts, 12% were malignant tumors, and 11% were functioning adenomas. In addition, 8 of 11 patients with Rathke’s cleft cysts and 1 of 4 patients with prolactinomas did not undergo surgery [13]. In the present series, we only investigated incidentaloma patients that underwent surgery. Thus, this study does not reflect details about incidentalomas that were conservatively followed up. Although this was a limitation of this retrospective study, definitive diagnoses were pathologically confirmed in all cases. Functioning adenomas were excluded from the study reported by Oyama et al., and Rathke’s cleft cysts that were conservatively followed up were included in the report from Ishii et al. [12, 13]. The reason for the differences in incidentaloma subtype frequencies between previous studies and the present study might be due to the difference in the populations of included incidentaloma patients.

Subsequently, we investigated differences in clinical features and surgical outcomes between incidentalomas and symptomatic tumors. For comparison, patients with a preoperative diagnosis of NFPA were recruited, and assigned to the incidentaloma or symptomatic tumor groups.

Symptomatic tumors require therapeutic intervention including surgery, whereas clinically non-functioning incidentalomas require surgery only if they cause visual field abnormalities, optic nerve compression, hypopituitarism or apoplexy, or if they increase in size. Few studies have investigated the differences in incidentaloma and symptomatic tumor characteristics after surgery. In this study, 145 patients considered to have non-functioning pituitary tumors who underwent eTSS were recruited, and assigned to the incidentaloma or symptomatic tumor groups.

Incidentalomas are often detected by brain imaging.
Incidentalomas and symptomatic tumors

569

studies conducted for headaches that are not suspected to be due to pituitary tumors. The significance of headaches in pituitary tumors is controversial.

Although headaches significantly resolved in patients with pituitary tumors after surgery in one study [14], another study indicated that the headaches did not always improve after surgery, unless the cause was pituitary apoplexy [15]. This suggests that headache alone is not a specific marker of the presence of pituitary tumors. Headaches were reported as the most common reason for undergoing CT of the brain, accounting for 27% of patients who received ambulatory care over a 1-year period in Ontario [16]. Headaches are caused by many conditions; therefore, we classified headaches, excluding pituitary apoplexy, as a factor leading to the detection of incidentalomas. In our study, 25 incidentalomas were detected by brain imaging studies because of complaints of headaches. Of these, one was caused by meningitis, which was treated with intravenous antibiotics, and the headache improved before surgery. Eleven of them had transient symptoms and also improved before surgery. Four patients felt that their headaches had disappeared after surgery, whereas the remaining nine patients were conscious of headaches even after surgery. In a previous large study of incidentalomas conducted in Japan, the indications for imaging studies were headache (37.5%), brain checkup (15.9%), dizziness/vertigo (11.2%) and head injury (8.9%) [8]. Similar to this study, 20% of incidentalomas of our patients were detected by health examination which was second reason for imaging studies following headache. Recent spreading of a brain health examination for healthy subjects unique in Japan might cause detecting more incidentalomas.

Symptomatic pituitary tumors were detected mainly because of visual disturbances caused by compression of the optic nerve. This may be explained by the larger size of symptomatic tumors than incidentalomas. Only those incidentalomas that were large with an indication for surgery were included, whereas small incidentalomas managed only by follow up were not included. However, we should keep in mind that even if patients are not aware of visual disturbances, they are often detected by formal visual field examinations. Compared with symptomatic tumors, the incidentalomas were smaller and had fewer pituitary hormone deficiencies both pre- and postoperatively. The incidences of new deficiencies and recovery of pituitary hormone levels after surgery were not significantly different between the two groups. In multiple models, the symptomatic tumor was the most significant related factor of the post-operative severe hypopituitarism among the other factors including age, sex, BMI and maximum tumor diameter. Symptomatic tumors were often found due to pituitary apoplexy or hyponatremia, which might be associated with severe pituitary hormone deficiencies. Unexpectedly, male sex was the secondary related factor following the symptomatic tumor group. There was no significant difference in the incidence rate of pituitary apoplexy between male and female in this study. Further studies might be needed. In any case, incidentalomas must be followed up carefully to determine whether surgery is needed to prevent pituitary hormone deficiencies and visual disturbances.

The total number of patients with postoperative complications was not significantly different between the two groups, and there were no differences in the frequencies of minor or major complications. Different from our series, Losa et al. reported that severe adverse events occurred more significantly in control group (patients with NFPAs who were not discovered incidentally) than in patients with asymptomatic incidentalomas [17]. They did not state on specific classification of serious adverse events, other than five patients in control group died due to surgical complications. On the other hand, no patient died because of surgical complications in our study. Incidentalomas were further subdivided into asymptomatic and symptomatic tumors in their study. Differences in the classification method of patients or number of deaths might cause the different results between two studies.

In this study, there were more patients in the incidentaloma than symptomatic tumor group who experienced symptomatic hyponatremia, but this difference was not statistically significant. Postoperative hyponatremia, which can be caused by syndrome of inappropriate antidiuretic hormone secretion, was improved after appropriate treatment in all cases. On the other hand, postoperative diabetes insipidus (DI) was less frequent in the incidentaloma than symptomatic tumor group. Patients who experienced DI in each group (shown in Table 4) required desmopressin therapy for more than 1 year. We must carefully observe the appearance of hyponatremia or DI symptoms by measuring urine volume, water intake, sodium levels and osmolality in plasma and urine, to adequately manage either.

This study did not assess long-term prognosis after surgery. Losa et al. reported that the 5-year recurrence free survival in patients with incidentalomas was higher in those with symptomatic tumors, which was associated with low risk of postoperative residual tumor in the incidentaloma compared with the symptomatic tumor group. In addition, postoperative residual tumor was related to extension into the cavernous sinus and maximum tumor diameter, while it was negatively related to tumor apoplexy and classification as incidentalomas [17]. Their study focused on tumor recurrence as postoperative outcome and they did not perform statistic comparison of postoperative pituitary hormone deficiencies between
incidentalomas and symptomatic tumors. In our study, maximum tumor diameter was the third related factor for early post-surgical severe hypopituitarism followed after symptomatic tumor and male sex in multivariate analysis. However, it was difficult to compare simply the results with those of Losa et al., as the clinical relevance of tumor size in postsurgical hypopituitarism was not referred in their study. Recent study showed that the pituitary incidentaloma (PI) group had a lower rate of postoperative anterior pituitary hormone deficiencies, smaller residual tumor size and a lower risk rate of reoperation as compared to the non-PI group [18].

The rate of recurrence of non-functioning pituitary adenomas after surgery was reported to be 19–43% [19–21]. Recurrence is influenced by the size and characteristics of the residual tumor, administration of postoperative radiotherapy and the length of follow up. Appropriate surgical management of incidentalomas before symptom development can lead to good perioperative outcomes at least immediately after surgery, although longer-term observation is essential.

Our study has some limitations. Incidentalomas that underwent observation were not included. If these incidentalomas had been added, there might have been higher proportions of NFPAs and Rathke’s cleft cysts. The medical data were collected retrospectively, and information on tumor size, radiological characteristics and GH stimulation test results was not available for some patients. Further studies are necessary for clarifying the long-term prognosis of incidentalomas after surgery. Our study also has several strengths. In this study, all incidentalomas that were surgically resected were investigated pathologically. Moreover, every NFPA was classified morphofunctionally. We directly compared incidentalomas and symptomatic tumors treated with surgery in terms of baseline clinical characteristics, how the tumor was detected, imaging characteristics, tumor pathology and pre- and postoperative pituitary hormone levels, including hormone stimulation test results.

In conclusion, surgically resected incidentalomas consisted primarily of NFPAs, functioning adenomas, and Rathke’s cleft cysts. Among NFPAs that required surgery, incidentalomas were detected most frequently by imaging evaluations for nonspecific headaches, whereas symptomatic tumors were detected by evaluations for visual disturbances. Compared with the incidentalomas that underwent eTSS, the symptomatic tumors were larger and more frequently associated with hypopituitarism persisting after eTSS. Although there was a difference in tumor size and no difference in improved hormone deficiency by surgery between the two groups, results suggest that it is important to make a close observation of incidentalomas and to judge whether to operate appropriately before they become symptomatic tumors.

**Disclosure**

The authors declare that they have no conflict of interest.

**References**

1. Agustsson TT, Baldvinsdottir T, Jonasson JG, Olafsdottir E, Steinhorsdottir V, et al. (2015) The epidemiology of pituitary adenomas in Iceland, 1955–2012: a nationwide population-based study. *Eur J Endocrinol* 173: 655–664.

2. Raappana A, Koivukangas J, Ebeling T, Pirilä T (2010) Incidence of pituitary adenomas in Northern Finland in 1992–2007. *J Clin Endocrinol Metab* 95: 4268–4275.

3. Costello RT (1936) Subclinical adenoma of the pituitary gland. *Am J Pathol* 12: 205–216.

4. Hardy J (1969) Transphenoidal microsurgery of the normal and pathological pituitary. *Clin Neuurosurg* 16: 185–217.

5. Daly AF, Rixhon M, Adam C, Dempegioti A, Tschomirowa MA, et al. (2006) High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. *J Clin Endocrinol Metab* 91: 4769–4775.

6. Fernandez A, Karavitaki N, Wass JA (2010) Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin Endocrinol (Oxf)* 72: 377–382.

7. Freda PU, Beckers AM, Katznelson L, Molitch ME, Montori VM, *et al.* Endocrine Society (2011) Pituitary incidentaloma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 96: 894–904.

8. Sanno N, Oyama K, Tahara S, Teramoto A, Kato Y (2003) A survey of pituitary incidentaloma in Japan. *Eur J Endocrinol* 149: 123–127.

9. Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, *et al.* (2016) Hormonal replacement in hypopituitarism in adults: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 101: 3888–3921.

10. Chihara K, Shimatsu A, Hizuka N, Tanaka T, Seino Y, *et al.* (2007) A simple diagnostic test using GH-releasing peptide-2 in adult GH deficiency. *Eur J Endocrinol* 157: 19–27.

11. Osamura RY, Lopes M.B.S, Grossman A, Kontogeorgos G, Trouillas J (2017) Introduction. In: Lloyd RV, Osamura RY, Klöppel G, Rosai J (eds) World health organization classification of tumours of endocrine organs (4th edition) IARC, Lyon, France: 13–18.
12. Oyama K, Sanno N, Tahara S, Teramoto A (2005) Management of pituitary incidentalomas: according to a survey of pituitary incidentalomas in Japan. Semin Ultrasound CT MR 26: 47–50.
13. Ishii K, Abe I, Kameda W, Sugimoto K, Morinaga Y, et al. (2019) Clinical investigation of pituitary incidentalomas: a two-center study. Intractable Rare Dis Res 8: 239–244.
14. Wolf A, Goncalves S, Salehi F, Bird J, Cooper P, et al. (2016) Quantitative evaluation of headache severity before and after endoscopic transsphenoidal surgery for pituitary adenoma. J Neurosurg 124: 1627–1633.
15. Siegel S, Weber Carneiro R, Buchfelder M, Kleist B, Grzywotz A, et al. (2017) Presence of headache and headache types in patients with tumors of the sellar region—can surgery solve the problem? Results of a prospective single center study. Endocrine 56: 325–335.
16. You JJ, Gladstone J, Symons S, Rotstein D, Laupacis A, et al. (2011) Patterns of care and outcomes after computed tomography scans for headache. Am J Med 124: 58–63.
17. Losa M, Donofrio CA, Barzaghi R, Mortini P (2013) Presentation and surgical results of incidentally discovered non-functioning pituitary adenomas: evidence for a better outcome independently of other patients’ characteristics. Eur J Endocrinol 169: 735–742.
18. Morinaga Y, Abe I, Nii K, Hanada H, Takemura Y, et al. (2020) Characteristics and clinical outcomes in pituitary incidentalomas and non INCIDENTAL pituitary tumors treated with endoscopic transsphenoidal surgery. Medicine (Baltimore) 99: e22713.
19. Losa M, Mortini P, Barzaghi R, Ribotto P, Terreni MR, et al. (2008) Early results of surgery in patients with nonfunctioning pituitary adenoma and analysis of the risk of tumor recurrence. J Neurosurg 108: 525–532.
20. Turner HE, Stratton IM, Byrne JV, Adams CB, Wass JA (1999) Audit of selected patients with nonfunctioning pituitary adenomas treated without irradiation—a follow-up study. Clin Endocrinol (Oxf) 51: 281–284.
21. Greenman Y, Ouaknine G, Veshchev I, Reider-Groswasser II, Segev Y, et al. (2003) Postoperative surveillance of clinically nonfunctioning pituitary macroadenomas: markers of tumour quiescence and regrowth. Clin Endocrinol (Oxf) 58: 763–769.