Incidence, Pathology, and Recurrence of Pituitary Adenomas: Study of 647 Unselected Surgical Cases

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Abstract

The incidence of various types of unselected pituitary adenomas based on correlation of pathologic and clinical data was assessed. We investigated 647 cases of unselected pituitary adenomas, which were surgically removed between 1980 and 1993. All cases were examined by immunohistochemistry and electron microscopy. The mean age of patients was 44.0 years with 40.0 years for women (55.2%) and 49.1 years for men (44.8%). Age distribution indicated a remarkable sex difference: 52.4% of women and 26.8% of men were between 21 and 40 years at the time of surgery. Based on immunohistochemistry and electron microscopy, prolactin (PRL) cell adenomas represented 26.3% of tumors, growth hormone (GH) cell adenomas 12.5%, adrenocorticotrophic hormone (ACTH) cell adenomas 12.4%, oncocytomas 12.4%, and gonadotroph cell adenomas 9.4%. Seventy-three percent of the prolactinomas occurred in women and 73.8% of the oncocytomas were found in men. The incidence of pediatrics pituitary adenomas was 4.6%. All 647 cases were followed up; the mean follow-up period was 96.6 months. In 40 patients (6.2%), the adenoma recurred. Recurrence was common in functioning ACTH cell adenomas (8 cases: 9.5%) followed by silent adenomas (7 cases: 25.9%). Recurrence was noted after 2–96 months (average 28.7 months) following surgery. The shortest remission period was found in a patient with oncocytoma followed by a patient with prolactinoma.

Key Words: Pituitary adenomas; incidence; histologic characteristics; recurrence; remission periods.

Introduction

Pituitary tumors comprise about 10–20% of intracranial neoplasms [1]. The annual incidence of pituitary adenomas in England and the United States was found to range from 0.8–1.0/100,000 population [2]. However, the incidence of pituitary adenomas in unselected autopsy cases has been reported to range from 3–20% [3–6]. Presently, pathologic diagnosis of pituitary tumors relies on immunohistochemical ultrastructural and clinical data [1]. However, limited information is available on unselected series of pituitary adenomas diagnosed by means of these techniques. The purpose of this study was to review the incidence, morphologic characteristics, prognosis, and relation between recurrence and histologic features of 678 surgically removed unselected pituitary adenomas that were previously diagnosed by immunohistochemistry and electron microscopy.

Materials and Methods

Unselected pituitary adenomas removed surgically between 1980 and 1993 were included in the study. Six hundred and seventy-eight cases of tumors and nontumorous lesions were available for clinicopathological analysis. They comprised 647 adenomas and 31 nonadenomatous

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lesions. Forty of the 647 (6.2%) of adenomas recurred. All pathologic diagnoses were made at St. Michael's Hospital, Toronto, Ontario, Canada, based on the classification criteria documented by Kovacs and Horvath [1].

For light microscopy, tissues were fixed in 10% buffered formalin and embedded in paraffin. Sections of 4–6 μm thickness were stained with hematoxylin and eosin (H & E) and the periodic acid-Schiff (PAS) method. For immunohistochemistry, the avidin–biotin–peroxidase complex technique was applied. The following antibodies were used: anti-growth hormone (GH; 1:1500 dilution; Dako, Santa Barbara, CA); anti-human prolactin (hPRL; 1:4000 dilution; donated by Henry Friesen, Department of Physiology, University of Manitoba, Winnipeg, Manitoba, Canada); anti-human adrenocorticotrophic hormone (hACTH; 1:2000 dilution); anti-human thyroid-stimulating hormone (hTSH; 1:2000 dilution); anti-human luteinizing hormone (hβLH; 1:4000 dilution); anti-human follicle-stimulating hormone (hβFSH; 1:2000 dilution) (all donated by Pituitary Hormone Distribution Program, National Institute of Arthritis, Diabetes, Digestive and Kidney Disease, Bethesda, MD, and monoclonal anti-α-subunit of glycoprotein hormones (1:800 dilution; Biogenex, Dublin, CA). Details of immunostainings have been described elsewhere [7,8]. For electron microscopy, tissues were fixed in 2.5% glutaraldehyde, postfixed in 1% osmium tetroxide, dehydrated in graded series of ethanol, processed through propylene oxide, and embedded in an Epon-Araldite mixture. Ultrathin sections were stained with uranyl acetate and lead citrate and studied with a Philips 410LS electron microscope.

In addition to the histologic characteristics of tumors, the presence or absence of amyloid deposition, psammoma bodies, fibrosis, pseudorosette formation, and lymphocytic infiltration also were examined.

The incidence of recurrence was studied as well. The period of follow-up ranged between 18.0 and 168.5 mo (average 96.6 mo). The relations between tumor types and length of remission period, and between tumor recurrence and histologic features including tumor type, cellular pleomorphism, cellularity, and mitosis also were investigated.

Table 1. Sex and Age Distribution in Unselected Surgical Cases of Pituitary Adenomas

Age	Women	Men
0–10	0	0
11–20	20	6
21–30	90	25
31–40	99	48
41–50	51	58
51–60	42	60
61–70	37	66
71–80	14	25
81+	4	2
Total	357	290

Results

Age and Sex of Patients with Pituitary Adenomas

General Features

The age of the patients at the time of surgery ranged from 11–87 yr. The mean age was 44.0 yr: 40.0 yr for women and 49.1 yr for men. There was an age-related sex difference: 66.3% of women were operated on between the ages of 30 and 50 yr, whereas 61.8% of men were between 50 and 70 yr (Table 1). Among the 647 primary pituitary tumors and tumorous lesions, 357 (55.2%) occurred in women and 304 (44.8%) in men. These results indicate slight female preponderance.

Table 2. Incidence of Pituitary Adenomas Based on Immunohistochemical and Electron Microscopic Examination

Type of adenoma	Number of cases	Frequency, %
PRL cell adenoma	178	26.3
Sparsely granulated	172	25.4
Densely granulated	6	0.9
GH cell adenoma	85	12.5
Sparsely granulated	49	7.2
Densely granulated	36	5.3
ACTH cell adenoma	84	12.4
Silent ACTH cell adenoma	13	1.9
Silent adenoma subtype 3	14	2.1
Null cell adenoma	57	8.4
Oncocytoma	84	12.4
Gonadotroph cell adenoma	64	9.4
Mixed GH and PRL cell adenoma	23	3.4
Mammosomatotroph adenoma	14	2.1
Plurihormonal adenoma	19	2.8
TSH cell adenoma	6	0.9
Acidophilic stem cell adenoma	3	0.4
Unclassified adenoma	3	0.4
Nonadenomatous lesion	31	4.6
Total	678	100.0

Pituitary Tumor Types

PRL Cell Adenomas

Immunohistochemically, PRL cell adenomas represented 26.3% of the primary pituitary tumors (Table 2). The majority (96.6%) were sparsely granulated PRL cell adenomas. A marked female preponderance (73.0%) was evident. In women, this adenoma type occurred in 34.8% of primary cases, and in men in 15.8%. Sparsely granulated PRL cell adenomas showed characteristic age-related sex differences: in women, most of them (76.0%) occurred between 21 and 40 yr, whereas in men within this age group, they represented 40.0% (Table 3). Five cases of densely granulated PRL cell adenomas were found in women and one in a man.

GH Cell Adenomas

Immunohistochemically, GH cell adenomas comprised 12.5% of all primary pituitary tumors and consisted of densely granulated GH cell adenomas and sparsely granulated GH cell adenomas. Forty nine cases were sparsely granulated (7.2%) and 36 cases were densely granulated (5.3%). No sex difference was apparent: GH cell adenomas were discovered in 11.0% of all primary adenomas in women and 14.5% in men. Sparsely granulated GH cell adenomas occurred most frequently in 31–40-yr-old women (Table 3). Staining with H & E revealed that 61% of densely granulated GH cell adenomas and 6% of sparsely granulated GH cell adenomas were acidophilic, the remaining tumors were chromophobic.

Functioning ACTH Cell Adenomas

Functioning ACTH cell adenomas represented 12.4% of all primary pituitary tumors. There was a marked sex difference, 79.8% of this tumor type occurred in women, and 71.6% of them were operated on while under 40 yr of age. The incidence of this tumor was 17.9% in women and 5.6% in men. By H & E and PAS staining, 51 tumors (60.7%) were basophilic and contained PAS-positive cytoplasmic granules.

Silent Adenomas

Based on immunohistochemical and electron microscopic findings [1,9,10] silent adenomas consisted of silent ACTH cell adenoma subtype 1 and subtype 2, and silent adenoma subtype 3. There were 27 cases (4.0%) of silent adenomas among primary pituitary tumors. The incidence was 3.7% in women and 4.3% in men. Six tumors represented subtype 1 and 7 cases of subtype 2 silent ACTH cell adenomas were found. Silent subtype 3 tumors [11] were found in 14 patients (2.1%). There was marked sex difference in silent ACTH subtype 1 and subtype 2 tumors, all of the former cases (6 cases) occurred in women older than 30 yr,

Table 3. Sex and Age Incidence of Various Types of Pituitary Adenomas

Tumor type	Sparsely granulated PRL cell adenoma		Sparsely granulated GH cell adenoma		Densely granulated GH cell adenoma		Functioning ACTH		Silent corticotroph and subtype 3 adenoma	
Age, yr	F	M	F	M	F	M	F	M	F	M
11–20	14	2	0	1	0	1	4	1	1	0
21–30	57	6	2	5	1	2	20	2	1	3
31–40	38	13	10	5	4	4	24	5	3	2
41–50	4	11	4	10	5	8	7	2	4	0
51–60	4	5	3	2	4	6	8	3	1	4
61–70	7	6	4	2	3	1	3	5	1	3
71+	1	1	1	1	0	0	0	0	1	1
Total	125	47	24	25	17	19	67	17	14	13

Tumor type	Pituitary oncocytoma		Null cell adenoma		Gonadotroph adenoma		Mammosomatotroph adenoma		Mixed cell adenoma	
Age, yr	F	M	F	M	F	M	F	M	F	M
11–20	0	0	0	0	0	0	1	0	0	0
21–30	0	0	2	1	0	1	3	1	4	4
31–40	3	6	6	2	8	6	0	3	3	0
41–50	3	6	4	8	6	4	0	1	4	3
51–60	8	14	5	12	5	9	3	1	1	2
61–70	3	25	5	7	7	11	1	0	1	1
71+	5	11	0	5	5	2	0	0	0	0
Total	22	62	22	35	31	33	8	6	13	10

whereas 5 cases (71.4%) of the latter (7 cases total) occurred in men. No sex difference could be demonstrated among subtype 3 tumors, but they tended to occur in men older than 51 yr and in women younger than 50 yr. By H & E and PAS staining, 9 cases (69.2%) of silent ACTH cell adenomas were chromophobic and PAS positive, and only 3 cases (23.1%) were basophilic and PAS positive. This indicates that the staining pattern of silent adenomas was different from that of functioning ACTH cell adenomas. In silent subtype 3 tumors described first by Horvath et al. [11], GH, PRL, ACTH, TSH, FSH, and LH immunoreactivities were detected in various combinations within the same tumor.

Null Cell Adenomas

Incidence of null cell adenoid was 8.4% in primary pituitary tumors. Male preponderance (61.4%) was evident. Null cell adenomas were found in 5.9% of pituitary adenomas of women and in 11.5% of men. They tended to occur in middle-age or older patients of both sexes (Table 3). By electron microscopy, 11 cases (19.3%) showed gonadotrophin differentiation, 6 cases (10.5%) indicated features of glycoprotein-producing cells, and 6 cases (10.5%) exhibited slight to moderate oncocytic transformation. By H & E and PAS staining, all of the tumor types were found to be chromophobic: in 29.8% of adenomas few cells with slightly acidophilic granules were noted, and PAS positivity was evident in 12.3% of cases.

Oncocytomas

The incidence of pituitary oncocytoma was 12.4% in primary pituitary adenomas. This tumor type occurred more frequently

in men (73.8%) than in women (26.2%). The incidence was 5.9% in primary adenomas of women and in 20.4% of men. This tumor type showed characteristic age distribution: 81% of the tumors occurred in male patients older than 51 yr (Table 3). Ultrastructurally, 31 cases (36.9%) showed gonadotrophin differentiation, and 23 cases (27.4%) showed glycoprotein hormone cell differentiation. By H & E and PAS staining, 60.7% of these tumors were chromophobic and PAS negative, 22.6% contained cells with acidophilic cytoplasmic granules, and PAS positivity was seen in 11.9% of these adenomas.

Gonadotropin (FSH/LH) Cell Adenomas

Adenomas showing widespread immunoreactivity for FSH, LH, and/or α-subunit and exhibiting typical ultrastructural features were diagnosed as gonadotroph adenomas. The incidence of gonadotroph adenoma was 9.4%, representing 8.3% of female and 10.9% of male patients' pituitary adenomas. Tumors with honeycomb Golgi complexes, which are the hallmarks of female gonadotroph cell adenoma [10], were observed in 19 cases (29.7%) and the less differentiated male type was found in 40.6% of this adenoma type. No specific age distribution was found (Table 3). H & E and PAS staining revealed that 70.3% of this tumor type was chromophobic and PAS negative. PAS positivity was observed in 29.7%, and acidophilia in 1.6% of tumors.

Mixed GH and PRL Cell Adenomas

Mixed GH and PRL cell adenoids were diagnosed in 3.4% of all primary pituitary tumors. The incidence was 3.5% in women and 3.3% in men. This tumor type occurred in various age groups and no sex difference was evident (Table 3). Cell types constituting mixed GH and PRL cell adenomas varied: The most common cell types were densely granulated GH cells and sparsely granulated PRL cells.

Mammosomatotroph (GH/PRL) Adenomas

The incidence of mammosomatotroph adenoma was 2.1%. No remarkable sex difference was evident; this tumor type occurred in various age groups of both sexes (Table 3). The incidence was 2.1% in women and 2.0% in men. The majority (64.3%) were acidophilic and PAS-negative adenomas.

Plurihormonal Adenomas

The incidence of plurihormonal adenoma was 2.8% in primary pituitary tumors. Sixty-eight percent of this tumor type occurred in middle-age men. Plurihormonal adenomas were divided into monomorphous and plurimorphous tumors. The frequency of the former was 84.2%. All tumors showed GH or PRL immunoreactivity. TSH immunoreactivity was seen in 52.7% of this tumor type. Immunoreactivity for α-subunit was noted in 40% and that for FSH or LH in 20% of these tumors.

Uncommon Types of Pituitary Adenomas

The following adenoma types were rare: TSH adenoma occurred in 0.9%, acidophil stem-cell adenoma in 0.4%, and unclassified adenomas in 0.4% of cases.

Miscellaneous Lesions

Thirty-one cases diagnosed clinically as pituitary adenomas contained no adenoma tissue and were diagnosed as nontumorous adenohypophyses. In addition, 6 cases of metastatic carcinoma, 5 cases of Rathke's cleft cyst, 4 cases of meningioma, 4 cases of craniopharyngioma, 4 cases of germinoma, 2 cases of lymphocytic hypophysitis, and one case of each of infarction, fibrosis, xanthogranuloma, hamartoma, plasmacytoma, and chordoma were identified.

Histologic Characteristics of Pituitary Adenomas

Distinct histologic changes were associated with the tumor type in several cases.

Table 4. Recurrence Rate of Pituitary Adenomas According to Histologic Types

Adenoma types	Number of cases	Recurrence rate *n*, %
Functioning ACTH	84	8 (9.5)
Pituitary oncocytoma	84	6 (8.3)
Null cell adenoma	57	5 (8.8)
Silent corticotroph and subtype 3 adenoma	14	4 (28.6)
Silent ACTH cell adenoma	13	3 (23.1)
Sparsely granulated PRL cell adenoma	172	5 (2.9)
Gonadotroph adenoma	64	3 (4.7)
Sparsely granulated GH cell adenoma	49	2 (4.1)
Mammosomatotroph adenoma	14	2 (14.2)
Plurihormonal adenoma	19	2 (10.5)

The changes included amyloid deposition, psammoma bodies, fibrosis, pseudorosettes, and hemorrhagic necrosis.

Amyloid Deposition

Amyloid deposition was evident in 13 adenomas including 8 sparsely granulated PRL cell adenomas (61.5%); in 2 GH cell adenomas, one was sparsely and another was densely granulated. In 4.7% of sparsely granulated PRL cell adenomas, amyloid deposition was noted.

Psammoma Bodies and Microcalcification

Large numbers of psammoma bodies were observed in 23 cases. Sixteen cases (69.6%) were sparsely granulated PRL cell adenomas. Calcified adenomas were observed in 25 cases. Twelve cases (48.0%) were sparsely granulated PRL cell adenomas. Psammoma bodies or microcalcification were found in 16.3% of sparsely granulated PRL cell adenomas.

Fibrosis

In 70 tumors, various degrees of fibrosis were noted. Thirty-eight cases (54%) were sparsely granulated PRL cell adenoma, and 7 cases (10%) were null cell adenoma. Sparsely granulated PRL cell adenomas contained interstitial and/or perivascular fibrosis in 22.1% of the cases.

Pseudorosettes

Marked pseudorosette formation wash observed in 13 cases. This pattern was most frequently observed in gonadotroph cell adenoma (8 cases, 61.5%) followed by pituitary oncocytoma (4 cases, 30.8%).

Necrosis or Hemorrhage

Large necrotic foci or hemorrhage were found in 13 pituitary adenomas. Five cases were oncocytomas, 3 cases gonadotroph cell adenomas, and 3 sparsely granulated PRL cell adenomas.

Adenoma Recurrence

Adenoma Types and Recurrence

Recurrence was defined as return of the clinical symptoms, increasing blood hormone levels, and/or demonstration of tumor by imaging methods. Tumor persistence was included in this definition. We believe that in most of the recurring cases, no new tumor was formed but the tumor was incompletely removed by the initial surgery and regrowth of the adenoma required repeated debulking procedures.

Recurrence was noted in 40 patients (6.2%) with primary adenomas within 1–96 mo after the first surgery (Table 4). Five cases recurred more than two times. Eight cases were functioning ACTH cell adenomas, 6 of them occurred in women. Seven cases were silent adenomas; 26% of this adenoma type recurred. Six recurrent tumors were oncocytomas; 4 of them occurred in men. Some types of adenomas showed characteristic remission period (Fig. 1), the average remission period was as follows: oncocytoma, 15.2 mo; sparsely granulated PRL cell adenoma, 15.6 mo; silent adenoma subtype 3, 16.8 mo.

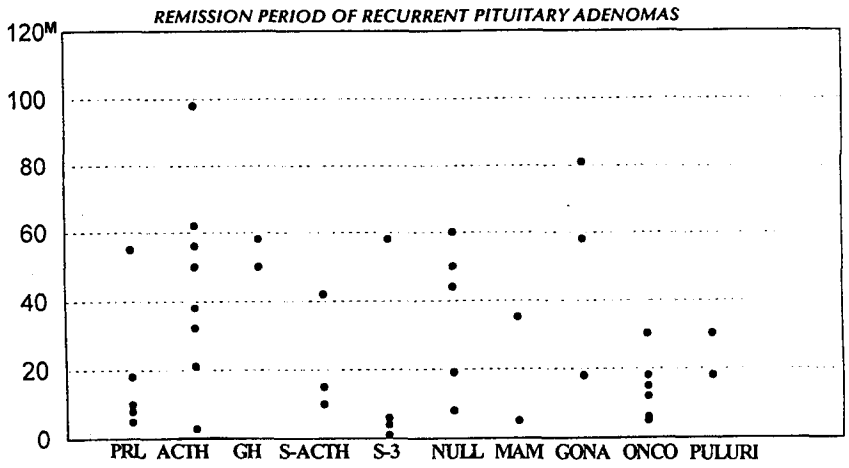

Fig. 1. Remission period of recurrent pituitary adenomas. Some types of adenomas showed characteristic remission period. Oncocytoma, PRL cell adenoma, and silent adenoma subtype 3 tended to recur more rapidly in comparison with other adenoma types (each dot indicates one recurrent case).

Discussion

In this article, we report the incidence, histologic characteristics, and recurrence rates of 678 surgically removed pituitary tumors and tumorous lesions which were investigated by immunohistochemistry and electron microscopy.

Age distribution, sex incidence, and frequency of tumor types were carefully analyzed. A significant age difference was revealed between women and men (40.0 and 49.1 yr, respectively). In the study group of Faglia [12], about 70% of the patients were between 30 and 50 yr, whereas in our study group, the proportion of patients in the same age range was 39.6%.

This proportion was reported as 38.5% in the United States [13] and 45.3% in Japan [14]. The number of patients younger than 20 yr and older than 71 yr was very low. There was a slight female preponderance in tumor occurrence with female:male ratio of 1:21. Also, this female preponderance was reported as 1:78 in the United States [13] and as 1:35 in Japan [14]. In women, about 52.4% of pituitary adenomas were observed between 30 and 50 yr, whereas, in men, in middle or older age. These findings are in general agreement with those of other authors [13–16]. As already reported [9,17,18], sparsely granulated PRL cell adenomas represented the most frequent tumor type, whereas TSH cell adenomas and acidophilic stem cell adenomas were rare tumors. The marked sex differences in silent subtype 1 and subtype 2 ACTH cell adenomas were not reported previously. Nonadenomatous miscellaneous lesions were found in 4.6% of our pituitary material. Among them, 22.6% were metastatic carcinomas and Rathke's cleft cysts. It was apparent that PRL cell adenomas, oncocytomas, and functioning ACTH cell adenomas showed characteristic age-related sex incidence. It was noted that 60% of pituitary adenomas in 21–30-yr-old women were sparsely granulated PRL cell adenomas, 21.1% functioning ACTH cell adenomas, whereas 36.8% of men between 61 and 70 yr had pituitary oncocytomas. According to previous reports, the incidence of pituitary tumors in children and adolescents between 9 and 20 yr varied from 1–10% [2,12–14,16,19,20]. In our series, 245 of 647 (4.0%) pituitary adenomas occurred in children and adolescents; 20 cases were observed in female and 6 in male patients. This remarkable female preponderance in pituitary adenoma occurrence in children and adolescents was not evident in Japan [14]. The most frequent type was sparsely granulated PRL cell adenoma in female patients followed by functioning ACTH cell adenoma in the same sex. The incidence of PRL cell adenoma and functioning ACTH cell adenoma in childhood was similar to that of previous reports [2,19,21]. However, Faglia [12] reported 67 patients with prolactinoma from 78 patients under 20 yr. A case of silent ACTH cell adenoma in a 19-yr-old man and a silent adenoma

subtype 3 in a 17-yr-old woman recurred. Previous reports [2,19] in children showed lower recurrence rate [7.7–8%] compared with that of adults, or higher rates (25%). In our series, the recurrence rate in children was 6.5%, close to that found in adult patients (6.2%). It is noteworthy that a silent ACTH cell adenoma, observed first in a woman when she was 19 yr old, recurred four times.

There were several histologic changes which accompanied pituitary adenomas, such as amyloid deposition, psammoma bodies, calcified deposits, fibrosis, necrosis, and hemorrhage. It was reported that the incidence of amyloid deposits in GH cell adenoma was 74% [22] and in PRL cell adenomas 5–79% [18,22]. In the present studies, the incidence was 4.7% in PRL cell adenomas, and 2.4% in GH cell adenomas; 67% of tumors with amyloid deposition were sparsely granulated PRL cell adenomas. Psammoma bodies and microcalcifications were not uncommon in pituitary adenomas [17,23–25] and the incidence varied from 6.6–9.0%. According to several reports, calcification occurred most frequently in PRL cell adenomas with an incidence of 9.5–19.8% [23–25]. In our series, the incidence was 17.4% (4 cases) in mixed GH, PRL cell adenoma, followed by sparsely granulated PRL cell adenoma 16.3% (28 cases). In our material, 58.3% of adenomas with psammoma bodies or calcification were sparsely granulated PRL cell adenomas. Calcification of pituitary adenoma was revealed as dystrophic calcification, indicating deposits in dead or dying tumor tissue [24]. Fibrosis was a common histologic characteristic of sparsely granulated PRL opal adenomas. It was most frequently found in sparsely granulated PRL cell adenomas followed by densely granulated GH cell adenomas and oncocytomas. It was noted that the incidence of intratumoral fibrosis tended to increase in recent cases. From 1986–1988, bromocriptine (2-bromo-α-ergocryptine), a dopamine agonist, and a long-acting somatostatin analog were used for treatment of PRL cell and GH cell adenomas [26,27]. Interstitial and perivascular fibrosis were described as effects of medication with bromocriptine [28]. The incidence of fibrosis in sparsely granulated PRL cell adenomas during 1980–1986 was 11.1%, and increased to 25% after 1987. In addition, the incidence of fibrosis was 0% in densely granulated GH cell adenomas during 1980–1986, but increased up to 27.3% after 1987. Presumably, treatment with bromocriptine or octreotide was responsible for intratumoral fibrosis. Pseudorosette formation was reported as one of characteristic features of gonadotroph cell adenomas [29]. In our senses, 8 of 13 cases with pseudorosette formation were gonadotroph cell adenomas and 4 cases were oncocytomas; 3 of them showed gonadotroph differentiation and 1 showed glycoprotein cell differentiation.

Most of pituitary tumors were benign and showed slow growth rate. However, our follow-up study indicated that 6.2% of primary adenomas recurred; this recurrence rate was close to that founded by Mukai [6] and Mindermann [30]. Mukai reported eight primary adenomas (5.3%) which recurred out of 150 random surgical cases; 4 cases were PRL cell adenomas, 2 cases immunohistochemically nonfunctioning adenomas, one GH cell adenoma, and one gonadotroph adenoma. Mindermann et al. [30] reported 65 recurrent cases (6.4%) from 1023 unselected adenoma cases; 31 cases of nonsecreting adenomas, 19 cases of functioning ACTH cell adenomas, 7 cases of GH cell adenomas, and 7 cases of PRL cell adenomas. Also, these authors reported the highest recurrence rate of functioning ACTH cell adenomas causing Nelson's syndrome and

Cushing's disease (9.1%) and followed by nonsecreting adenomas (8.7%). Nakane et al. [31] reported eight recurrent functioning ACTH cell adenomas (8.6%) from 93 long-term follow-up patients with this adenoma type. In our studies, recurrence was most common in silent adenomas and functioning ACTH cell adenomas. Silent adenomas showed the highest recurrence rate (25.9%) which was more than three times higher than that of functioning ACTH cell adenomas (9.5%). In our series, so-called nonsecretory adenomas consisted of oncocytomas, null cell adenomas, and silent adenomas. These nonsecretory adenomas showed a 10.7% recurrence rate, which was close to the data of Mindermann et al. [30]. In addition, our study revealed that some types of adenomas had a characteristic remission period. Thus, it was noted that oncocytomas tended to recur most rapidly, followed by both PRL cell adenomas and silent subtype 3 adenomas; functioning ACTH cell adenomas showed marked variation of remission period, and GH cell adenomas had the longest one. This remission period of functioning ACTH cell adenomas was similar to that reported by Nakane et al. [31]. The long remission period of GH cell adenomas also was found by Partington et al. [21]. In five recurrent adenomas (four null cell adenoma and one mammosomatotroph adenoma), the hormone content demonstrated by immunohistochemistry differed from that of primary adenomas. However, null cell adenoma often showed transformation to oncocytoma or glycoprotein-producing adenoma, so these cases should not be regarded as new adenomas. Tumor size or growth rate may be responsible for adenoma recurrence, but we could not reveal the reason of tumor recurrence because, unfortunately, clinical and radiological data of several patients were not available.

In conclusion, careful morphologic investigation of pituitary adenomas including immunohistochemistry and electron microscopy provides important practical information and is valuable in assessing prognosis. The morphologic findings can also affect therapeutic decisions in cases when the preoperative diagnosis is unknown or when the tumor is incompletely removed and the question arises whether medical, surgical, or radiation therapy should be instituted.

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