# Characteristics of mixed prolactin and adrenocorticotropin secreting pituitary adenomas and the differences in patients with merely prolactin-secreting adenomas

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## ABSTRACT

**الأهداف:** تقييم خصائص أورام الغدة النخامية التي تنتج كلا من البرولاكتين وموجهة قشر الكظر.

**الطريقة:** خلال الفترة من 2002م حتى 2011م جمعت 336 مريض خضع لجراحة الغدة النخامية في مستشفى مقاطعة شاندونغ التابع لجامعة شاندونغ، جينان، الصين. كما تم تقسيم المرضى إلى مجموعتين: مرضى يعانون من إفرازات أورام الغدة النخامية برولاكتين وموجهة قشر الكظر، ومرضى يعانون من إفرازات البرولاكتين للغدة النامية فقط. تمت مراجعة البيانات السريرية وبيانات الغدد الصماء، والتصوير والتقرير المرضي والنتائج. واستخدام برنامج الحزمة الإحصائية لمعرفة الاختلافات بين المجموعتين نسخة البرنامج 16 باعتبار القيمة الإحصائية أقل من $p<0.05$ مهمة إحصائية.

**النتائج:** بمقارنة المرضى الذين يعانون من إفرازات البرولاكتين للغدة النامية فقط كان المرضى الذين يعانون من إفرازات أورام الغدة النخامية برولاكتين وموجهة قشر الكظر أصغر سناً ($p<0.001$)، مع ارتفاع آلام الرأس والغثيان ($p=0.021$)، وتطور السمنة ($p<0.001$)، واضطرابات الدورة الشهرية ($p=0.006$)، وكثرة التبول والعطش ($p<0.001$)، وارتفاع ضغط الدم ($p<0.001$)، والسكر ($p=0.001$) وارتفاع معدل نقص صوديوم الدم بعد العملية الجراحية ($p<0.001$). كان معدل تكرار في المرضى الذين يعانون من إفرازات أورام الغدة النخامية البرولاكتين 19.1% و إفرازات أورام الغدة النخامية برولاكتين وموجهة قشر الكظر 35.1% ($p=0.023$). لكن كان معدل الغدد الصماء الطبيعي أقل لدى المرضى الذين يعانون من إفرازات أورام الغدة النخامية البرولاكتين وموجهة قشر الكظر ($p=0.004$).

**خاتمة:** أظهرت نتائج الدراسة الحاجة إلى فترة مراجعة طويلة للمرضى الذين يعانون من إفرازات أورام الغدة النخامية برولاكتين وموجهة قشر الكظر.

**Objectives:** To evaluate the characteristics of pituitary adenomas that produce both prolactin and adrenocorticotropin.

**Methods:** Between 2002 and 2011, we reviewed the data of 336 patients undergoing transsphenoidal surgery at Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China. Patients were divided into 2 subgroups: patients with mixed prolactin and adrenocorticotropin secreting adenomas, and patients with merely prolactin-secreting adenomas. Clinical and endocrinological data, imaging, histopathological reports, and outcomes were reviewed. Differences between the 2 groups were statistically analyzed, and $p<0.05$ was considered statistically significant.

**Results:** Compared to patients with merely prolactin-secreting adenomas, patients with mixed prolactin and adrenocorticotropin secreting adenomas were younger ($p<0.001$), had higher incidences of headaches and dizziness ($p=0.021$), progressive obesity ($p<0.001$), menstrual disorders ($p=0.006$), polyuria and polydipsia ($p<0.001$), hypertension ($p=0.001$), diabetes mellitus ($p=0.001$), and had higher rates of postoperative hyponatremia ($p<0.001$). Recurrence rates in patients with prolactin-secreting adenomas were 19.1% and patients with mixed prolactin and adrenocorticotropin secreting adenomas were 35.1% ($p=0.023$). However, the endocrine normalization rate in mixed prolactin and adrenocorticotropin secreting adenomas was lower ($p=0.004$).

**Conclusion:** Careful long-term follow-up is needed for patients with mixed prolactin and adrenocorticotropin secreting adenomas.


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Prolactin-secreting pituitary adenomas (prolactinomas, PRL) represent the most frequent subtype of all pituitary adenomas.[1] Surgery is generally reserved for patients who do not respond to medical therapy, patients with unstable pituitary hemorrhage, or pregnant patients with progressive tumor enlargement.[2] Adrenocorticotropin (ACTH)-secreting pituitary adenomas (Cushing's disease [CD]) is the result of the pituitary gland producing excess amounts of ACTH causing the overproduction of cortisol. First-line treatment of CD is surgery by a surgeon with experience in this condition. While most adenomas are monoclonal, immunohistochemical staining has shown some to produce plurihormone.[3] Plurihormonal pituitary adenomas have been already described, but mixed PRL- and ACTH-secreting adenomas are rare. Egger et al[4] reported the diagnostic significance of patients with elevated preoperative PRL levels in patients with ACTH-secreting pituitary adenomas. Most of the previous studies focused on adenomas secreting growth hormone (GH), PRL, and one or more glycoprotein hormone sub-units.[5] However, there is a lack of comprehensive data on the mixed PRL- and ACTH-secreting adenomas. In addition, there is limited information on the clinical differences between mixed PRL- and ACTH-secreting adenomas, and patients with merely PRL-secreting adenomas. In order to evaluate the prevalence and characteristics of patients with mixed PRL- and ACTH-secreting adenomas treated with transsphenoidal surgery, we retrospectively reviewed 299 patients with mixed PRL- and ACTH-secreting adenomas, and 37 prolactinomas patients surgically treated between 2002 and 2011. Our study emphasizes the importance of the characteristics of plurihormonal adenomas with PRL and ACTH production. This study will provide a basic understanding of the characteristics and the long-term follow up of patients with mixed PRL- and ACTH-secreting adenomas, and will improve the diagnosis and treatment of these adenomas.

**Methods.** In this retrospective study, data collection was performed between 2002 and 2011 at the Department of Neurosurgery, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China. The Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong University (No. 2012-004) approved the research protocols, and all aspects of the study complied with the Declaration of Helsinki. Informed consent was obtained from each individual above 18. In the case of participants under 18, this was obtained from their guardian. Based on the preoperative hormonal levels and immunohistochemical results, patients were divided into 2 groups: patients with mixed PRL- and ACTH-secreting adenomas (PRL+ACTH), and patients with merely PRL- secreting adenomas (PRL). In order to accurately assess the effects of surgery, only patients treated by surgery alone were included in this study. Indications for surgical therapy of PRL were severe resistance, or intolerance to medical therapy, acute complications (such as rapid visual loss or cranial nerve palsies), CSF leak, cystic macroprolactinomas with neurological symptoms, and patients who did not wish to take prolonged medical treatment.[6-8] All operations were performed by 2 experienced neurosurgeons.

The inclusion criteria for the PRL+ACTH group were signs and symptoms of CD, increased serum PRL, serum cortisol levels and 24-hour urine cortisol levels, loss of diurnal rhythm of serum cortisol, normal or slightly elevated plasma ACTH levels, and/or lack of suppression of serum and urine cortisol after low-dose dexamethasone loading, suppression of serum and urine cortisol after high-dose dexamethasone, adenoma with positive PRL and ACTH immunochemistry, and the presence of a pituitary mass on MRI. The inclusion criteria for the PRL group were increased serum PRL levels, adenoma with positive PRL immunochemistry, and the presence of a pituitary mass on MRI. The exclusion criteria required for the PRL+ACTH group were adenomas with 2 or more than 2 types of hormonal hypersecretion (except for PRL and cortisol), adenomas with immunohistochemical staining positive for 2 or more than 2 types of hormone different from PRL and ACTH, other causes of elevation of PRL and cortisol. The exclusion criteria for the PRL group were adenomas with 2 or more than 2 types of hormonal hypersecretion, immunohistochemical staining positive for 2 or more than 2 types of hormone, and other causes of elevation of PRL. Subjects without follow-up were also excluded. The time interval was defined from the onset of symptoms and signs to the date of diagnosis. Tumor size was measured by MRI. According to Lania et al,[9] macroadenomas were defined as a tumor with a diameter of more than 10 mm, whereas microadenomas were defined as a tumor with a diameter of 10 mm or less. Adenomas with extension into the cavernous

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sinus were defined as 'cavernous sinus invasion'.[10] The PRL level was measured using commercially available chemiluminescence kits (Beckman Coulter, Inc., South Kraemer Boulevard Brea, CA, USA). The normal range of PRL was 2.64-13.13 ng/ml in males, 3.34-26.72 ng/ml in premenopausal females, and 2.74-19.64 ng/ml in postmenopausal females. Sensitivity for PRL was 0.25 ng/ml. The intra-assay variation coefficients of these assays were <10% and inter-assay were <15%. Cortisol was measured using an electrochemiluminescent immunoassay kit (Roche Diagnostics GmbH, Mannheim, Germany) with a sensitivity of <8.5 nmol/L. The intra-assay variation coefficients of these assays were <10% and inter-assay were <15%. The normal range of cortisol was 171-536 nmol/L. Immunohistochemical analysis was performed on surgical specimens using specific antibodies against ACTH, PRL, growth hormone (GH), follicle stimulating hormone (FSH), luteinizing hormone (LH), and thyroid stimulating hormone (TSH). The incidence of diabetes insipidus (DI) in this study may only represent transient DI. Transient DI was diagnosed when hypotonic polyuria (40 ml/kg body weight daily), usually self-remitting in a few days, ensued soon postoperatively. Hyponatremia was diagnosed when the sodium level was lower than 135 mmol/L. Endocrine normalization was defined as hormone levels in the normal range after surgery. According to the results of hormone levels and MRI examinations performed on patients 12 months after surgery, recurrence was diagnosed when hormonal function and residual tumor were found.

Analyses were performed using the Statistical Package for Social Sciences Version 16.0 (SPSS Inc., Chicago, IL, USA). The differences in mean age, time interval, and tumor size between the 2 groups were compared by Mann-Whitney U tests. The Chi-square test was used to compare gender, invasion, presence of apoplexy, tumor classification, remission rate, and recurrence rate between the 2 groups. The 95% confidence interval (CI) was estimated. Group differences of endocrine outcome at the same follow-up time and different follow-up times were estimated by Student's t-test. $P<0.05$ was considered statistically significant.

**Results.** The medical records of all patients were reviewed for medical history, clinical presentation, hormone evaluation, pituitary images, immunohistochemical staining, and postoperative outcomes. Clinical characteristics of patients and adenomas are shown in **Table 1**. Of 336 patients who underwent transsphenoidal surgery, 244 were females and 92 were males. Patients with PRL+ACTH were younger than that of the patients with PRL ($p<0.001$). However, there were no significant differences in gender, the mean time interval, tumor size, and incidences of invasion and apoplexy between the 2 groups. In addition, there was no statistical difference for the incidences of microadenomas or macroadenomas between the 2 groups. Pre-operative clinical manifestations and complications are shown in **Table 2**. Compared with the PRL group, the incidences of headaches and dizziness, progressive obesity, menstrual disorders, polyuria and polydipsia, hypertension, and diabetes mellitus were significantly higher in the PRL+ACTH group.

Pre- and post-operative hormone levels are shown in **Table 3**. Significantly elevated preoperative serum cortisol and PRL levels were detected in patients with PRL+ACTH. Patients with PRL+ACTH had relatively higher PRL levels than patients in the PRL group before and after surgery. Based on the postoperative hormone levels at 12 months, we also found that the overall endocrine normalization rate in the PRL+ACTH group was significantly lower than that in the PRL group (40.5% versus 64.9%, $p=0.004$).

**Figure 1** shows the endocrine normalization rate of microadenomas and macroadenomas in the 2 groups. In patients with PRL, endocrine normalization occurred in 30 patients (96.8%) with microadenomas

**Table 1 -** Preoperative characteristics of patients and adenomas in the 2 groups.

| Characteristics | PRL (n=299) | PRL + ACTH (n=37) | *P*-value |
|---|---|---|---|
| Age (years) mean +SD | 45.08 ± 13.30 | 31.38 ± 15.76 | <0.001 |
| ***Gender n (%)*** | | | |
| Male | 82 (27.4) | 10 (27) | 0.959 |
| Female | 217 (72.6) | 27 (73) | |
| Time interval (months) mean +SD | 39.94 ± 52.93 | 32.85 ± 34.84 | 0.609 |
| Tumor size (cm) mean +SD | 2.50 ± 1.15 | 2.44 ± 1.30 | 0.773 |
| Invasion n (%) | 139 (46.5) | 13 (35.1) | 0.191 |
| Apoplexy n (%) | 59 (19.7) | 6 (16.2) | 0.609 |
| Microadenomas n (%) | 31 (10.4) | 2 (5.4) | 0.556 |

PRL - prolactinomas, ACTH - adrenocorticotropin

**Table 2 -** Pre-operative clinical manifestations and complications in the 2 groups.

| Characteristics | PRL (n=299) | | PRL+ACTH (n=37) | | *P*-value |
|---|---|---|---|---|---|
| Headache/dizziness | 142 | (47.5) | 25 | (67.6) | 0.021 |
| Progressive obesity | 0 | (0) | 7 | (18.9) | <0.001 |
| Vomiting | 26 | (8.7) | 4 | (10.8) | 0.758 |
| Visual impairment | 150 | (50.2) | 19 | (51.35) | 0.892 |
| Visual field defects | 124 | (41.5) | 12 | (32.4) | 0.291 |
| Menstrual disorders | 116/217 | (53.5) | 22/27 | (81.5) | 0.006 |
| Galactorrhea | 125/217 | (57.6) | 14/27 | (51.9) | 0.569 |
| Sexual dysfunction | 23/81 | (28.4) | 2/10 | (20.0) | 0.721 |
| Polyuria and polydipsia | 10 | (3.3) | 8 | (21.6) | <0.001 |
| Hypertension | 28 | (9.4) | 11 | (29.7) | 0.001 |
| Diabetes mellitus | 6 | (2.0) | 6 | (16.2) | 0.001 |

Data are expressed as number and percentage (%). PRL - prolactinomas, ACTH - adrenocorticotropin

**Table 3 -** The levels of prolactinomas (PRL) and cortisol in the 2 groups.

| Group | Hormone | Measurements at different time points | | | | *P-value |
|---|---|---|---|---|---|---|
| | | Before surgery | 3 days after surgery | 3 months after surgery | 12 months after surgery | |
| PRL (n=299) | PRL (ng/ml) | 143.21±133.84* | 32.34±22.12* | 31.47±22.50* | 33.59±21.82* | <0.001 |
| | Cortisol (nmol/L) | 258.32±131.8† | 240.93±149.6† | 253.24±129.97† | 257.52±106.34† | 0.992 |
| PRL+ACTH (n=37) | PRL (ng/ml) | 228.94±187.61 | 71.07±66.68 | 72.90±62.47 | 75.74±70.15 | <0.001 |
| | Cortisol (nmol/L) | 671.91±65.11 | 377.90±185.32 | 387.06±184.29 | 370.60±169.05 | <0.001 |
| †*p*-value | | 0.010 | 0.001 | <0.001 | 0.001 | |
| ‡*p*-value | | <0.001 | <0.001 | <0.001 | <0.001 | |

Data were expressed as mean±SD. *Comparative analysis in the 2 groups before surgery and 3 days after surgery. †Difference between the 2 groups at the same time point of PRL level. ‡Difference between the 2 groups at the same time point of cortisol level. ACTH - adrenocorticotropin

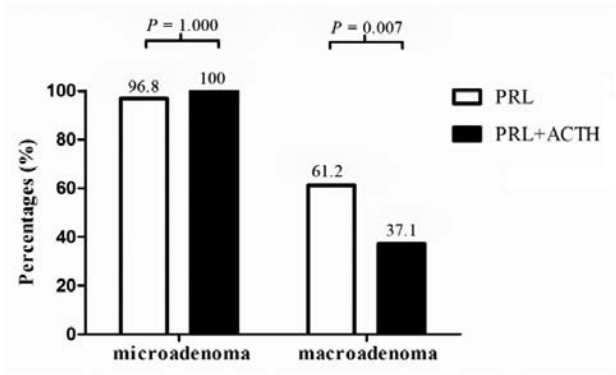


**Figure 1 -** Endocrine normalization rate of microadenomas and macroadenomas in the 2 groups. *P* values was determined using a Chi-square test. A $p<0.05$ was considered statistically significant.

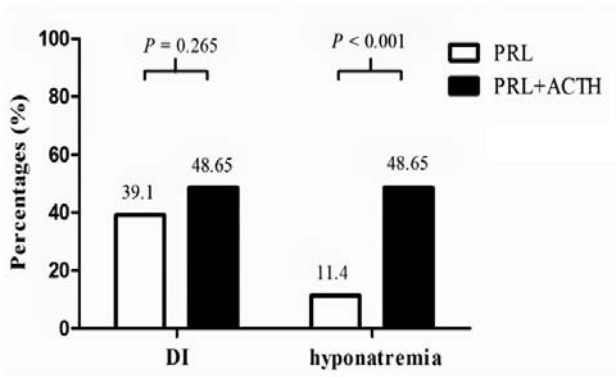


**Figure 2 -** The rate in percentage of postoperative complications (diabetes insipidus [DI], and hyponatremia) in patients undergoing trans-sphenoidal surgery for pituitary adenoma. *P* values was determined using Chi-square test. A $p<0.05$ was considered statistically significant.

and 164 patients (61.2%) with macroadenomas. These rates in the PRL+ACTH group were 100% and 37.1%. There was a significant difference in the endocrine normalization rate in macro-adenomas between the 2 groups ($p$=0.007). Post-operative complications in the 2 groups are summarized in **Figure 2**. Diabetes insipidus was observed in 39.1% of patients with PRL, whereas the incidence in patients with PRL+ACTH was 48.7%. The incidence of hyponatremia in the PRL group was 11.4%, and 48.7% in patients with PRL+ACTH. There was no significant difference in DI between the 2 groups, but the incidence of hyponatremia in the

PRL+ACTH group was significantly higher than that of the PRL group. After a median follow-up of 31 months (range from 14-78 months), all cured patients were still alive. The recurrence rate for the entire series was 20.8%. The recurrence rates in the PRL group was 19.1% and in PRL+ACTH group was 35.1%. The more frequent recurrence occurred in the PRL+ACTH group ($p$=0.023).

**Discussion.** Secreting adenomas are mainly represented by prolactinomas, followed by GH- and ACTH-secreting adenomas.[11] Plurihormonality was found to be a frequent finding in both functioning and non-functioning pituitary adenomas.[12,13] Pawlikowski et al[14] showed that over one-third of the investigated adenomas expressed more than one hormone. Control of excessive hormone production and the improvement of pituitary function are the main reasons for surgery. Surgery offers several advantages, including rapid decompression and endocrine response.[11] It has been hypothesized that plurihormonal adenomas may be caused by polyclonal diffusion or monoclonal expansion. There is a lack of comprehensive data on adenomas that secrete both ACTH and PRL. Reports of large series of surgeries for PRL+ACTH and merely PRL that include clinical features and detailed endocrine and surgical outcomes are rare. This comparative study demonstrated differences in the clinical presentation of patients with mixed PRL- and ACTH-secreting adenomas and patients with merely PRL-secreting adenomas. Patients were retrospectively evaluated over a 9-year period.

Most of the patients were diagnosed in their forties. There were significant age differences between the 2 groups. Patients in the PRL group were older, while patients with PRL+ACTH were younger. In agreement with Andersen et al,[15] we found that a large proportion both were females. As also shown here, the mean maximal diameter of the adenomas were similar in the 2 groups. In addition, we found that all patients in the 2 groups were more likely to have macroadenomas. The reason, macroadenomas were more likely in the 2 groups might be related to the characteristic of prolactin.[16] Adenomas in post-menopausal women often remain undetected until they enlarge significantly and cause visual disturbances, headaches, and hypopituitarism. Moreover, we found that the incidence of apoplexy in the 2 groups was 16.2% and 19.7%. We postulate that patients might experience infarction of their adenomas, leaving residual lesions in the pituitary region.

The biology of pituitary adenomas is complex, and they can cause a variety of endocrine syndromes and disorders.[17] Compared with the PRL group, the incidence of headaches and dizziness, progressive obesity, menstrual disorders, polyuria and polydipsia, hypertension, and diabetes mellitus was higher in the PRL+ACTH group. This data supports findings in the literature[18,19] that ACTH and cortisol levels were positively associated with systolic and diastolic blood pressure, triglycerides, fasting glucose and insulin resistance, and metabolic syndrome. The ACTH has antagonistic effects on protein and lipid metabolism, which can lead to uncontrolled hypertension and other serious complications. This data also supported the findings that hypersecretion of PRL has a variety of manifestations as PRL affects many organs.[20,21] Prolactinoma hypersecretion is usually associated with headache and hyposexuality, and in women, menstrual disorders, and galactorrhea. Pituitary compression by the tumor might present with headaches and dizziness. Higher incidences of complications in the PRL+ACTH group, compared with the PRL group, may be due to the elevated cortisol and PRL levels.

Trans-sphenoidal surgery for pituitary tumors is a relatively safe procedure. However, even in the most experienced hands, post-operative complications are still unavoidable. Post-operative DI and hyponatremia have been reported, and were also found in our patients. The DI occurred in 48.7% of PRL+ACTH patients and in 39.1% PRL patients. The rate of DI reported in the literature varied widely.[22,23] Relatively higher rates of DI were observed in recent patients, probably due to early diagnosis and increased awareness regarding DI. This wide range likely reflects inconsistencies in the working definition of DI across the literature. The incidence of hyponatremia in patients with PRL+ACTH was significantly higher than in patients with PRLs. Relatively higher rates of hyponatremia were observed in our results compared with the literature.[15] Therefore, patients with PRL+ACTH were more likely to develop hyponatremia after surgery. Future prospective studies of the impact of trans-sphenoidal surgery on DI and electrolyte abnormalities are needed.

The majority of reported pituitary adenomas are monoclonal. Mixed ACTH- and PRL-secreting adenomas occur rarely.[5] The PRL+ACTH patients had relatively higher PRL levels than patients in the PRL group before and after surgery. As already reported by previous authors,[8,12,24] a lower PRL level at diagnosis was independently associated with a successful surgical outcome. In microadenomas, the endocrine normalization rates in the PRL+ACTH group and PRL group were similar. However, in macroadenomas, the rate in the PRL+ACTH group was lower than the PRL group. When surgery is

performed by an experienced and pituitary dedicated neurosurgeon, transsphenoidal surgery has the potential to achieve endocrine normalization in patients with microadenomas. However, PRL+ACTH patients harboring macroadenomas will have persistent tumor following surgery.

A wide variation of surgical outcomes and recurrence rates has been reported with hormone-secreting tumors, depending on the tumor characteristics, the surgeon's experience and the duration of follow-up. In the last 2 decades, a large series from specialized centers has shown the possibilities of surgery regarding recurrence rates in the treatment of hormone secreting pituitary adenomas.[25,26] We found that recurrence rates for the PRL+ACTH group and PRL group were 35.1% and 19.1%, with the higher being in the PRL+ACTH group. The recurrence rate in the PRL group was similar to that reported by others.[27,28] The recurrence rate in PRL+ACTH was similar to the literature reported by Primeau et al,[29] and higher than those reported in the literature.[30] Therefore, careful long-term follow-up is needed in these patients, even if surgery is considered successful.

Immunostaining of the pituitary tumor was positive for PRL as well as for ACTH. This pituitary tumor is one of the few mixed PRL- and ACTH-secreting tumors documented by immunostaining. Bălinişteanu et al[12] reported that plurihormonality seemed to be connected with co-expression of ACTH. Many hypotheses have been proposed to explain the existence of plurihormonal adenomas. First, some tumors could originate from uncommitted stem cells. The neoplastic transformation of stem cells caused by subsequent stimulation could result in different cell types. One type of cell could differentiate into another type of cell during tumor growth. Second, different hormones could be derived from 2 distinct types of cells within the borders of a single adenoma. Mixed ACTH and PRL adenomas usually show no clinical evidence of CD, or CD and prolactinoma co-exist.[5] Third, 'conjoined tumors' could be instead by plurihormonal adenomas. According to the literature,[3,31] 'conjoined tumors' are posited to occur when 2 separate tumors growing in a small space become conjoined and appeared grossly as a single mass. It is conceivable that ACTH and PRL hormones in pituitary lesions originate from different areas of the pituitary tissue. Each area may be composed of one cell type. Thus, adenomas that appear as single tumors, but demonstrate immunohistochemical variation may be multiple tumors.

Our study was a single institutional and retrospective cohort study. One limitation was the short follow-up for some patients, which had limits in evaluating the real recurrences. The adenomas might reoccur with longer follow-up.

In summary, careful long-term follow-up is needed for patients with mixed prolactin and adrenocorticotropin secreting adenomas to better assess the effects of surgery and treatment outcomes. These patients were younger, had more complications, had lower endocrine normalization rates, and had more frequent recurrence rate compared with PRL patients. Patients with mixed PRL- and ACTH-secreting adenomas were associated with a variety of clinical manifestations resulting from excessive hormone secretion and tumor mass effects, and require a multidisciplinary management approach. Our observations extend our knowledge of the characteristics of patients with mixed prolactin and adrenocorticotropin secreting adenomas. This study provides novel insights to help us improve the diagnosis and treatment of these patients. Future study should be aimed at the severe and prolonged mechanism in these patients. The examination of the molecular processes will provide important insights into the functions and the control of pituitary cell differentiation.

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