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Original Article

Clinical characteristics and surgical treatment of pituitary adrenocorticotropin-secreting macroadenomas: experience from a single-centre study

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Abstract: Cushing's disease due to adrenocorticotropin (ACTH)-secreting macroadenomas is rare. The aim of this study was to evaluate the clinical characteristics and biochemical assessment of patients with corticotroph macroadenomas,and the early and late outcomes of transsphenoidal surgery as the first surgical approach during a long-term follow-up. We performed a retrospective review of 20 patients with Cushing's disease due to macroadenomas and 126 patients with ACTH-secreting microadenomas. We found that macroadenomas patients presented with higher ACTH levels than those of microadenomas. The percentage of patients having >50% suppression (of ...?) was significantly different between the patients with macroadenoma and microadenomas. The mean of cortisol and ACTH levels evaluated at the first day after operation was significantly reduced. Immediate remission was achieved in 90 of 126 (71.4%) microadenoma patients, and delayed remisson (within a month after operation) was achieved in 109 of 126 (86.5%). UFC levels before operation was significantly higher in non-remission patients than that of remission group. For imaging, the tumour size was significantly larger in non-remission patients than in remission ones. In a word, patients with ACTH-secreting pituitary macroadenomas show higher baseline ACTH levels but increased glucocorticoid suppressibility compared with patients with microadenomas, Increased tumor size or UFC level are unfavorable factors to indicate remission after transsphenoidal surgery. Moreover, TSS plays an important role in achieving long-term remission not only for intrasellar microadenomas but also for extrasellar macroadenomas.

Keywords: Cushing's disease, macroadenoma, clinical characteristics, transsphenoidal surgery

Introduction

Cushing's disease (CD) is characterized by hypercortisolism in the setting of excessive adrenocorticotropin (ACTH) secretion by a pituitary corticotroph adenoma. While rare, it is associated with significant morbidity and mortality [1, 2]. By high-resolution magnetic resonance imaging (MRI), a pituitary microadenoma defined as being less than 1 cm in maximal diameter can be found in most patients. However, an ACTH-secreting pituitary macroadenoma presents in only 4-10% of patients with Cushing's disease [3]. As a rare disease, the incidence of Cushing's disease is estimated to be 1-3 cases per million inhabitants per year [4]. Patients with CD are exposed to excessive endogenous glucocorticoids that induce many characteristic endocrine consequences. Unlike microadenoma, ACTH-secreting macroadenomas can grow rapidly and become so large as to induce symptoms due to mass effect. Macroadenomas can lead to visual field disturbances, compression of cranial nerves, hypopituitarism, and infiltration of the cavernous sinuses [5]. Because the occurrence of macroadenomas is such rare, there are few literatures regarding the characteristics and treatment of patients with pituitary macroadenomas. It has been reported that patients with pituitary ACTH-secreting macroadenoma is characterized by different biochemical features compared with microadenomas. The baseline hormonal assessment of patients with macroadenomas sh-

owed a clear difference from the microadenomas. Both ACTH and cortisol levels is significantly higher in patients with macroadenoma than those of microadenom as, moreover, reduced ACTH and cortisol suppressibility after standard dexamethasone testing presented in macroadenoma patients [3, 6]. In another study, it was suggested that increased plasma ACTH concentrations may be a more sensitive indicator of neoplastic corticotrophs than the UFC or 17-OHCS response to standard high dose dexamethasone testing [7]. Some studies showed that increased tumor size or invasion of the cavernous sinus were unfavourable prognostic factors for surgical therapy and macroadenomas are more refractory to conventional treatments than microadenomas [8, 9], however, the correlation between tumor size and surgical outcome remains controversial [10].

Pituitary macroadenomas are histologically benign and do not undergo malignant transformation, but subsequent pressure of important structures, makes them difficult to cure. Transsphenoidal surgery treatment is useful for pituitary adenoma especially for intrasellar tumors. The aim of this study was to compare the clinical and biochemical characteristics of pituitary macroadenomas compared with microadenomas, and present the results of transsphenoidal surgery as the first surgical approach for patients with macroadenomas, a long-term follow-up results was also showed in our study.

Methods

Patients

In a period from July 2007 until May 2015, a total of 20 patients newly diagnosed with Cushing's disease due to ACTH-secreting pituitary macroadenomas at the Department of Neurosurgery of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. The study population also comprised 126 patients with ACTH-secreting microadenomas. The patients who underwent second surgery or received first time treatment in other hospital and patients have no visible adenoma on MRI were not included in this study. All patients with CD confirmed by histology, or by bilateral inferior petrosal sinus sampling (BIPSS) and pituitary imaging technique, or by remission of clinical signs from retrospective assessment after pituitary surgery.

Data was retrospectively collected by reviewing inpatient medical records, outpatient medical records and reports of the surgical procedure. Pituitary functions were evaluated at the time of medical assessment, and endocrine deficiencies were determined according to normal range adopted by Clinical Laboratory for Endocrinology of Ruijin Hospital.

Patients' demographic characteristics, preoperative imaging features (size, location and characteristics) and follow-up were reviewed.

Imaging

Dynamic pituitary MRI was obtained in all patients, using a superconducting magnet 1.5-tesla scanner (Signa; General Electric, Milwaukee, WI, USA). The size of the adenoma was recorded as the largest diameter on any plane from pre-operative imaging studies, 'microadenoma' if a pituitary adenoma <10 mm of diameter was evident, or 'macroadenoma' if tumour diameter was ≥10 mm. Imaging studies were independently reviewed by the neuroradiologist, endocrinologist and the patient's neurosurgeon. Tumor location was classified according to the preoperative radiology report as CSI (cavernous sinus invasion), SS (supra-sellar), IS (intra-sellar).

Statistical analysis

The statistical analysis was performed using SPSS (version 13.0). Continuous data was analyzed using the Mann-Whitney test, whereas qualitative differences were evaluated with χ^2 test or Fisher's exact test as appropriate. Data was presented as mean ± SEM or median (range) for continuous variables and as number (percent) for categorical variables. The criterion of $P \leq 0.05$ was chosen for statistical significance.

Results

Clinical characteristics

Patients with macroadenomas had a mean age at diagnosis of 38.8±3.1 yr while 36.9±1.1 yr of patients with microadenomas. The population of macroadenoma patients comprised 18 fe-

Table 1. Age, gender, BMI, disease duration, tumor size, and follow-up duration of all patients

No.	Age (years)	Sex	BMI (Kg/m^2)	Disease duration (months)	Tumor size (mm)	Surgical procedures	Follow-up (months)
1	57	M	27.04	120	17.7	TSS	72
2	35	F	25.81	28	10.0	TSS	84
3	26	F	22.94	48	10.0	TSS	24
4	58	F	27.76	144	11.0	TSS	60
5	54	F	28.30	6	24.0	TSS	48
6	27	F	25.00	36	12.0	TSS	12
7	19	F	22.76	24	12.1	TSS	16
8	20	F	21.78	3	10.0	TSS	18
9	36	F	25.48	24	10.0	TSS	12
10	56	F	33.96	12	25.0	TSS	12
11	34	F	25.39	14	14.0	TSS	24
12	30	F	25.39	36	11.0	TSS	6
13	36	F	26.45	24	14.0	TSS	6
14	37	F	20.70	12	22.0	TSS	4
15	35	F	30.36	84	13.5	TSS	0
16	38	F	22.83	12	10.0	TSS	9
17	34	F	29.09	120	10.0	TSS	5
18	72	F	23.05	240	17	TSS	3
19	41	M	26.03	60	10.1	TSS	0
20	31	F	23.83	24	10.1	TSS	0

M, male; F, female.

males and 2 males patients (the female-to-male ratio is 9:1). The median duration of follow-up was 12 months (range 0-84 months), and the mean disease duration (estimated by the time elapsed from the appearance of the first signs and symptoms of hypercortisolism to diagnosis) was 53.5±13.5 months. Only one patient was younger than 20 years. As regards clinical features, the major clinical features noted were moon facies (81.3%), buffalo-hump (50.0%), obesity (56.3%), facial plethora (50.0%), hypertension (62.5%), dropsy (37.5%), muscle atrophy (31.3%), hirsutism (50.0%), purple striae (50.0%), ecchymoses (31.3%), and acne (50.0%). None of these features was significantly different from those patients with microadenomas. Eight of twenty patients with macroadenomas (40%) had evidence of a visual field defect. Age, gender, BMI and other characteristics of macroadenoma patients are presented in **Table 1**.

Baseline endocrine evaluation and response to dexamethasone

Patients with macroadenomas presented with higher ACTH levels (161.0±33.1 vs 114.3±6.9 pg/ml, P<0.05) than those of microadenomas, whereas plasma cortisol and UFC levels were similar in patients with macroadenomas and microadenomas, difference between them did not reach statistical significance (28.7±3.1 vs 30.4±1.6 ug/dl, P>0.05; 602.9±160.4 vs 570.1±36.74 ug/24 h-urinary, P>0.05) (**Figure 1**). Low-dose dexamethasone administration did not adequately inhibit cortisol levels in any of the patients. Only 1 of 20 macroadenoma patients (5%) showed decreased plasma ACTH, serum cortisol and/or UFC levels while in 16 patients (12.7%) of microadenoma, however they did not significantly differ between the two groups (P> 0.05). As regards high-dose dexamethasone administration (HDDST), the full results were available in all patients, including patients with macroadenoma and microadenomas, the percentage of patients having >50% suppression was significantly different between the two groups (95.0% vs 75.3%, P<0.05). An impairment of the hypothalamic-pituitary function and some complications of macroadenomas patients were also detected, central hypothyroidism (as proven by low baseline serum free thyroxine, free triiodothyronine and thyrotrophin (TSH) levels) was detected in 8 cases (40%), hypogonadism (evaluated on the basis of clinical history or serum levels of FSH, LH, PRL and sex hormones: estradiol, progestin, testosterone) in 5 cases (25%). Lipid profile, coagulation and fibrinolysis function were evaluated at diagnosis in all patients, using standard methods, we observed 4 cases (20%) presented with hypercoagulability and 8 cases (40%) with dyslipidaemia.

Radiological features

The mean diameter of pituitary macroadenoma was 13.7±4.9 mm (range 10-25 mm). Imaging revealed a suprasellar extension in eight of 20 (40%), and cavernous sinus invasion in 6 of 20

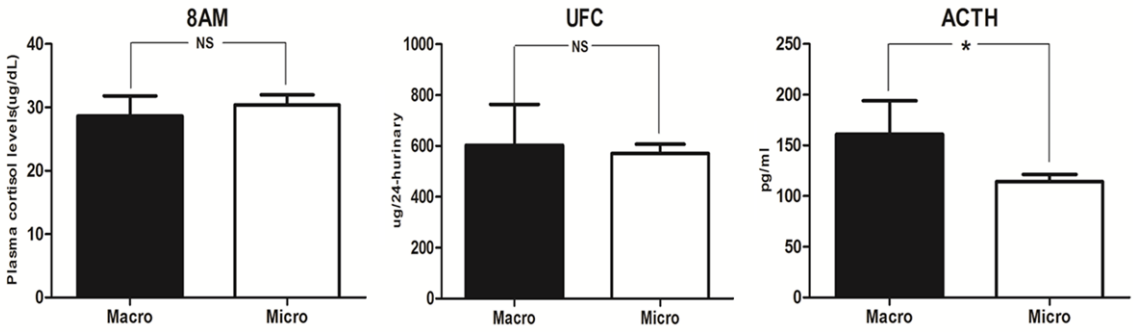

Figure 1. Plasma ACTH, serum cortisol and urinary free cortisol (UFC) levels at entry in patients with macroadenomas and microadenomas. *P<0.05.

Table 2. Tumor characteristics, visual field defect and outcome after surgery of all patients

Patient No.	Visual disturbances	Tumor location	CSI	BIPSS	Short-term outcome	Recurrence
1	+	SS	+	-	Remission	-
2	-	SS	-	-	Remission	-
3	-	IS	+	-	Not Remission	-
4	-	IS	-	-	Remission	-
5	+	SS	-, +	-	Not Remission	+
6	+	IS	-	-	Remission	-
7	-	SS	+	N	Remission	-
8	-	IS	-	Left	Remission	-
9	+	IS	-	Right	Remission	-
10	-	SS	-	-	Not Remission	+
11	-	IS	+	Right	Remission	-
12	+	IS	-	-	Remission	-
13	-	IS	-	Left	Remission	-
14	+	SS	+	-	Not Remission	-
15	-	SS	-	-	Remission	Death
16	+	IS	-	Right	Remission	-
17	-	IS	-	-	Remission	-
18	+	SS	-	-	Not Remission	-
19	-	IS	-	-	Remission	-
20	-	IS	-	-	Remission	-

CSI: Cavernous sinus invasion; SS: supra-sellar; IS: intra-sellar; BIPSS, Bilateral Inferior Petrosal Sinus Sampling; Left, higher secretion of ACTH in left side; Right, higher secretion of ACTH in right side; N, no distinction between left and right side for ACTH secretion.

(30%), among the six patients, one presented with cavernous sinus invasion after recurrence (**Table 2**). The tumor was partly cystic (20%). No other brain involvement was observed on initial MRI of all 20 patients. MRI evaluation was taken at least one time after the first operation in 17 of twenty patients, only two of them showed recurrent pituitary adenoma. Imaging characteristic are showed in **Figure 2**.

Initial surgical outcome

All patients underwent transsphenoidal surgery (TSS) as first line treatment after diagnosed as Cushing's disease due to pituitary macroadenoma. Immunohistochemistry was performed and was positive for ACTH in all cases. Compared with pre-surgical endocrine evaluation results, 15 cases (75.0%) showed decreased ACTH, cortisol and UFC levels within a week after operation while 4 (20.0%) cases within a month after transsphenoidal surgery, one case without decreased endocrine hormone levels during two years follow-up. However, the mean of cortisol and ACTH levels evaluated at the first day after operation significantly lower than at baseline (cortisol 28.7±3.1 vs 14.5±4.8 ug/dl, P<0.01; ACTH 161.0±33.1 vs 53.7±24.1 pg/ml, P<0.01), the UFC level of pre- and post-operation did not differ significantly (602.9±160.4 vs 439.3±118.9 ug/24 h-urinary, P>0.05). Thus, only one patient (No. 3) was considered primary treatment failures because of postoperative absolute or relative hypercortisolism. By way of comparison, remission immediate (within a week after operation) was achieved in 90 of 126 (71.4%) microade-

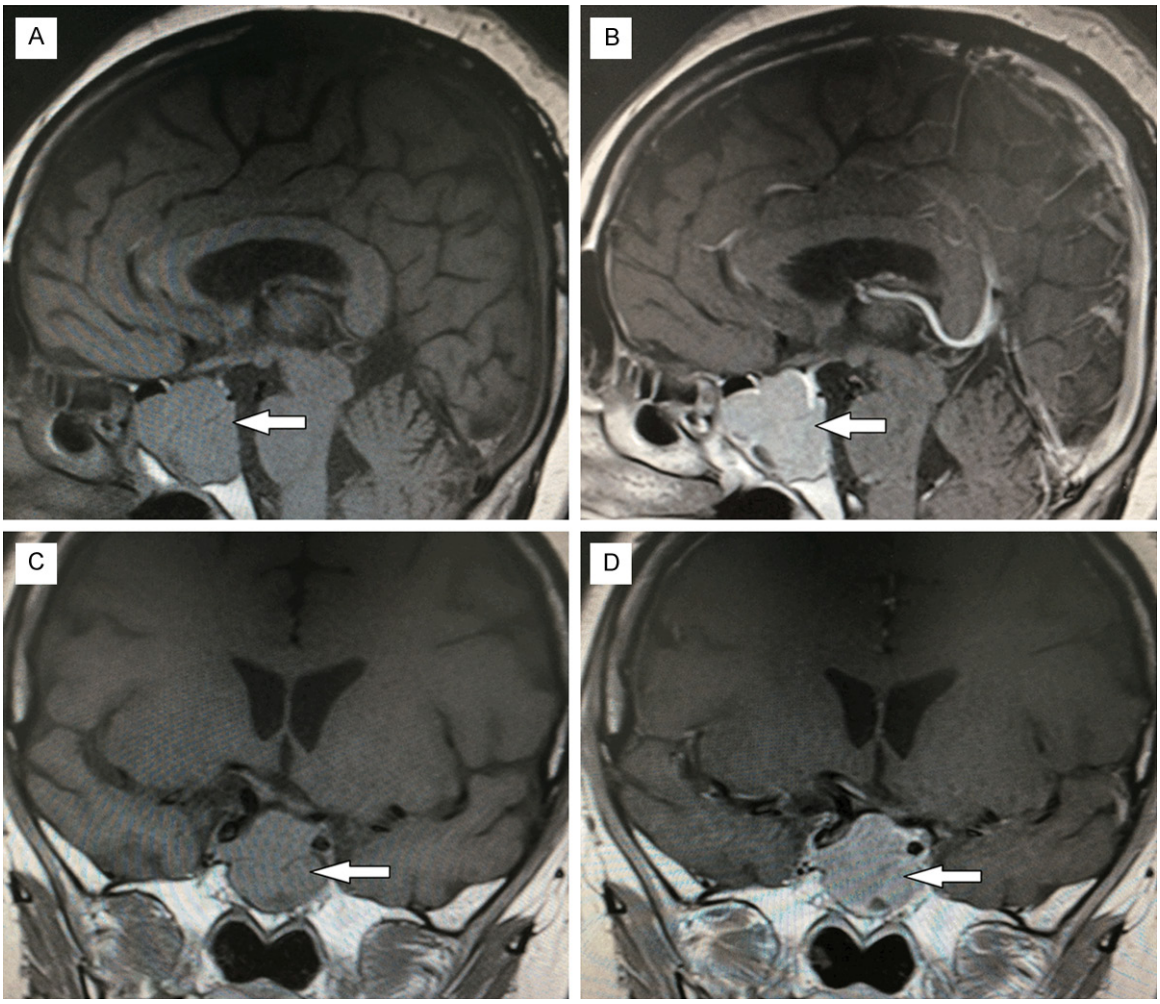

Figure 2. Magnetic Resonance Imaging evaluation before TSS (case 14). A and B showing sagittal T1 MRI scans and contrast enhanced T1 MRI image through pituitary fossa; C and D showing the coronal and contrast enhanced T1 MRI scans. A pituitary macroadenoma was detected from the image, which demonstrating even uptake of contrast and a lower enhancement than surrounding normal pituitary gland, and elevating and compressing optic chiasm. The adenoma extended to the sphenoid sinus with destructing the sellar floor. The right cavernous sinus was compressed and the adenoma surrounded the right internal carotid artery partially.

noma patients, and remisson delayed (within a month after operation) was achieved in 109 of 126 (86.5%), difference of the two remission rate between micro- and macroadenomas did not reach statistical significance (75.0% vs 71.4%, P>0.05; 95.0% vs 86.5%, P>0.05). The evaluation of demographic characteristics, imaging features and endocrine hormone assessment between remission and non-remission group (including remission delayed and not remission during follow-ups) are showed in **Table 3**. UFC levels were significantly higher in non remission patients than that of remission group (786.8 (288.9-3352.0) vs 349.9 (146.5-1240.0), P<0.05), while serum cortisol and ACTH levels were not significantly different between the two groups. For imaging, the tumour size was significantly larger in non-remission patients (22.0 (10.0-25.0) mm) than in remission ones (11.0 (10.0-17.7) mm, P<0.05). The percentage of adenoma with cavernous sinus invasion or suprasellar extension did not differ significantly between two groups. CSI was detected in 3 out of 15 remisson patients (20.0%) and 2 out of 5 non-remission ones (40.0%). Age at diagnosis, gender, duration of symptoms and BMI (Body Mass Index) were also not significant different between two groups. After surgery, two patients (No. 12 and No. 15) presented with cerebrospinal fluid leak-

Table 3. Demographic, clinical characteristics and biochemical assessment of patients between remission and not remission (including remission delayed and not remission during follow-up) patients with macroadenomas

	Remission immediate (n=15)	Remission delayed and not remission (n=5)	*P* value
Demographic characteristics			
Age (years)	35 (19-58)	54 (26-72)	0.149
Male gender	2/15	0/5	1.000
BMI (kg/m^2)	25.48 (21.78-30.36)	23.05 (20.70-33.96)	0.760
Disease duration (months)	28 (3-144)	12 (6-240)	0.455
Characteristic of tumor			
Tumor size (mm)*	11.0 (10.0-17.7)	22.0 (10.0-25.0)	0.034
CSI	3/15	2/5	0.560
SS	4/15	4/5	0.109
IS	11/15	1/5	0.109
Visual field defect	5/15	3/5	0.347
Endocrine hormone assessment			
8AM	23.9 (15.6-61.5)	29.10 (20.3-49.0)	0.206
UFC*	349.9 (146.5-1240.0)	786.8 (288.9-3352.0)	0.032
ACTH	100.4 (25.7-556.5)	171.5 (68.2-499.3)	0.206
Follow-up (months)	12 (0-84)	12 (3-48)	0.765

CSI: Cavernous sinus invasion; SS: supra-sellar; IS: intra-sellar; *p<0.05.

age, bost of them can not relieve by lying flat, then conducted lumbar drainage, No. 12 patient did not show CSF leakage any more after drainaging, however it did not work for No. 15 and required reoperation to re-patch, however, No. 15 patients died after second transsphenoidal surgery with the cause unknown. No patients suffered from post-operative meningitis within the first 30 days after surgery and during follow-up.

Follow-up

The median duration of follow-up was 12 months (range 0-84 months). Nine patients needed substitution with cortisone acetate for a long time while four patients of them need life-long replacement treatment (patients 5, 7, 9, 12). Cushing's disease recurred in two which had clinical, biochemical evidence of recurrent hypercortisolism and evidence of adenoma by pituitary MRI evaluation (No. 5, No. 10) out of 19 patients (one patient died). No. 5 patient underwent conventional radiotherapy in Ruijin Hospital, endocrine hormone level decreased after radiotherapy, but then showed hypoadrenalism that need life-long replacement treatment after three years. The other relapsed patient (No. 10) underwent transsphenoidal surgery again. One patient (No. 3) was considered primary surgical treatment failure which presented with persistent hypercortisolism, one year after first TSS in our hospital, the patient received Gamma Knife treatment in other hospital, but was lost at follow-up after that. Flow chart summarizing the outcomes of therapy of 20 patients with Cushing's disease due to macroadenoma are showed in **Figure 3**.

Discussion

Cushing's disease is a rare endocrine disorder characterized by excess secretion of ACTH due to a pituitary adenoma. In the majority of cases, adrenocorticotrophin secreting pituitary adenomas are small, intrasellar and less than 1 cm in maximal diameter. Cushing's disease due to macroadenoma is characterized by different biochemical features compared with microadenomas. We performed a retrospective case review of 20 patients with ACTH-secreting macroadenomas to assess the clinical and biochemical features and the effectiveness of transsphenoidal surgery, and the outcome after a long-time follow-up. Patients with active CD are exposed to excessive endogenous glucocorticoids levels that lead to many characteristic clinical features, including obesity, signs of protein wasting, high blood pressure, increased rate of infections, gonadal dysfunction and

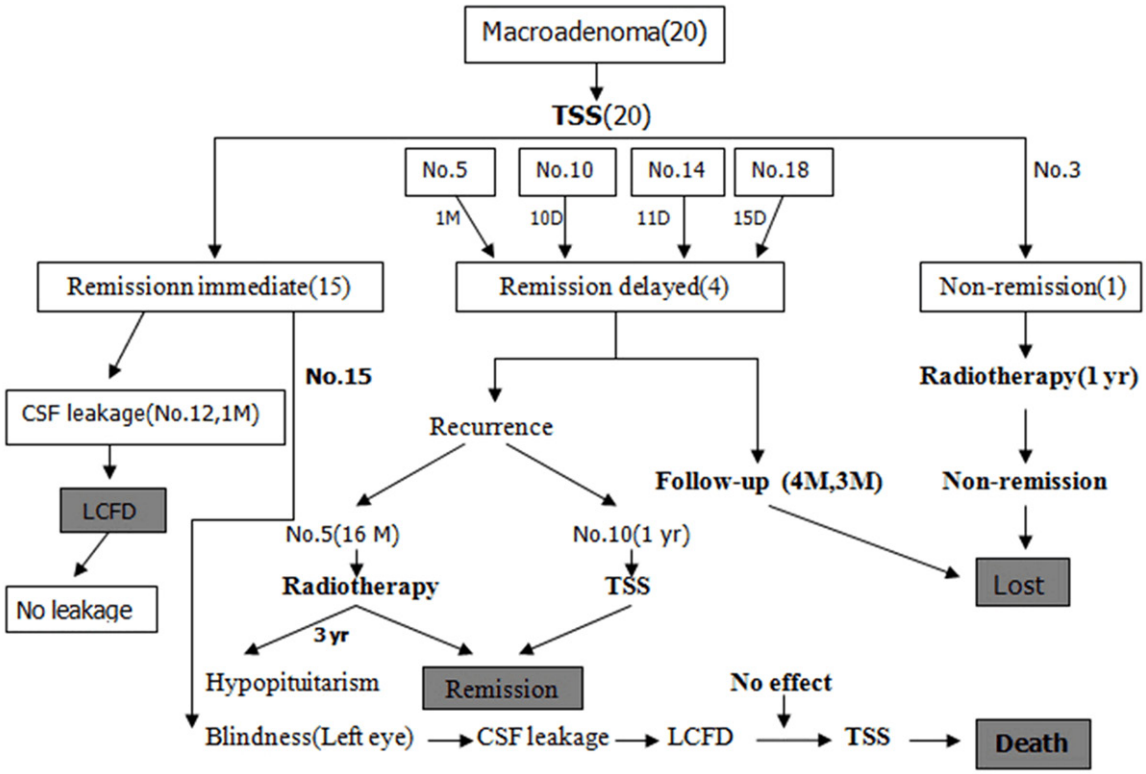

Figure 3. Flow diagram summarizing the outcomes of therapy in 20 patients with ACTH-secreting pituitary macroadenomas. TSS, transsphenoidal surgery; M, month; D, day; CSF, cerebrospinal fluid; LCFD, continued Lumbar Cerebrospinal Fluid Drainage.

even severe psychic disturbances [11, 12]. Our study demonstrated the clinical features are broadly similar between patients with macroadenomas and with microadenomas. None clear distinguishing features was detected other than visual field defect in macroadenoma patients, which is in accordance with other reports [3, 13]. In our study, eight of twenty patients with macroadenomas (40%) had evidence of a visual field defect which result from progressive mass effect secondary to pituitary macroadenoma. The patients did not differ significantly in age at diagnose and the female-to-male ratio is 9:1 (a marked female preponderance with the ratio generally assumed to be close to 3-8:1 [14]). In Cushing's disease, relationship between the size of the adenoma, the severity of hypercorticism and the clinical presentation has never been studied systematically before, but it was reported that the baseline hormonal assessment of patients with macroadenomas showed a clear difference from the microadenomas [3], and we also found ACTH levels being significantly higher than those in microadenomas, however, no significant difference in urinary free cortisol or serum cortisol levels were detected in our study. As adrenocorticotropin secretion derived from pituitary adenoma, our results may suggest that concentration of ACTH is related to the size of the adenoma. CD patients due to macroadenomas present higher plasma ACTH levels than those with microadenomas, but mean plasma cortisol levels and UFC were similar between them, these facts may suggests a more pronounced secretory activity of the pituitary macroadenomas and indicates an weakened adrenal sensitivity to ACTH. Moreover, we observed that corticotroph microadenomas are less responsive to suppression by high-dose dexamethasone compared with macroadenomas, but our results seem not to corroborate the previous findings [3, 7]. Moreover, we found no different suppression of cortisol after low-dose dexamethasone administration. The mechanisms why macroadenomas secrete higher ACTH has been studied previously, it was proposed that macroadenomas preferentially

secrete biologically inactive precursors of ACTH that could interfere with ACTH measurements and the secretion of which is not regulated like that of ACTH [15]. Some suggest that the microenvironment of the tumor is different in micro and macro-adenomas, including hypoxia, accessibility to regulating agents and exposure to auto/paracrine factors, moreover, it was reported that various mutations were responsible for the escape of the adenoma from glucocorticoid feedback, and for various patterns of tumour growth [16-18]. All in all, further investigations of the mechanisms are essential. Transsphenoidal surgery has evolved much over nearly 100 years as treatment for Cushing's disease due to pituitary adenoma [19]. With advances in the understanding of the biology of pituitary tumours and co-operation between endocrinologists, surgeons and oncologists, and huge advances in imaging technique, the effectiveness of surgical approach has been improved largely. The objective of TSS is to normalize hypercortisolism, alleviate clinical symptoms, reduce the risk of tumour recurrence, and preserve normal pituitary function. The tumor size, extension, configuration, the magnitude of hormonal oversecretion and the experience of the operating surgeon are the essential factors that decide the effectiveness of transsphenoidal operation [19]. Transsphenoidal surgery is the best approach for pituitary microadenoma that are primarily intrasellar. On the first day post-surgery, cortisol levels have been determined for all patients in our study, if serum cortisol levels are still high, further evaluation was conducted in the next days. We assessed the outcome of TSS for 20 patients with pituitary macroadenoma, 15 cases showed decreased ACTH, cortisol and UFC levels within a week after operation and 4 cases within a month after transsphenoidal surgery, only one case underwent primary treatment failures and presented with postoperative absolute or relative hypercortisolism during follow-up. Overall remission rate was 95%. But one patient died after second transsphenoidal surgery with the cause unknown, two patients presented with cerebrospinal fluid leakage that need lumbar drainage or reoperation, no patients suffered from post-operative meningitis. Nine patients needed substitution with cortisone acetate for a long time and four patients of them needed life-long replacement treatment. For all the 19 patients, clinical symptoms were partial alleviated after surgery. In all cases the C-arm image intensifier had been used for a lateral skull radiograph during the surgical procedure to check the trajectory. Although some complications (including CSF leakage, hypocortisolism) existed after surgery, transsphenoidal approach is still an effective and safe treatment for pituitary adenoma even for large intra and suprasellar or cavernous sinus invasion pituitary macroadenomas in our study. CSF leakage is one of the most commonest surgical complications which usually evident during surgery and after surgery, so a meticulous repair of the floor of the pituitary fossa is essential. In two cases with CSF rhinorrhea after operation, we did not use muscle mash and fascia or fat from thigh to repair the sellar floor. We suggest that it is still necessary for using subcutaneous fat, muscle mash or fascia lata to repair the floor of the pituitary fossa to reduce CSF leakage although we have no sufficient evidence to verify the effectiveness.

For experienced surgeons, the remission rate following transsphenoidal surgery for microadenomas ranges from 65%-90% [20]. In our study, total remission rate is 95% for patients with macroadenomas while 86.5% for microadenomas, and they did not reach statistical significance, however, higher remission rate in patients with microadenomas than those of macroadenomas was reported by some authors [8, 21], and they proposed that these observed differences in remission rates may be due to differences in biologic behavior (size and invasiveness), our results seem to be inconsistent with previous studies, but we found tumour size was significantly larger in non-remission patients than remission ones, so whether tumor size of pituitary adenoma is a reliable predictor of the results of surgery is still unclear and need studied deeply. We analyzed various factors between remission and non-remission group (including remission delayed and not remission during follow-up), only UFC and tumor size were significant different between two groups, and we proposed that these two factors may be predictors of postoperative cure or the likelihood of remission.

In this study, the median duration of follow-up was 12 months, short term follow-up become a defect in this study. Cushing's disease recurred in only two cases that one underwent conven-

tional radiotherapy and the other underwent transsphenoidal surgery again. Late recurrence can occur, even in patients defined as remission during a long time follow-up, so lifelong follow-up for patients with CD is essential, particularly for patients who have shown rapid normalization of hypercortisolism.

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Disclosure of conflict of interest

None.

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