

# Reoperation of Cushing's Disease for Recurrence and Persistence without Visible MRI Finding

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# Abstract

**Purpose:** Transsphenoidal surgery (TSS) is the first-line treatment for Cushing's disease (CD), even with negative preoperative MRI results. It is not rare that patients experiencing hypercortisolism persistence or recurrence have negative MRI after the initial surgery. We aim to analyze the efficacy of repeat surgery in these two groups of patients and assess if there is association of the positive MRI finding with early remission.

**Patients and methods:** Clinical, imaging and biochemical information from 42 patients who underwent repeat surgery by a single neurosurgeon between 2002 and 2021 were retrospectively analyzed. The endocrinological, histopathological and surgical outcomes before and after the repeat surgery of 14 CD patients with negative MRI findings were compared with 28 patients with positive findings.

**Results:** Immediate remission was achieved in 29 patients (69.0%) underwent repeat surgery. Of all patients, 28 (66.7%) had MRI findings consistent with solid lesion. There was no difference of remission rate between the recurrence group and the persistence group (77.8% vs. 57.1%, Odds Ratio = 2.625, 95% Confidence Interval = 0.651 to 10.586). In patients with remission after the repeat surgery was not associated with the positive MRI finding (Odds Ratio = 3.667, 95% Confidence Interval = 0.920 to 14.622).

**Conclusions:** In terms of recurrence, the repeat surgery with either positive or negative MRI showed a reasonable remission rate. For persistent disease with positive MRI finding, repeat surgery is still an option, while more solid evidence is needed to define if the negative MRI is predictor for failure reoperation of persistent hypercortisolism.

## Introduction

Transsphenoidal pituitary surgery is the primary choice of treatment for patients with Cushing's Disease (CD), which has a reported remission rate ranging from 70–90%[1–4]. However, it exists in some cases among those operated patients that hypercortisolism persists, or recurs in 3%-29% of patients even on those who has benefited from a remission for more than a decade[5–7].

In those cases where the primary surgery failed, several treatments are taken into consideration which including reoperation, medication, conventional radiotherapy, radiosurgery and bilateral adrenalectomy[5, 8, 9]. With a remission rate up to 87%[10], a second operation is a feasible option worth considering[9]. Although there are a few papers concentrating on the risk factors and long-term outcome of repeated transsphenoidal surgery[11, 12], the necessity of reoperation in patients with varied clinical, imaging and pathological characteristics were not adequately discussed. A repeated operation is considered with visible lesion remained in the magnetic resonance imaging (MRI), given that removal of tumor highly likely leads to remission even it is located into cavernous sinus[13]. Nevertheless, the positive incidence of MRI was not usually satisfactory in CD patients with either recurrence or persistent disease[8, 10, 14, 15]. Furthermore, the MRI has its limitations on revealing accurate structures of the operated area due to distorted anatomy related to granulation tissue formation and inflammatory changes after the initial

surgery[16, 17]. Unlike the considerable remission rate achieved after the first operation despite a negative MRI finding[2], a second operation without visible lesion detected on MRI is still a challenge for neurosurgeons. These uncertainties remind us to discuss the risk factors and the necessity of the repeat surgery, especially for those cases with negative radiological result.

Our retrospective study aims at ascertaining the treatment preference of reoperation on persistent and recurrent CD patients and probing into the significance of imaging findings of MRI for selecting patients probably benefit from a reoperation. Thus, we provide reference for surgeons on applying a repeat surgical intervention for those who is supposed to obtain a benefit, and in the meantime, improve remission rate of reoperation.

## **Patients And Methods**

We retrospectively identified patients with Cushing's disease treated with repeated transsphenoidal surgery between 2002 and 2021 in our institution. The patients with 3 or more pituitary surgeries were excluded from the present study. As the preoperative and postoperative evaluations of the first surgery shown in Table 1, all patients fulfill the criteria for the study: persistent hypercortisolism after initial surgery or recurrence after remission with a period of normocortisolism or adrenal insufficiency.

Table 1  
Preoperative characteristics of the initial surgery

	Recurrence Group	Persistence Group
<i>Age (Mean ± SD)</i>	41.7 ± 12.3	33.4 ± 10.6
<i>Gender</i>		
Male	3	6
Female	24	9
<i>MRI</i>		
Visible lesion	27	12
Negative	0	3
<i>HDDST</i>		
+	14	10
-	1	1
NA/NP	12	4
<i>BIPSS</i>		
+	5	2
-	3	0
NA/NP	19	13
<i>The surgeon of the initial procedure</i>		
Same	15	7
Different	12	8
Age, age at the initial operation; MRI negative, no tumor identified; HDDST -, failure of suppression after dexamethasone administration; HDDST +, both of serum cortisol & 24 hrs UFC suppressed after dexamethasone administration; BIPSS +, central to peripheral ACTH gradients ≥ 2 without CRH/DDAVP stimulation; BIPSS -, central to peripheral ACTH gradients < 2 without CRH/DDAVP stimulation; NA, no available record; NP, not performed		

The study included 42 patients aged 44.4 ± 14.6 yrs at the repeat operation (details shown in Table 1S). The median interval time between the two operations is 43 months (IQR = 90 – 18). The median follow-up duration after the second operation is 15.5 months (IQR = 59 – 4).

## Diagnosis

The diagnostic criteria for recurrence in the present study included new onset or recurrence of symptoms, clinical features, serum cortisol, 24hrs urinary free cortisol (UFC) and biochemical tests (LDDST and HDDST), those which are frequently used in defining CD remission, recurrence and persistence[18]. A proposed algorithm currently used in biochemical assessment as well as management of recurrence and persistent disease is shown in Fig. 1. All tests were performed in a College of American Pathologists (CAP) accredited laboratory (no. 7217913). Serum cortisol and UFC were examined by using an Access Immunoassay System (Beckman Coulter Inc., Fullerton, CA, USA). The normal ranges were 6.7–22.6 µg/dl and 21–111 µg/24 h, respectively. Plasma ACTH levels were measured by using an ELSA-ACTH immunoradiometric assay method (Cisbio Bioassays, Codolet, France). The normal range was 12–78 pg/ml. A serum cortisol value less than 5 µg/dL was considered as remission. Patients who were not considered to be in remission were discharged and re-evaluated routinely in 6 months after surgery for possible delayed remission. Patients were administered with oral cortisone and withdrew gradually to physiologic replacement doses in 1 month. The yearly follow-up visit included physical examination, assessment of serum cortisol, UFC and plasma ACTH. MRI was not performed routinely after surgery unless hypercortisolism persistence or recurrence confirmed biochemically, as postoperative imaging may not be reliably interpreted for hormone-active pituitary adenoma.

Contrast-enhanced pituitary MRI in our center was all conducted to facilitate diagnosis and the surgical planning, using superconducting magnet 1.5/3.0 Tesla scanner (Signa; General Electric, Milwaukee, WI). Before gadolinium injection (0.01 mmol/kg gadopentetate dimeglumine; Magnevist, Berlex Laboratories, Montville, NJ), T1-weighted spin echo and T2-weighted turbo spin echo images were obtained in the coronal and sagittal plane. Beginning simultaneously with gadolinium injection, coronal and sagittal T1-weighted spin echo images were obtained 2 minutes after the injection. Imaging studies were independently reviewed by the neuroradiologist, endocrinologist, and the patient's neurosurgeon. Pituitary imaging prior to the first surgery performed outside our center were acquired and re-interpreted by the same team. Full agreement was reached on the positive nature of MRI findings. Otherwise, when MRI appeared normal or interpretation was ambiguous, MRI was considered negative.

In the meanwhile, bilateral inferior petrosal sinus sampling (BIPSS) with or without vasopressin (available after 2015) stimulation was performed in 9 patients who experienced recurrence but lacked positive ACTH staining on first histology in order to re-confirm whether their diagnoses of Cushing's syndrome were pituitary-dependent. 2 patients were evaluated by BIPSS although the initial pathology was positive. For persistent disease, among 8 patients without a positive ACTH staining in their first pathology, 5 cases confirmed by positive BIPSS result and 5 cases were confirmed by the visible radiological lesions. Only one patient with a negative ACTH staining adenoma were underwent the repeated surgery with either negative BIPSS result or negative imaging finding.

## **Surgical Procedure**

The same surgeon performed surgery on all patients via the mono-nostril transsphenoidal approach under the microscope or endoscope (available from December 2015). The initial location prior to first operation was not guiding the resection during repeat surgery. For each patient with MRI-position result,

the imaging-identified areas for an adenoma were biopsied as frozen sections for pathological evaluation at the first place. Subsequent resection with a rim of pituitary tissue around the tumor cavity was conducted to confirm neoplasm-free margins. No further exploration was performed before frozen pathology confirmation were available, unless the BIPSS result showed an increased ACTH level on the other side.

For invisible tumor on MRI, the dura mater was opened widely to facilitate the whole gland exploration, which start from the initial location shown in MRI before the first surgery or the side with higher ACTH level in BIPSS if available. If no obvious tumor was identified in this side by the neurosurgeon intraoperatively, the half of the gland was resected by the guidance of BIPSS lateralization.

If a tumor was frozen pathologically identified after half of the gland had been removed, the residual gland remained unresected and was only gently explored and sampled in the most suspected area or, in some circumstances that the frozen section is negative, was subjected to a subtotal adenohipophysectomy with intermediate lobe and neurohypophysis remained.

If the invasive characteristics of the adenoma were also identified, the involved dura and medial wall of the cavernous sinus were resected or coagulated. The sample was collected for postoperative pathological confirmation if available.

## **Outcome**

Patients were defined as being in remission with an immediate postoperative serum cortisol nadir < 5 µg/dl or 24-hours UFC on a normal level[19], and persistent hypercortisolism as having an increased postoperative UFC level while recurrence was defined as reappearance of hypercortisolism[19, 20] after a period of normocortisolism or adrenal insufficiency.

## **Statistical Analysis**

Descriptive statistics are presented as mean values ± SD when normally distributed or the median and range when not normally distributed to describe patient outcome measures and incidence of remission in the study population. Statistical significance in the results was accepted at a P value < 0.05. Fisher's exact test was used to compare proportions between groups on categorical measures. All analyses were conducted using InStat (GraphPad Software, San Diego, CA).

## **Results**

### **Patients' features**

The basic information and perioperative evaluation of the two operations is shown in Table 1 and Table S1. In all those 27 recurrent cases, the preoperative MRI prior to the first operation showed a definite pituitary adenoma. The other 12 patients with persistent hypercortisolism had positive MRI finding before

the first surgery. The rest 3 patients with negative radiographic finding were diagnosed as CD and underwent the first TSS based on their endocrinological results.

For those patients who was confirmed persistence or recurrence of CD, the imaging finding prior to the second operation of 14 individuals was negative (no solid evidence of tumor), and 28 had clearly positive results for the presence of a solid lesion. All patients who underwent a second surgery dealing with a recurrent or persisting hypercortisolism after the initial surgery were endocrinological re-evaluated before the repeat surgery. There were 38 cases with positive in HDDST in 42 patients. BIPSS was performed in 18 patients with only 1 case did not reach the criteria of pituitary origin.

## Outcome

In our study, 29 of the 42 patients (69.0%, 22 recurrent and 7 persistent cases) were in remission after the repeated operation without additional therapy during follow-up (details showed in Table 1S). At follow-up, compared with patients with persistent disease, the recurrence group had a higher remission rate, but not significantly (77.8%, 21/27 in recurrence vs. 57.1%, 8/15 in persistence,  $p > 0.05$ , Odds ratio = 2.625, 0.651 to 10.586). A negative preoperative MRI was not associated with lower odds of immediate remission after the repeat surgery ( $p > 0.05$ , Odds ratio = 3.667, 95% Confidence Interval = 0.920 to 14.622; Table 2).

Table 2

The remission rate of the recurrent and persistent hypercortisolism patients with or without positive MRI finding

	Recurrence Group		Persistence Group		Combined	
	MRI +	MRI -	MRI +	MRI -	MRI +	MRI -
Remission	15	6	7	1	22	7
Non-Remission	2	4	4	3	6	7
Remission Rate	88.2%	60.0%	63.6%	25.0%	78.6%	50.0%

## Association between outcome and MRI

The remission rates of groups of persistent and recurrent disease with positive/negative MRI finding prior to the second procedure are shown in Table 2. 29 patients whose MRI revealing the existence of pituitary adenoma achieved a successful outcome of the reoperation (Representative case, #19, Fig. 1). The other 7 patients who suffered from recurrent/persistent hypercortisolism without clear imaging evidence of tumor appearance also benefited from the reoperation (Representative case, #11, Fig. 2).

## Pathology

Respectively 15/27 (55.6%) and 7/15(46.7%) patients with recurrent and persistent hypercortisolism have ACTH-positive staining in the first pathological finding. In those who have achieved remission in the 2nd operation, 20 out of 29 patients has confirmed adenoma with positive ACTH staining in the pathology,

while 3 patients with adenoma was ACTH-negative. There are 5 patients did not get a remission even though they have a positive ACTH staining adenoma in the 2nd pathology. In the meanwhile, 5 patients achieved remission although no adenoma were found in their pathological specimens. Overall, the positive pathology of either the initial or the repeated surgery is not a quite significant predictor for the remission of the second surgery.

## Complications

4 of those 42 patients experienced postoperative major complications and underwent a medical or surgical intervention. Most patients recovered well after the second operation except in one case with persistent hypercortisolism where a severe intracranial infection led to death. Other 3 cases with CSF leakage related to the second operation were successfully surgical repaired afterwards.

## Discussion

In the present study, we reported outcomes for 42 patients undergoing repeat TSS for recurrent and persistent disease, achieving an overall remission rate of 69.0%. According to literatures, the immediate remission rate of the reoperation after recurrence is reported up to 87%[3, 9, 21], which is not lower than other second-line therapy such as radiation therapy and medical treatment. The recurrence rate of CD after the initial TSS is 10–25% with a follow-up time of 10 years[22–24]. Ram et al reported that the surgeon applied a second TSS right after the first once the postoperative serum cortisol level didn't meet the standard of remission. With an interval time of 1 to 6 weeks, 71% of those patients with persistent disease achieved immediate remission and 53% (9/17) are in a long-term remission[19]. The other authors showed a remission rate of 70% with the reoperation within 10 days[25]. Second TSS leads an additional 8% of the patients to long-term CD remission[6]. The recurrence groups have a slightly higher remission rate without significance comparing to the persistence groups in the present study. Similar finding is shown in a study of Ram implicating that the failure of the initial surgery suggested being more difficult to treat successfully with surgery than most patients with recurrence[19]. Therefore, the criteria of selecting the potential patients and the strategy of the reoperation are still worth discussing.

## Surgical strategy

The surgical strategy for the first-time operation of CD varies depending on the major concern of different pituitary surgeons. Some surgeons intend to preserve more normal gland in the surgery while others chasing higher remission rate. Selective adenectomy is a reasonable choice for the visible tumor. Several authors adopt a slight extended resection with a rim or sometimes 2-3mm like-normal tissue around the tumor, which could also be called as a partial hypohypsectomy[26, 27]. Hemi-hypohypsectomy is more common in the case that no tumor was identified in the operation, while the MRI or BIPSS indicating remarkable lateralization of the tumor origin[28]. The widely exploration on contralateral side should also be conducted in case of whose BIPSS results is inconsistent with those of MRI, as it might help to find the very tiny tumor. Regarding some author, more extend procedures including subtotal or sometimes total pituitary gland resection will be done to maximize the remission rate, which could be up to 75.9–81.8%

[27, 29]. It might be a reasonable recommendation where imaging/intraoperative findings are not definitive, considering that the negative impact on these reoperated patients with persistent hypercortisolism rather than hypopituitarism. It is interesting that the pathology confirm is pretty low in these cases with extended resection even though it showed a high remission rate. Now there seems to be a trend that surgeons performing less total hypophysectomy as this can lead to hypopituitarism[10, 29, 30], given that it might not apparently increase remission rate but decrease the quality of life[31].

## **MRI finding**

When it comes to radiology, we need to emphasize that negative MRI doesn't necessarily mean the inexistence of pituitary adenoma or a negative pathological result. A number of cases from Wagenmakers et al showed that the remission after the repeated transsphenoidal surgery was not predictable by having a positive finding on MRI before either the first or second operation[14]. Preoperative MRI provides reference for diagnosis of pituitary adenoma but has limited predictive function of prognosis of the patients[8], especially for the repeat operation in which the original anatomy structure is more or less destroyed in the initial surgery. A positive result of MR imaging before the second operation is supposed to provide confidence for the surgeons. The reported remission rate of the redone operation with a positive MRI respectively was up to 72.7%[14]. According to our study, the two positive-MRI groups with different initial surgical outcome show higher remission rate albeit non-significantly. Positive MRI finding suggests that better endocrinological outcomes are achieved by second operation in both recurrent and sustained group compared to those with negative imaging. Excellent remission rate (more than 80%) was achieved in the recurrent group with positive-MRI, and thus encourages a repeat TSS. Acceptable remission rate (over 60%) which is close to the alternative treatment options in the recurrence group with negative-MRI as well as persistence group with positive-MRI. It is noted that one patient with persisting CD and negative-MRI achieved remission after reoperation. Therefore, a second surgical treatment for these patients needs to be carefully considered whether it will be beneficial.

Generally, as for the recurrent or persistent cases of CD patients underwent an initial surgery, we regard MRI as a possible assistant method for decision making. A second operation is considered with visible lesion remain in the MRI under assumption that removal of residual tumor leads to remission of the disease. Meanwhile, some recurrent and persistent patients with negative MRI findings also benefit from a reoperation. Furthermore, the MRI has its limitations on revealing accurate structures of the original operated area. The distortion and cicatrization of the previous operation and material packing in sellar region lead to confusion[16, 17]. Unlike the considerable remission rate achieved after the initial operation despite a negative MRI, a reoperation without certain lesion detected on MRI has a dissatisfactory remission rate[2], parallel to the result in our study. Nevertheless, U.J. Knappe and D.K. Lüdecke[8] put forward different opinion about the significance of MRI that it was not usually helpful in determine the therapeutic strategies due to its low incidence of detecting of the existence of microadenomas (missed diagnosis in 38%-70% cases). However, the BIPSS in those cases where MRI provided no certain information of tumor is therefore critical for the surgeons to ascertain the pituitary origin of the disease[15, 32], although there's also a voice suggesting that MRI and BIPSS are not helpful in locating

the recurrent tumor[14]. It might not help to identify the tumor in cavernous sinus or other parasella regions.

## **Pathology**

By comparing the pathology results and remission situations of those recurrent patients as well as persisting patients, we failed to find any relation between pathology results and remission expectations. These findings are supported by series of Ram[19], with 11 of the 17 patients had no tumor found at the second procedure, and 6 of the 11 achieved remission. In the series of Marco Locatelli[15], 8 out of 12 patients had no tumor found at the second operation, and 5 had surgical remissions. Even in those remission cases, the positive rate of pathological exams is not as high as expected. There's no significant difference of remission rate between patients grouped by pathological results or one-to-one correspondence between histopathological confirmation and the surgical outcome[15]. So far, less evidence supports the prediction of the repeat operation outcome by either of two pathology results.

## **Other consideration/factors**

For the initial preoperative assessment with the BIPSS in those MRI negative cases is critical in providing confidence of increasing the remission rate as reconfirming the pituitary origin[15, 32], since prediction accuracy was high and remission rates were acceptable[33]. In the patients with recurrence and persistent hypercortisolism after their first operation, it is not easy to identify a solid lesion on MRI compared with the initial preoperative scanning. It is worth mentioning that BIPSS might provide more information especially for those who did not underwent this test before the first operation. Also, it might avoid unnecessary transsphenoidal surgery twice in patients with persistent hypercortisolism, by revealing a false positive for pituitary ACTH overproduction. The results of BIPSS have the potential value not only to confirm the pituitary origin in the condition that the first histology did not show an ACTH-positive staining, but also to guide the exploration and decision making for hemi-hypophysectomy or accessing into the cavernous sinus, especially for those without obvious tumor identified intraoperatively. A careful dissection is highly recommended on the side of obviously lateralized BIPSS result, which sometime also indicating the cavernous sinus invasion not shown on the MRI and the necessity of opening the medical wall to achieve an extended exploration. The predictive value of BIPSS lateralization in repeated surgery need further investigated although it is not optimal in native patients with Cushing's disease[34, 35].

In Burke's study, there was a comparison between the historic cohorts with microscope and current cohorts with endoscope[10]. Although the result did not show statistically significant difference in either remission or recurrence, a trend for better outcome was observed more common after the operation with endoscopy. On the basis of a study of Lonser et al[36], over 20% of CD patients have cavernous sinus invasion confirmed histologically. The authors advocated a complete resection including invaded sella dura and the medial cavernous sinus wall in experienced surgeons' hand. In fact, it is worth noting that endoscopy with magnification and lighting provide a panoramic view to perform extended exploration of the sella including the cavernous sinus, compared to the microscope-based approach. Micko et al demonstrated that endoscope allows radical inspection of the entire medial wall of the cavernous

sinus[37]. It increased the lateral angle of visualizations and facilitate the differentiation between tumor and other tissues. These advantages over microscopic transsphenoidal approach are critical for recurrent and unremitted cases, which still require larger size to verify the conclusion.

## **Other treatments adjunctive to the repeat surgery**

Medications being used for CD include centrally acting inhibitors of ACTH secretion including cabergoline and pasireotide, adrenal steroidogenesis inhibitors to block several steps in cortisol synthesis, as well as glucocorticoid-receptor antagonists[38]. They are typically only considered as methods of disease control prior to surgical resection, as well as adjunctive methods for the radiation therapy of persistent and recurrent disease. On the other hand, the literature has noted that Ketoconazole may also contribute to enhance tumor appearance on MRI to facilitate pituitary resection in some circumstance[39]. Castinetti et al. described that visible lesions may be identified on the MRI in one third of patients who undertook a Ketoconazole administration[40].

In literature, the reoperation for persistence cases without visible lesion on MRI is rarely satisfactory[41], whereas these patients may benefit from the radiosurgery by using the entire sellar region as a therapeutic target[5]. The hormonal normalization was achieved after radiosurgery in half of the cases, including those with negative MR finding[42]. In general, the outcome of radiosurgery and less commonly radiotherapy is more favorable particularly in MRI-negative cases with persistent hypercortisolism compared to the repeat surgery. It is plausible that complications may be less and length of stay in hospital may be shorter[43, 44]. Salvage TSS for refractory CD after radiation therapy has been reported rarely[45], owing to the difficulty of disruption of surgical landmarks, the formation of scar tissue, and the effects of preoperative radiotherapy[43].

Bilateral adrenalectomy is generally considered the ultima ratio in patients who fail to respond to all other treatment options. However, patients undergoing bilateral adrenalectomy will require lifelong surveillance of the corticotroph tumor progression leading to Nelson's syndrome via MRI and ACTH measurements. Most experts agree that selective transsphenoidal adenomectomy should be recommended as first-line therapy in patients with Nelson's syndrome before extrasellar expansion of the tumor occurs[46].

## **Limitations**

Similar to previous studies, our sample size was not large enough to conduct powerful statistical analyses. Some patient lost in follow-up very soon made the current study has limited long-term outcome. There is a trend of predictable value of positive preoperative MRI findings, which is not solid to support an apparent relationship. Some potential weakness of the present study also includes that the outcome is only focused on the biochemical benefits of the remission with the surgical intervention. And also, it might underestimate the risks of hypopituitarism and decreased quality of life. We admit that larger series are needed to further investigate the potential predict factors and the best surgical strategy.

## **Conclusions**

Patients with initial surgical treatment may experience hypercortisolism without a positive MRI finding no matter for recurrent or persistent disease. Our findings suggest that for most patients suffer from recurrence or persistence of CD, reoperation is supposed to be an option even with a negative MRI. However, we call on a comprehensive investigation on recurrent or persisting CD patients. Larger groups of surgical treated CD with long follow-up ought to be evaluated the outcome of reoperation and further confirmation of the appropriate selection criteria of repeated surgery especially for persistence patients.

## Statements And Declarations

### *Compliance with Ethical Standards*

This study involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. It was approved by the Ruijin Hospital ethics committee of the Shanghai Jiao Tong University School of Medicine (approval number 2020-64).

### *Informed consent*

The need for individual consent was waived by the committee.

### *Conflicts of interest*

The authors have no relevant financial or non-financial interests to disclose.

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### *Author Contributions*

Baofeng Wang and Yuhao Sun provided contribution to study conception and design. Shuying Zheng drafted the article. Jie Ren, Zhihong Zhong, Hong Jiang, Qingfang Sun, Tingwei Su and Weiqing Wang provided contributions to acquisition of data or analysis and interpretation of data. Baofeng Wang and Yuhao Sun revised it critically for important intellectual content. Yuhao Sun and Liuguan Bian take final responsibility for this article.

### *Data Availability Statement*

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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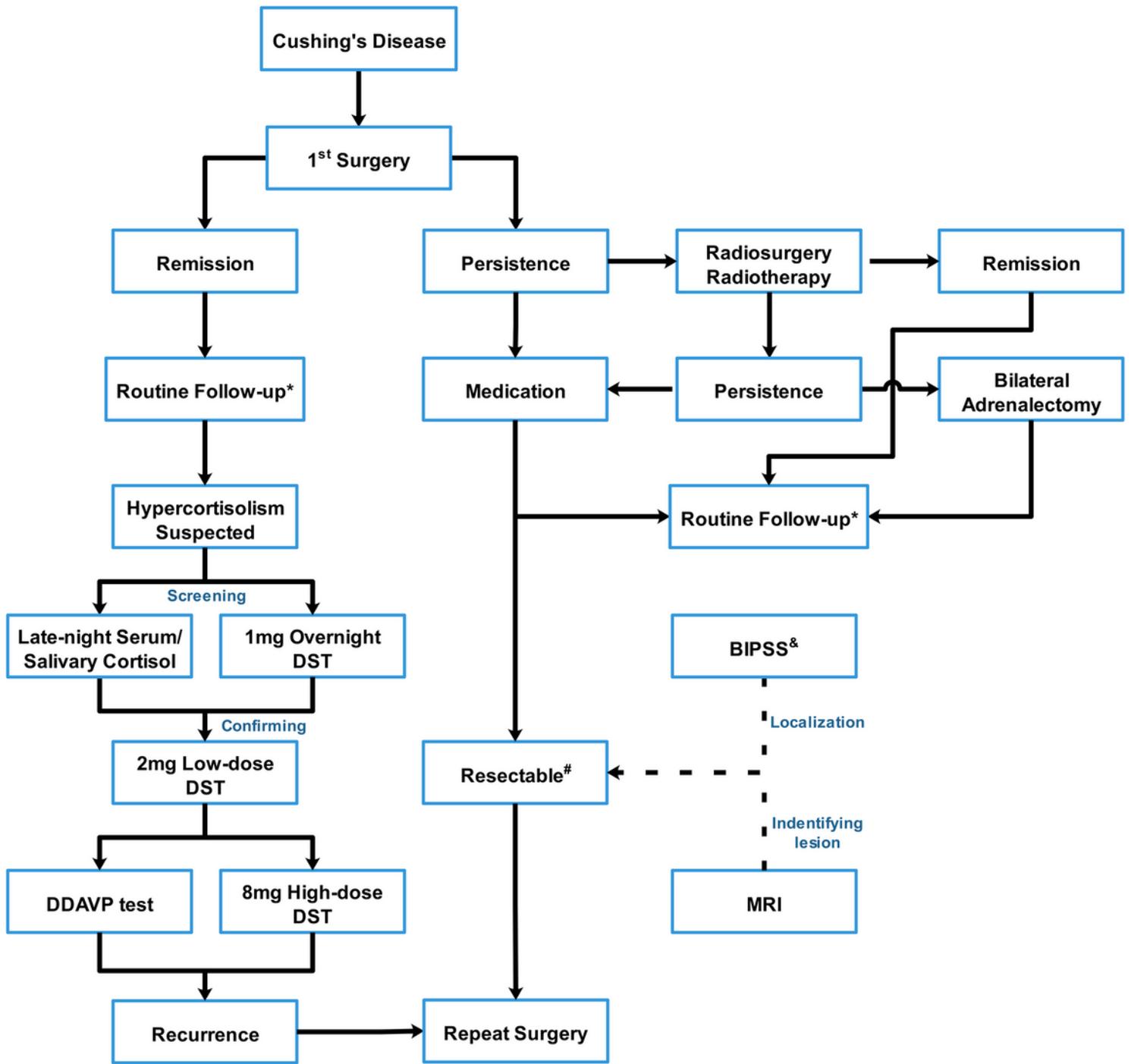
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## Figures



\*Biochemical assessment including 8AM serum cortisol, 24h-UFC and plasma ACTH

#Confirming pituitary origin for cases with absent or negative BIPSS results prior to the 1<sup>st</sup> surgery

#Confirmed by either positive BIPSS or MRI results

Figure 1

Algorithm of the biochemical assessment and treatment of persistent and recurrent Cushing's disease.

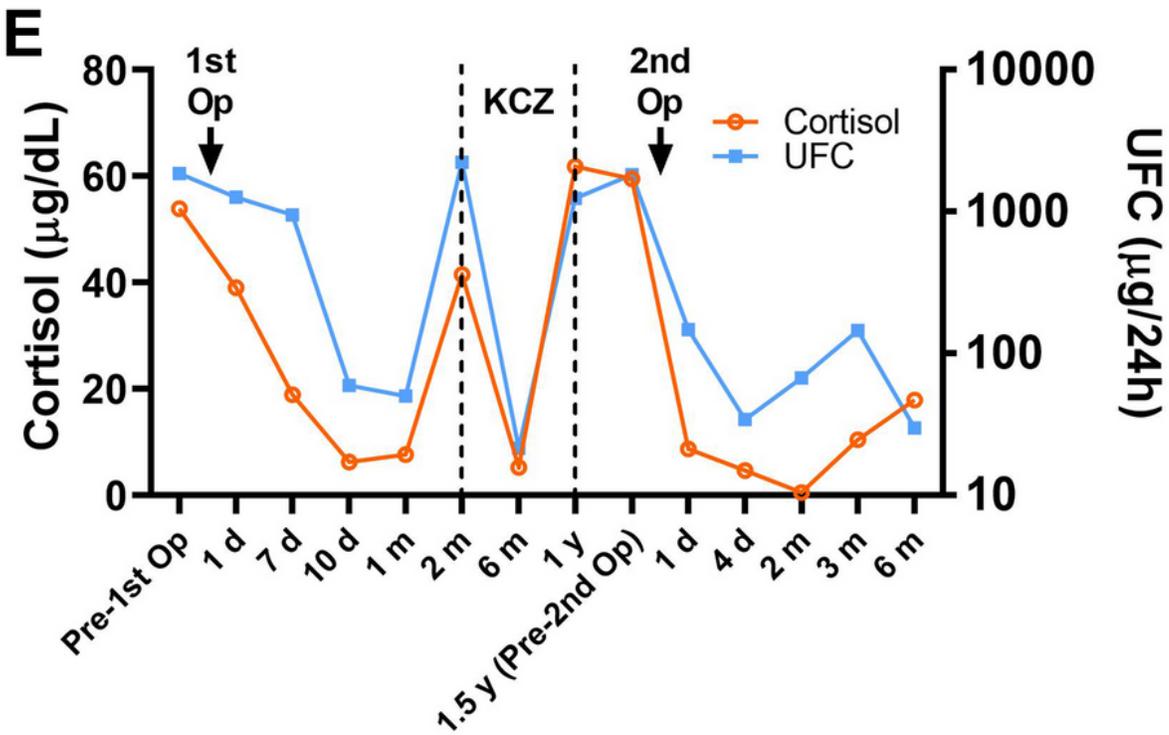
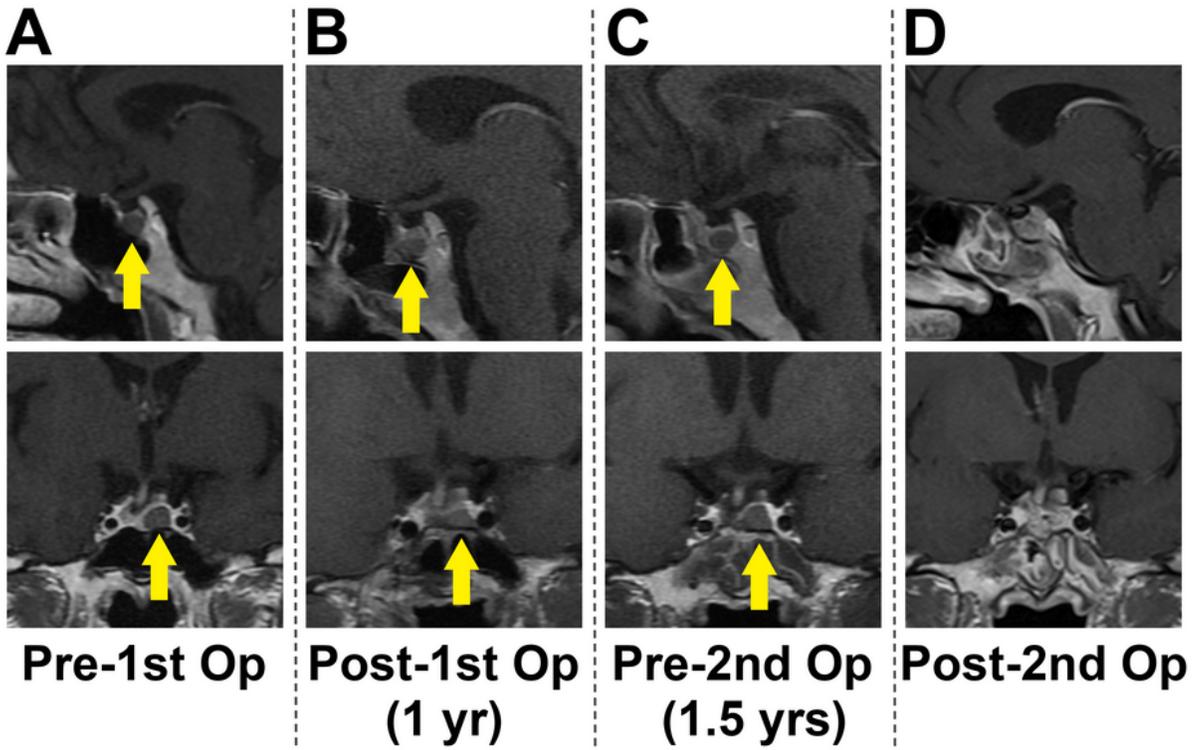


Figure 2

Preoperative and postoperative MR images throughout of the two operations (A-D) demonstrate an in situ relapsed intrasellar mass (yellow arrow). And biochemical results obtained before and after the operations (E) showed the tumor-related hormone change. KCZ, ketoconazole.

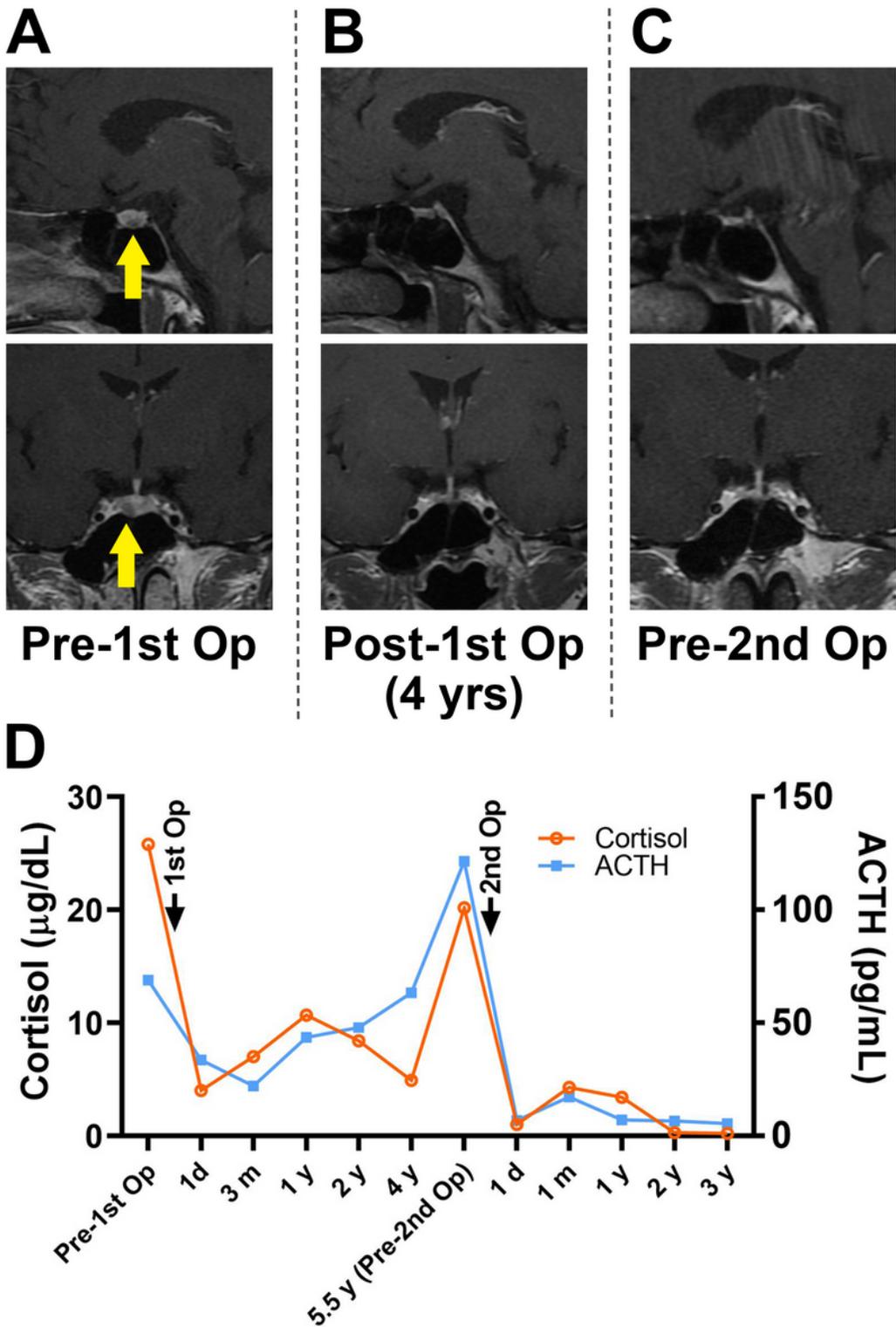


Figure 3

MR images (A) demonstrated a pituitary microadenoma on the left side (yellow arrow) before the first operation but not at the subsequent follow-ups (B & C). The biochemical results obtained before the second operations (D) revealed the hypercortisolism and indicated the relapse without obvious MRI confirmation.

## Supplementary Files

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