CLINICAL REVIEW: The Strategy of Immediate Reoperation for Transsphenoidal Surgery for Cushing’s Disease

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Context: Transsphenoidal surgery is currently the primary therapeutic option for Cushing’s disease. Despite considerable initial success, 10–30% of patients fail to achieve lasting remission.

Evidence Acquisition: We evaluated a strategy of immediate reoperation in surgical failures judged by plasma cortisol levels that did not fall to 2 μg/dl or less within 72 h of surgery. Of 215 patients with presumed ACTH microadenomas, treated between 1993 and 2004, 12 met inclusion criteria and had prompt (within 15 d) reoperation for residual or missed ACTH microadenoma. These 12 patients represent 28% of those who did not have evidence of postoperative adrenal insufficiency.

Evidence Synthesis: Based on an outcome measure of sustained subnormal or normal plasma cortisol levels, eight of 12 patients (67%) achieved remission from the two operations. Adjunctive therapies (radiotherapy, gamma knife radiosurgery, and adrenalectomy) led to remission in another three patients. It is recognized that this outcome required either total hypophysectomy (one patient) or postoperative hypopituitarism (all patients in remission).

Conclusion: Magnetic resonance imaging was not usually helpful in determining therapeutic strategies; however, inferior petrosal sinus sampling was critical in providing confidence that the disease was of pituitary origin. A treatment algorithm is recommended, based on this study.

CUSHING’S DISEASE IS defined as hypercortisolism caused by an ACTH-secreting pituitary adenoma. The majority of these tumors are microadenomas with a diameter of less than 10 mm.

At present, the therapy of choice for Cushing’s disease is selective transsphenoidal resection of an ACTH-secreting microadenoma, with reported rates of postoperative remission varying from 70–85%, a mortality rate of less than 1%, and morbidity of approximately 1.8% in major published series (1–8). Subnormal or undetectable levels of serum cortisol in the immediate postoperative period have been suggested as predictive of long-term remission (9–15). In cases of surgical failure, repeat exploration of the sella represents a treatment option that has been advocated by Hardy, Zervas, Trainer and colleagues, Oldfield and colleagues, and others (10, 16–19). Repeat surgical treatment several days after the first transsphenoidal operation allows the surgeon to reexplore the sella with minimal additional trauma and no major concern about altered surgical anatomy.

Few data are available from the literature on the effect of repeat transsphenoidal surgery for persistent Cushing’s disease (10, 16, 18, 19). In particular, only two studies have focused on the results and complications of this procedure when performed within a short interval of time after the first operative procedure (10, 19).

The aim of this study was to determine the safety and the potential efficacy of redo transsphenoidal surgery within 15 d of the first such operation in patients with persistent postoperative hypercortisolism.

 Patients and Methods

Between August 1993 and January 2004, 215 patients underwent an initial transsphenoidal operation for a presumed pituitary microadenoma associated with Cushing’s disease at the neuroendocrine unit of the University of Virginia Health Sciences Center. Twelve of the patients fulfilled the criteria for the study: persistently high postoperative serum cortisol levels, followed by a second transsphenoidal operation for ACTH-secreting pituitary adenoma within 2 wk of the first procedure. One of these 12 patients presented with recurrent Cushing’s disease after initial surgery elsewhere. A retrospective analysis of the patients’ records was conducted. The study included nine women and three men with a mean age of 37.4 yr (range, 21–61 yr). The mean follow-up was 27 months (range, 4–76 months).

The major symptoms and their frequency were typical (6) and reflected the severity of disease in this subset of Cushing’s disease patients; the average duration of symptoms was 40.2 months (range, 4–84 months).

The diagnosis of Cushing’s disease was based upon currently accepted laboratory criteria (20). The endocrinological tests were performed both at the neuroendocrine unit of the University of Virginia and at other institutions. In the latter case the results were confirmed by endocrinologists in our Pituitary/Neuroendocrine Center.

The diagnostic protocol included a magnetic resonance imaging (MRI) study of the sellar region, which was performed in all cases before surgery. The contrast-enhanced MRI scans (pituitary protocol) were examined by the reporting radiologist and the operating neurosurgeon. They were defined as negative when a normal gland and a normal sellar region were present, equivocal when it was possible to recognize subtle

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Abbreviations: CSF, Cerebrospinal fluid; IPSS, inferior petrosal sinus sampling; MRI, magnetic resonance imaging.

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changes suggestive, but not diagnostic, of adenoma, and positive when a tumor was identified.

The indication for inferior petrosal sinus sampling (IPSS) was related to the results of the endocrinological tests and the MRI. Eleven patients underwent IPSS preoperatively. This study was considered confirmatory of pituitary Cushing’s disease when the basal central to peripheral ACTH ratio was 2 or more or the CRH-stimulated central to peripheral ACTH ratio was 3 or more. The test was considered positive for lateralization when the side to side ACTH ratio was greater than 1.4 (21, 22).

The patients had unremarkable past medical histories, except for one who had undergone transphenoidal surgery elsewhere 2 yr before admission to our institution (she had developed recurrent Cushing’s disease after 1 yr of clinical remission). Two patients had had previous thyroid surgery for Graves’ disease and goiter, respectively.

A single surgeon performed each microsurgical transphenoidal operation via the endonasal [with the hemitransfixion or the pushover technique as previously described (23)] or sublabial route. When appropriate, endoscopic assistance was also used. Perioperative corticosteroid therapy was not administered. Our standard postoperative assessment after both the initial and second procedures consisted of the measurement of serum cortisol every 6 h for at least 3 d (14) or until serum cortisol, g/dl or less. Patients were defined as being in remission when they developed clinical symptoms and laboratory evidence of adrenal insufficiency (serum cortisol, ≤2 μg/dl). The level of postoperative serum cortisol for definition of remission was 2 μg/dl or less. The second transphenoidal operation was performed within 15 d of the first procedure; the median interval between the two procedures was 5.08 d (range, 3–14 d). Serum cortisol was again measured every 6 h after surgery to assess the outcome. If the serum cortisol declined to 2 μg/dl or less, glucocorticoid replacement therapy was instituted immediately. The patients were followed regularly to assess adrenal function and clinical symptoms.

Of the 215 patients treated by initial transphenoidal surgery, a total of 43 (20%) failed to achieve postoperative remission. Twelve of these patients had immediate reoperation. Among the others, five had undergone total hypophysectomy and did not have obvious ectopic paraspinal pituitary tumor on MRI; they were not offered another operation. Seven were treated with radiation therapy, all but one with the gamma knife; four of these had locally invasive tumors. Six had not had IPSS and were followed. Thirteen patients either refused repeat surgery or were not offered another procedure, usually because they had a decrease toward normal serum cortisol levels. Desire for fertility and concern about full pituitary replacement therapy were also factors considered. Of the 32 patients who were not treated by immediate reexploration, none was later operated upon transphenoidally.

### Results

The preoperative laboratory findings are presented in Table 1. In nine patients the MRI was defined as equivocal, in one it was clearly positive for the presence of a microadenoma, and two patients had normal imaging studies (negative). IPSS was performed in 11 of the 12 patients; in five cases excess ACTH production was lateralized to the right, and in three cases to the left, and there was no lateralization gradient in three patients. IPSS was not performed in the patient with the positive MRI scan who had typical clinical and diagnostic laboratory features of Cushing’s disease.

At initial surgery 11 patients were operated upon using the endonasal approach; in three cases the hemitransfixion submucosal technique was used, and in eight cases a septal pushover was employed. In one previously operated upon patient a sublabial approach was used. In two cases endoscopic assisted surgery was performed. At initial surgery the procedure was selective adenomectomy in three cases and hemihypophysectomy in nine cases.

Complications of the initial transphenoidal operation consisted of an alar tear in one case. Two patients had intraoperative cerebrospinal fluid (CSF) leaks successfully repaired using an abdominal fat graft.

In all cases the gross surgical findings were thought by the surgeon to be consistent with the presence of pathological tissue compatible with a microadenoma (size range, 2–8 mm). The initial pathology reports, however, were positive for ACTH adenoma in two cases and negative in 10 (Table 2).

Postoperative cortisol levels were above the 2 μg/ml cut-off level in all 12 patients.

The second operation was performed via the endonasal route in 10 cases (two cases by the hemitransfixion submucosal method and eight by the septal pushover technique). A sublabial approach was chosen in two cases. In 10 cases a total hypophysectomy was performed, and in two cases a subtotal hypophysectomy was completed (Table 3).

The complications of immediate reoperative surgery consisted of 10 cases of intraoperative CSF leak (all repaired by fat graft), a case of suspected transient meningitis (remission of symptoms within 2 d of antibiotic therapy), a superficial infection at a fat graft donor site, one case of nonfatal pulmonary embolism from a presumed deep venous thrombosis, and a urinary tract infection. The latter two complications occurred 5 d after the second operation in the same patient who had severe Cushing’s disease and cardiomyopathy.

At follow-up, eight of the 12 patients (67%) were in remission after the two transphenoidal operations; three other patients achieved remission after subsequent treatment (one patient underwent conventional radiotherapy of the sellar region, one bilateral adrenalectomy, and one gamma knife radiosurgery, followed by bilateral adrenalectomy). These three patients received medical therapy with ketoconazole, but it was discontinued in two patients because of liver toxicity and in one patient who failed to achieve a significant reduction of 24-h urinary free cortisol. The remaining patient, who had severe Cushing’s disease, died of heart failure before definitive therapy could be given. All 11 surviving patients are receiving appropriate hormonal replacement therapy.

### Discussion

Despite the high success rate of transphenoidal surgery for Cushing’s disease caused by ACTH microadenomas, it is
estimated that 10–30% of the patients fail to achieve long-term remission (18, 24, 25). Once a correct diagnosis of Cushing’s disease is made and ectopic sources of ACTH/CRH or pseudo-Cushing syndromes are excluded, two reasons for surgical failure (recurrent or persistent pituitary tumor and consequent endocrinopathy) can be identified. The first is the presence of residual tumor remaining hidden in the gland or ectopic in the intrasellar or perisellar region (25); the second

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<th>TABLE 2. Surgical and pathology findings of 12 patients with Cushing’s disease due to presumed ACTH microadenoma</th>
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ACTH, Pituitary adenoma immunopositive for ACTH; (CSF), intraoperative CSF leak; DVT, deep venous thrombosis; Adenomec, adenomec-tomy; Hemihypo, hemihypophysectomy; Hypophysect, total hypophysectomy; Micro, presumed microadenoma; R/L, right/left position of the adenoma in the pituitary gland; UTI, urinary tract infection.

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<th>TABLE 3. Postoperative evaluation of 12 patients with Cushing’s disease due to presumed ACTH microadenoma, after second transsphenoidal operation</th>
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Postoperative evaluation of 12 patients with Cushing’s disease due to ACTH microadenoma.

ACTH FU, ACTH at follow-up; bil adren, bilateral adrenalectomy; cort, corticosteroid replacement; gon, sex hormone replacement; γK, gamma knife; keto, ketoconazole; panhypo, panhypopituitarism; rad, conventional radiotherapy; SC FU, serum cortisol at follow-up; thy, thyroid hormone replacement.

a UFC normal at 29 (normal range, 5–47).
b Also present preoperatively (U, undetectable).
is residual invasive tumor within the dura mater of the sella turcica or of the cavernous sinus (24, 25).

In patients who are not cured by surgery, four therapeutic options remain: repeat transsphenoidal operation, medical therapy, radiation therapy (conventional or radiosurgery), and bilateral adrenalectomy. The optimum treatment or sequence of different treatments has not yet been established. Because of the serious effects of Cushing’s disease, hypercortisolism must be treated as promptly and effectively as possible with the fewest adverse effects.

The efficacy and toxicity of medical and radiation therapy have been assessed previously as well as those of repeat reexplanation of the sella (10, 18, 19). The role of immediate reoperation (within 15 d of the first operation) has rarely been investigated. Previous studies include those by Trainer et al. (10), who studied 10 patients with repeat surgery within 10 d, with a 70% remission rate. Ram and colleagues (19) reported on 17 patients who had a second operation 7–46 d after the first, with a 53% remission rate. The rationale of immediate reoperative transsphenoidal surgery is to remove the presumed residual accessible tumor or gland without the disadvantages (altered anatomy and scar tissue) of delayed surgery. This strategy, when successful, also limits the consequences of progressive Cushing’s disease. The presence of a positive IPSS test provides the surgeon with a significantly enhanced level of confidence when considering a secondary operative procedure.

After the two transsphenoidal operations, eight of our 12 patients (67%) are alive and in remission following surgical management alone. Three additional patients achieved remission after combined therapy.

Every reported series of transsphenoidal surgery for presumed ACTH-secreting microadenomas includes some 15–30% of patients in whom the histopathology is negative for tumor. This occurs even in patients with positive IPSS, and a significant proportion of these patients may achieve postoperative remission of Cushing’s disease. In Ram’s report of Oldfield’s series (19), 11 of the 17 patients had no tumor found at the second procedure, and six of the 11 achieved remission. In our series, eight of the 12 patients had no tumor found at the second operation, and five had surgical remissions. This phenomenon is often explained by the loss of the critical pathological material in the operative suction apparatus or in transport or handling in the pathology laboratory. It remains a vexing problem in the analysis of outcome.
In our patients the surgical complications consisted of one case of pulmonary embolism due to deep venous thrombosis, one urinary tract infection, a superficial abdominal (fat graft) wound infection, and one patient with suspected transient meningitis and an alar tear. An intraoperative CSF leak occurred in two patients during the first operation and in 10 patients during the immediate redo operation. There were no cases of persistent or delayed postoperative CSF leak. Moreover, no cases of operative mortality (30 d) or of classical major morbidity (vascular injury/occlusion, sellar abscess, complicated meningitis, sellar pneumatocele, cranial nerve palsy, visual loss, or CSF rhinorrhea) occurred.

This study highlights a number of different considerations. First, an interesting point arises from the MRI data. A large number of patients had nondiagnostic studies (11 of 12 cases). This finding partially explains the high number of IPSS procedures performed (11 of 12). Considering the reluctance of a surgeon to operate on a patient with an equivocal or negative MRI scan, a positive IPSS study is without any doubt a powerful factor, allowing the surgeon to feel more confident in recommending an operation.

It is generally true in neurosurgery and certainly true for transsphenoidal surgery that complication rates are higher with reoperations, and outcomes are generally less favorable than after the initial operation (26, 27). Although the small number of patients can be considered a limitation of this study, the balance between positive results and surgical complications suggests that immediate reoperative transsphenoidal surgery for pituitary Cushing’s should be considered a safe and effective therapeutic strategy.

The management of patients with Cushing’s disease who fail to achieve postoperative remission is difficult, poorly defined, and often discouraging. Accordingly, a therapeutic algorithm for the management of Cushing’s disease incorporating immediate reoperative transsphenoidal surgery in this process has been developed (Fig 1). This algorithm reflects our experience and our outcome data.

This algorithm is designed to be a guide rather than a rigid protocol. As mentioned above, many factors must be considered in making a recommendation for repeat surgery. These include the patient’s willingness to consider reoperation, severity of disease, desire for fertility, concern about replacement therapy, and risk factors related to Cushing’s and other concurrent disease. Obviously each patient is different, and each deserves a carefully considered recommendation for additional therapy.

It is important to note that successful management of this relatively uncommon, but often devastating, disease is most likely to occur in collaborative centers where experience in diagnosis, surgery, and adjunctive therapy is available.

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