OUTCOMES AFTER REPEAT TRANSSPHENOIDAL SURGERY FOR RECURRENT CUSHING'S DISEASE

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OBJECTIVE: To systematically analyze patient outcomes after repeat transsphenoidal (TS) surgery for recurrent Cushing's disease.

METHODS: We retrospectively reviewed records of all patients with recurrent Cushing's disease who underwent repeat TS surgery for resection of a pituitary corticotroph adenoma at the University of Virginia Medical Center from 1992 to 2006. Remission at follow-up was defined as a normal postoperative 24-hour urine free cortisol, or continued need for glucocorticoid replacement after repeat TS surgery. Recurrence of the disease was defined as an elevated 24-hour urine free cortisol with clinical symptoms consistent with Cushing's disease while not receiving glucocorticoid replacement. Multivariate logistic regression was performed to evaluate the effect of potential predictors on remission. Recurrence rates, subsequent treatments, and the final endocrine status of the patients are presented.

RESULTS: We identified 36 patients who underwent repeat TS surgery for recurrent Cushing's disease. The mean age of the patients was 40.3 years (range, 17.1–63.0 yr), and 26 were women. The median time to recurrence after initial successful TS surgery was 36 months (range, 4 mo–16 yr). Remission after repeat TS surgery was observed in 22 (61%) of the 36 patients. During the same time period, of the 338 patients who underwent first-time TS surgery for Cushing's disease, remission was achieved in 289 (85.5%). The odds of failure (to achieve remission) for patients with repeat TS surgery for recurrent Cushing's disease were 3.7 times that of patients undergoing first-time TS surgery (odds ratio, 3.7; 95% confidence interval, 1.8–7.8). Two of the 22 patients with successful repeat TS surgery had a second recurrence at 6 and 11 months, respectively. Complete biochemical and clinical remission after stereotactic radiosurgery, adrenalectomy, and ongoing ketoconazole therapy was achieved in 30 (83.3%) of the 36 patients, and active disease continued in 6 patients (16.7%).

CONCLUSION: Although the success of repeat TS surgery for recurrence of Cushing's disease is less than that of initial surgery, a second procedure offers a reasonable possibility of immediate remission. If the operation is not successful, other treatments, including pituitary radiation, medical therapy, and even bilateral adrenalectomy, are required.

KEY WORDS: Cushing's disease, Recurrence, Remission, Repeat transsphenoidal surgery

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Successful long-term management of patients with recurrent Cushing's disease after initial successful transsphenoidal (TS) surgery remains a major challenge. Several large studies have reported a recurrence rate of 5 to 27% after initial successful TS surgery (3, 7, 11, 15, 17). Given that Cushing's disease has a 5-year cardiovascular mortality rate of 50%, achieving remission in patients with recurrent disease is paramount (12). The treatment modal-

ABBREVIATIONS: ACTH, adrenocorticotropic hormone; **CSF**, cerebrospinal fluid; **CT**, computed tomography; **DI**, diabetes insipidus; **GK**, gamma knife; **H & E**, hematoxylin and eosin; **MRI**, magnetic resonance imaging; **TS**, transsphenoidal; **UFC**, urine free cortisol

ities used after recurrence include repeat TS surgery, medical therapy to inhibit adrenal function, targeted radiotherapy/radiosurgery, and bilateral adrenalectomy (9, 14, 16).

Few studies have specifically reported outcomes of patients who undergo repeat TS surgery after recurrence of Cushing's disease (1, 5, 6, 9). Some surgeons have advocated repeat selective adenomectomy, whereas others have recommended a more aggressive reoperation. Hofmann et al. (6) reported remission in 6 of 13 patients with recurrent disease after selective TS adenomectomy. They reported no increased endocrine deficits or major complications after repeat TS surgery. However, other authors with more aggressive surgical strategies have reported up to a 45% rate of postoperative panhypopituitarism (10) and a 16% incidence of cerebrospinal fluid (CSF) leak and meningitis (9).

In this study, we report outcomes of 36 patients treated with repeat TS surgery for recurrent Cushing's disease. The selection criteria for repeat TS surgery, postoperative outcomes, and the role and efficacy of other treatment modalities are discussed.

PATIENTS AND METHODS

Inclusion Criteria

Patients with recurrent Cushing's disease who underwent repeat TS surgery at the University of Virginia Medical Center between 1992 and 2006 were analyzed. Inclusion criteria included documented remission (normal 24-h urine free cortisol [UFC]) for at least 3 months before subsequent recurrence. In addition, all patients included in our series were on cortisol replacement before their recurrence/reoperation.

Diagnostic Criteria

Each patient was carefully screened before repeat TS surgery was offered. An elevated 24-hour UFC level was used to establish hypercortisolemia and recurrence of Cushing's disease in all patients. Only patients who had clinical and biochemical recurrence as well as the following were offered repeat TS surgery: 1) histopathological confirmation of an adrenocorticotropic hormone (ACTH)-staining tumor at initial surgery, 2) recurrence of tumor on magnetic resonance imaging (MRI), or 3) centralized ACTH gradient on inferior petrosal sinus sampling and high-dose dexamethasone suppression.

Surgical Management

All operations were performed by a single neurosurgeon (ERL). The surgical technique and strategy used have been described in detail previously (13). Briefly, resection was performed via the TS approach using the operative microscope. After the sella was exposed and the dura was incised, the entire pituitary gland was carefully examined, and all abnormal tissue was submitted to pathological examination. Aggressiveness of surgery was individualized, taking into account patient characteristics, preoperative morbidity, severity of clinical symptoms, and patient preference. For example, given that one surgery had already failed in these patients, if their clinical symptoms were severe and if they had significant preoperative comorbidities, a total hypophysectomy was recommended to them.

Specimen Handling and Histological Analysis

Resected specimens were immediately placed on a moist dressing, bagged, and submitted in their entirety to a neuropathologist (13). A hematoxylin and eosin (H & E) stain was initially used to evaluate loss of acinar organization. If a pituitary adenoma was not identified on the H & E stain, a "Cushing's panel" was ordered. This consisted of 30 sequential 5-μm-thick sections with every third slide stained with H & E. Intervening unstained sections were stained for reticulin and ACTH if the adjacent H & E sections were suspicious for adenoma. If no adenoma was identified, more "Cushing's panels" were ordered until the tissue block was exhausted (13).

Endocrine Follow-up and Remission Criteria

A senior neuroendocrinologist supervised the endocrine evaluation of all patients. Patients did not receive any exogenous glucocorticoids pre- or intraoperatively. Postoperatively, glucocorticoids were administered to patients only after adrenal insufficiency was confirmed by determination of a serum cortisol level of less than 5. Remission at follow-up was defined as a normal postoperative 24-hour UFC or continued need for glucocorticoid replacement after TS surgery. Recurrence was defined as an elevated 24-hour UFC with clinical signs and symptoms consistent with Cushing's disease.

Laboratory Analysis

ACTH was measured by chemiluminescence immunoassay, and UFC was analyzed by immunoassay.

Statistical Analysis

Descriptive statistics such as mean age, mean length of follow-up, percentage of patients in remission after repeat TS surgery, and percentage of patients with recurrence were tabulated. For patients who underwent treatment with other modalities, the response to those treatments was analyzed. Logistic regression was performed to evaluate the effect of potential predictors, including age, sex, magnetic resonance imaging (MRI) appearance, tumor identification at surgery, extent of surgical resection, and pathology on remission. Remission rates after initial TS surgery and after repeat TS surgery for recurrent Cushing's disease were compared using χ^2 analysis. A probability value of less than 0.05 was considered significant. Statistical analysis was performed using SAS software (version 9.1; (SAS Institute, Inc., Cary, NC).

RESULTS

Of the 455 patients who underwent TS surgery for Cushing's disease between 1992 and 2006, 40 patients were identified as having undergone repeat TS surgery for recurrent Cushing's disease. Follow-up endocrine evaluation was available in 36 of the 40 patients. The mean age of the patients was 40.3 years (range, 17.1–63.0 yr), and 26 patients were women (*Table 1*). The mean duration of follow-up from the second operation was 36 months (median, 24 mo; range, 2–126 mo). All 36 patients had biochemical and clinical recurrence of Cushing's disease. Thirty-one patients had pathology reports that verified the presence of an ACTH-staining tumor at the initial TS surgery. Of the remaining five patients, three had an MRI-confirmed recurrence, whereas the other two had positive inferior petrosal sinus sampling studies and high-dose dexamethasone suppression. None of the patients in this series had tumors with cavernous sinus invasion on MRI or at surgery.

The average time between successful initial TS surgery and recurrence of symptoms was 53.1 months (median, 36 mo;

TABLE 1. Preoperative characteristics of patients who underwent repeat transsphenoidal surgery for recurrent Cushing's disease (n = 36)[a]

Characteristic	Value (range or %)
Mean age (yr)	40.3 (17.1–63.0)
Sex	
Male	10 (27.8%)
Female	26 (72.2%)
Pathology at initial operation	
Positive for ACTH-staining tumor	31 (86.1%)
Negative for ACTH-staining tumor	2 (5.56%)
Unknown	3 (8.33%)
Mean remission time (mo)	53.1 (4–192)
Laboratory values	
Serum ACTH (pg/mL)	111.2 (12–1180)
24-h UFC (μg/24 h)	361.6 (59–2253)
Preoperative MRI findings	
Microadenoma	23(63.9%)
Macroadenoma	3 (8.33%)
Negative for tumor presence	10 (27.8%)

[a] ACTH, adrenocorticotropic hormone; UFC, urine free cortisol; MRI, magnetic resonance imaging.

TABLE 2. Potential preoperative and intraoperative predictors of remission after repeat transsphenoidal surgery for recurrent Cushing's disease[a]

Potential predictors of disease remission	No. of patients (n = 36)	No. of patients in remission after repeat TS surgery (remission rate)
Radiographic appearance on MRI		
Microadenoma	23	13 (56.5%)
Macroadenoma	3	0
Negative MRI	10	9 (90%)
Extent of resection		
Selective adenomectomy	24	14 (58.3%)
Hemihypophysectomy	1	0
Subtotal hypophysectomy	6	4 (66.7%)
Total hypophysectomy	5	4 (80.0%)
Final pathology		
Positive for ACTH-staining tumor	24	12 (50.0%)
Negative for ACTH-staining tumor	12	10 (83.3%)
Intraoperative identification of lesion		
Positive identification of tumor	32	19 (59.5%)
Tissue suspicious for tumor	3	2 (66.7%)
No tumor seen intraoperatively	1	1 (100 %)

[a] TS, transsphenoidal; MRI, magnetic resonance imaging; ACTH, adrenocorticotropic hormone.

range, 4 mo–16 yr). The mean preoperative 24-hour UFC and ACTH were 361.6 μg/24 h (range, 59–2253 μg/24 h) and 111.2 pg/mL (range, 12–1180 pg/ml), respectively. Preoperative MRI findings revealed 23 patients with microadenomas, 3 patients with macroadenomas, and 10 patients with no evidence of tumor on MRI.

Of the 36 patients confirmed to have recurrent Cushing's disease, 24 underwent selective adenomectomies, 1 had a hemihypophysectomy, 6 had subtotal hypophysectomies, and 5 had total hypophysectomies. Intraoperatively, the neurosurgeon visually identified a tumor in 32 patients, encountered tissue suspicious for tumor in 3 patients, and did not visualize any abnormal tissue in 1 patient. The pathological examination confirmed the presence of an ACTH-staining tumor in 24 patients and was negative for ACTH-staining tumor in 12 patients (*Table 2*).

Outcomes

Of the 36 patients who underwent repeat TS surgery for recurrent Cushing's disease, 22 patients (61.1%) were found to be in remission after surgery. During the same time period, remission was attained in 289 (85.5%) of the 338 patients who underwent first-time TS surgery for Cushing's disease. Patients who underwent repeat TS surgery for recurrence were less likely to achieve postoperative remission than patients who had first-time TS surgery (a failure rate of 39.9 versus 14.5%, respectively, $P = 0.0005$). The odds of failure (to achieve remission) for patients with repeat TS surgery were 3.7 times that of patients undergoing first-time TS surgery (odds ratio, 3.7; 95% confidence interval, 1.8–7.8).

Fourteen patients (38.9%) did not achieve remission after repeat TS surgery and, hence, required further treatments (*Fig. 1*). Of these 14 patients, 12 underwent gamma knife (GK) radiosurgery (the other 2 patients were offered radiosurgery and are deliberating their treatment options). Five (41.7%) of the 12 patients attained remission after radiosurgery. An additional three patients achieved remission on ketoconazole, and one patient obtained remission after bilateral adrenalectomy. The remaining three patients who were treated with radiosurgery, the two patients who are yet to undergo further treatment, and the one patient who had a second recurrence of Cushing's disease, continue to have active disease (*Fig. 1*). Hence, final biochemical and clinical remission was achieved in 30 (83.3%) of the 36 patients after repeat TS surgery and, if required, GK radiosurgery, ketoconazole, and/or bilateral adrenalectomy.

Of the 22 patients in remission after repeat TS surgery, 2 (9.1%) subsequently experienced recurrences after being in remission for 6 and 11 months, respectively. The two patients who had recurrences both had negative preoperative MRI scans, positive ACTH-staining pathology, and positive identification of tumor at time of surgery. One of them underwent a selective adenomectomy and the other a total hypophysectomy. Both patients were treated with GK radiosurgery after the sec-

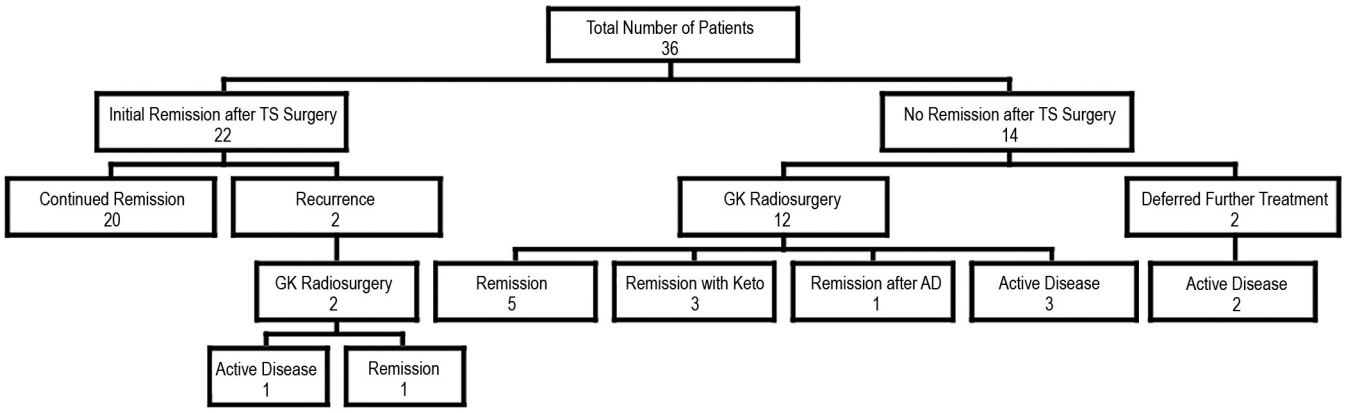

FIGURE 1. *Flowchart summarizing management and treatment outcomes of patients with recurrent Cushing's disease.* GK, *gamma knife;* Keto, *ketoconazole;* TS, *transsphenoidal;* AD, *bilateral adrenalectomy.*

ond recurrence. At present, both are receiving ketoconazole therapy; one patient is in biochemical and clinical remission, whereas the other has active disease but satisfactory control of clinical symptoms.

Multivariate logistic regression showed that age ($P = 0.94$), sex ($P = 0.59$), MRI-confirmed microadenoma ($P = 0.43$), tumor identification at surgery ($P = 0.50$), selective adenomectomy ($P = 0.66$), and pathology positive for an ACTH-staining tumor ($P = 0.21$) did not significantly predict remission after repeat surgery. All three patients with macroadenomas failed to achieve remission, and these patients were associated with a higher risk of failure after repeat TS surgery ($P = 0.02$).

Complications

Complications from TS surgery included diabetes insipidus (DI) and panhypopituitarism. New-onset DI was diagnosed in six patients (two patients had transient DI, and four had permanent DI). Postoperative panhypopituitarism occurred in 2 patients (6.5%) (excluding those who underwent total hypophysectomy). None of the operations were complicated by a CSF leak, meningitis, vessel injury, or other major complication.

DISCUSSION

We have reported outcomes of 36 patients with recurrent Cushing's disease who underwent repeat TS surgery. Remission was achieved in 61% of patients after repeat TS surgery and in 83% after additional treatments. The odds of remission for patients who underwent repeat TS surgery for recurrent Cushing's disease were nearly fourfold lower than for patients who had first-time TS surgery. Few small studies have specifically analyzed and reported outcomes of patients with recurrent Cushing's disease. Knappe and Lüdecke (9) found that 17 (70.8%) of 24 patients treated with repeat TS surgery for recurrent hypercortisolism entered biochemical remission. After additional treatments (radiation therapy and adrenalectomy), 21 (87.5%) of their 24 patients achieved final biochemical remission. Hofmann et al. (6) performed a similar study, in which 6 (46%) of 13 patients with recurrent Cushing's disease obtained remission after repeat selective adenomectomy. After delivery of adjuvant therapy, their remission rate increased to 77% (6).

In our study, with a mean follow-up period of 3 years, 2 (9.1%) of the 22 patients who achieved remission after repeat TS surgery had a second recurrence. The second recurrence was diagnosed after 6 and 11 months of remission, respectively. The incidence of a second recurrence after repeat TS surgery has not been widely reported and has ranged from 0 to 23.5%. Knappe and Lüdecke (9) found four (23.5%) of 17 patients with a second recurrence after initial successful repeat TS surgery, whereas Hofmann et al. (6) reported no recurrences in six patients treated with repeat TS surgery and followed for a mean of 23 months. Finally, Friedman et al. (5) reported that three (13%) of the 24 patients who were in remission after repeat surgery developed recurrent hypercortisolism 10 to 47 months after surgery.

The prognostic value of pre- and intraoperative findings in predicting outcomes of patients with recurrent Cushing's disease is not well studied. Friedman et al. (5) were able to demonstrate that intraoperative tumor identification and preoperative computed tomographic (CT) evidence of inadequate exposure of the sella at the time of a previous surgery were helpful indicators for selecting patients who may benefit from additional surgery. In our analysis, we failed to find a significant effect of patient age, sex, preoperative MRI findings, intraoperative tumor identification, extent of surgical resection, and tumor pathology on postoperative surgical remission. All three patients with macroadenomas identified on preoperative MRI failed to achieve remission after repeat TS surgery. Hence, the presence of a macroadenoma was the only significant predictor of poor outcome in our study.

Complications after repeat TS surgery include hypopituitarism, DI, carotid injury, CSF leak, and meningitis. Chee et al. (3) reported a significantly higher incidence of CSF rhinorrhea

in patients who underwent repeat TS surgery, compared with patients who underwent initial TS surgery (46 versus 13%). CSF leak and meningitis rates of more than 16% with repeat TS surgery have been published (9). In our series, none of the patients developed a CSF leak or meningitis. In addition to CSF rhinorrhea, some authors have reported a high rate of panhypopituitarism (45.5%) after an aggressive reoperation strategy (10). In our study, none of the patients who underwent a selective adenomectomy developed postoperative panhypopituitarism. All patients who had a total hypophysectomy and 6.5% of patients who had a partial hypophysectomy developed postoperative panhypopituitarism. Similar to our experience, Hofmann et al. (6) reported no significant deterioration of pituitary function or serious morbidity after repeat TS surgery. Our data support the belief that meticulous, systematic resection of a recurrent ACTH-secreting tumor by an experienced pituitary surgeon yields a complication rate similar to that seen after initial TS surgery.

In our study, approximately 39% of patients with recurrent Cushing's disease did not achieve remission after repeat TS surgery. Hence, additional treatments with other therapeutic modalities were required in these patients. Patients who did not achieve remission after repeat TS surgery were offered GK stereotactic radiosurgery. In our study, 42% of patients treated with GK radiosurgery achieved remission. This remission rate is similar to that described by other large radiosurgical series (2, 4, 8). Adrenal function was suppressed with ketoconazole in patients who did not achieve remission after surgery and radiosurgery. Patients who failed all the above treatments were offered bilateral laparoscopic adrenalectomy. Remission after repeat TS surgery and, if necessary, additional treatments (GK radiosurgery, ketoconazole therapy, and adrenalectomy) was achieved in the majority of patients (83%). These results emphasize the importance and necessity of a multidisciplinary, multispecialty team for managing Cushing's disease.

CONCLUSION

For carefully selected patients with recurrent Cushing's disease, repeat TS surgery is a safe and effective treatment. However, remission rates after repeat TS surgery are significantly lower than those achieved after initial TS surgery. Therefore, a multidisciplinary team that can offer multiple treatment modalities is essential for the successful management of patients with recurrent Cushing's disease.

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COMMENTS

The outcome of patients undergoing repeat transsphenoidal surgery for recurrent Cushing's disease (CD) is reviewed by Dr. Laws and his highly experienced team. Of 36 patients, 61% achieved biochemical remission by surgery alone. Ultimately remission was achieved in 83% of patients using multimodality therapy consisting of radiosurgery, bilateral adrenalectomy, and/or ketoconazole. There were no significant surgical complications other than a relatively low rate of expected new hypopituitarism. These excellent results support the assertion that in experienced hands, repeat transsphenoidal surgery is safe and effective for achieving re-remission in the majority of patients; however, in a sizable minority, multimodality therapy is still needed to regain remission. Finally, their experience reminds us that long-term regular follow-up is essential for our patients with CD, given that there may be a recurrence well over a decade after initially successful surgery.

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CD is a rare condition that demands significant dedicated medical and surgical expertise. The authors present a carefully considered report of outcomes in the rather challenging scenario of recurrent CD. Of note, no patients developed a cerebrospinal fluid leak, which can result with reoperations or aggressive surgery (e.g., extended explo-

rations or hypophysectomy in a reoperative field). Recurrences after second operations also responded well to adjuvant therapies. This result argues for concentration and regionalization of practitioners and investigators. Novel insights into basic and applied biology to treat hypercortisolism will probably provide additional options in the future

Nelson M. Oyesiku
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This is an excellent review of repeat surgery for recurrent CD. Several points are made and should be emphasized. First, before patients can be considered to have recurrent disease, they must have had a remission resulting from the first surgery and adjunctive therapy, if given. Remissions are well defined here, and these guidelines should be followed by all who treat patients with CD. Second, the operation can be performed by those with experience without an increased incidence of complications. Third, the success rate is not nearly as high as it is for the first operation, but it is still 61% here, which is excellent for recurrent disease and makes the very low incidence of complications acceptable. The response to surgery is much more rapid than that with any other treatment plan, and the operation will not interfere with plans for adjunctive therapy if it is not successful. The goal with CD is that the disease must be brought into remission and that may require different modalities at different times, but primary removal of the adenoma, if possible, is by far the best alternative. Furthermore, patients must be followed for very long periods as there may be a recurrence very late after treatment.

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This study, coming from one of the most renewed pituitary centers and from the most experienced "pituitary neurosurgeon," reviews the outcomes of patients undergoing reoperation for recurrent CD. It is known that remission rates range from 64 to 93%, with the highest rates of 86 to 98% in patients with magnetic resonance imaging-defined noninvasive microadenomas treated with primary transsphenoidal tumor removal (1). On the other hand, repeat transsphenoidal surgery usually represents a challenging task in CD, especially if the surgical route is via a submucosal transseptal approach. Nevertheless, as demonstrated by this study, reoperation may help a relatively important percentage of patients and still cure them, especially if we consider that no definitive medical treatment exists for CD and the alternative to repeat surgery is radiotherapy and/or bilateral adrenalectomy.

I agree with the authors when they state that in experienced hands reoperation does not yield a higher complication rate than that for the initial surgery. The surgeon, the endocrinologist, and the patient should all be aware of this fact before considering the alternative of radiotherapy, adrenalectomy, or both.

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Paolo Cappabianca
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