Outcome of Transsphenoidal Surgery for Cushing Disease: A Single-Center Experience Over 32 Years

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BACKGROUND: Transsphenoidal surgery is the standard approach for treating Cushing disease. Evidence is needed to document effectiveness.

OBJECTIVE: To analyze results of transsphenoidal surgery in 276 consecutive patients, including 19 children.

METHODS: Medical records were reviewed for patients treated initially with surgery for Cushing disease from 1980 to 2012. Radiographic features, pathology, remissions, recurrences, and complications were recorded. Patients were categorized for statistical analysis based on tumor size (microadenomas, macroadenomas, and negative imaging) and remission type (type 1 = morning cortisol ≤3 μg/dL; type 2 = morning cortisol normal).

RESULTS: Females comprised 78% of patients and were older than men. Imaging showed 50% microadenomas, 13% macroadenomas, and 37% negative for tumor. Remission rates for microadenomas, macroadenomas, and negative imaging were 89%, 66%, and 71%, respectively. Patients with microadenomas were more likely to have type 1 remission. Pathology showed adrenocorticotropic hormone-secreting adenomas in 82% of microadenomas, in 100% of macroadenomas, and in 43% of negative imaging. The incidence of hyperplasia was 8%. The finding of hyperplasia or no tumor on pathology predicted treatment failure. The recurrence rate was 17%, with an average time to recurrence of 4.0 years. Patients with type 1 remission had a lower rate of recurrence (13% type 1 vs 50% type 2) and a longer time to recurrence. Children had similar imaging findings, remission rates, and pathology. There were no operative deaths.

CONCLUSION: Transsphenoidal surgery provides a safe and effective treatment for Cushing disease. For both adults and children, the best outcomes occurred in patients with microadenomas and/or those with type 1 remission.

KEY WORDS: Cushing disease, Microadenoma, Pituitary tumor, Transsphenoidal surgery

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The initial treatment of pituitary-dependent Cushing disease remains the surgical removal of the adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma causing the disease. Fortunately, in most situations, the benign tumor is small and can be safely and effectively removed surgically. This article does not focus on the still-considerable challenges in reaching the diagnosis of pituitary-dependent Cushing disease, but rather on the outcomes of surgery in adults and children. Of all the patients who undergo transsphenoidal surgery for pituitary adenomas, patients with Cushing disease still pose the greatest challenge to the surgeon. Nearly 40% of patients have a negative result on magnetic resonance imaging (MRI) and therefore rely on the judgment of the surgeon to identify very small microadenomas within normal-appearing pituitary glands. Even though inferior petrosal sinus sampling (IPSS) can verify the etiology of the hypercortisolism to the pituitary and can predict the sidedness of a microadenoma by 70%, finding a nonimageable microadenoma remains a challenge. Many patients are young women of child-bearing age to whom the preservation of a functioning pituitary postoperatively is very

ABBREVIATIONS: ACTH, adrenocorticotropic hormone; **IPSS,** inferior petrosal sinus sampling

important. Preserving complete pituitary function is, of course, a goal in every patient. The challenge for the surgeon lies in the balance between being aggressive in the face of a debilitating disease and a more conservative approach to retain pituitary function.

In this article, we review outcomes after surgery including remission, pathology, and recurrence in 276 consecutive patients operated on at 1 institution by a single surgeon. Initial postoperative remissions are reviewed in relationship to the size of the tumors on preoperative MRI and recurrences are considered in relationship to the initial level of remission as well as pathology and size of the tumors. The 19 children in this series are separated out to look for any differences between adults and children.

METHODS

Approval for this study was granted by the university institutional review board.

Patient Identification and Data Collection

We reviewed medical records and imaging studies of 276 consecutive patients undergoing an initial microscopic transsphenoidal operative procedure for Cushing disease as performed by a single surgeon (first author) at a university hospital. These patients were operated on between the years 1980 and 2012. Clinical information collected included patient age, sex, presenting symptoms, preoperative serum and urinary free cortisol, ACTH levels, imaging characteristics, operative findings, pathology, immediate and delayed postoperative cortisol and ACTH, and recurrence status. Microadenomas were defined as tumors less than or equal to 10 mm at the greatest dimension; macroadenomas were greater than 10 mm. Patients with negative imaging had no discernable tumor identified on preoperative contrast-enhanced computed tomography (CT) or MRI. When the 28 patients treated before 1988 with only CT-negative imaging were eliminated, the remission rate in the remaining 75 with MRI-negative imaging was unchanged. The inclusion of CT-negative patients in this series does not change the percentage of negative imaging and, thus, should not bias the results.

Preoperative laboratory studies were reviewed to verify the diagnosis, and the postoperative laboratory studies were reviewed to judge the presence or absence of biochemical evidence of disease remission. All patients were studied preoperatively and followed postoperatively by an expert pituitary endocrinologist. Postoperatively, patients were routinely assessed at 2 days, 1 and 3 months, and then every 6 months. Because IPSS did not become routine until the early 1990s, we did not analyze those results in this report. Since 1991, we have routinely performed IPSS in every instance in which a distinct adenoma could not be imaged on MRI. When a significant gradient in ACTH between peripheral blood and petrosal sinus blood was present, we assumed that the pituitary was the source of the hypercortisolism. Sidedness of the gradient directed the initial side of exploration during surgery.

One patient was eliminated from the study because of the lack of postoperative information. Patients aged 17 years and under were considered to be children for this analysis. This is the most common age used in previously reported series.[1-5]

Evaluation of Treatment Response

Similar to our previous report,[6] patients believed to be in remission were further subdivided into those with adrenal insufficiency (type 1) and those with normal cortisol levels (type 2). Patients in the type 1 group had cortisol levels of 3 μg/dL or less and usually felt poorly without cortisol replacement. Those in the type 2 group had morning cortisol levels that were markedly reduced from their preoperative levels and were within the normal laboratory range. Patients in both type 1 and type 2 groups had normal 24-hour urinary free cortisol levels. Patients who continued to have elevated cortisol and 24-hour urinary free cortisol levels were considered surgical failures.

Patients were considered to have recurrence of their Cushing disease when they had recurrence of symptoms and biochemical evidence of active disease, including an elevated 24-hour urinary free cortisol level and lack of suppression of the morning cortisol after a late evening dose of dexamethasone.

Statistical Analysis

Statistical significance for continuous variables was determined using the Student t test or analysis of variance. Categorical variables were analyzed using either the Pearson χ^2 test or Fisher exact test. Pearson χ^2 testing for determination of statistical significance was performed by using either a 2×2 contingency table or test for independence if greater than 2 outcomes were being analyzed. Fisher exact test was used if any expected values were less than or equal to 5. Statistical significance was defined as a P value less than.05. All statistical analyses were completed by using SPSS software, version 22 (SPSS, Inc, Chicago, Illinois).

RESULTS

Of the 275 patients, 215 (78%) were female. The average age of all 275 patients was 39.9 years, and the average age of males (34.7 years) was significantly lower than that of females (41.3 years) (Table 1; $P = .003$). Patient ages ranged from 8 to 76 years. There were 19 children included in this series.

Patients were classified by their preoperative imaging into 3 groups (Table 2). Those groups included microadenoma, macroadenoma, and negative imaging. Of the 275 patients, 137 (50%) demonstrated a microadenoma, 35 (13%) demonstrated a macroadenoma, and 103 (37%) had negative imaging. Females comprised 82% of the microadenoma group, 91% of the macroadenoma group, and 72% of the negative imaging group. Males were more likely than females to have negative imaging (48% vs 34%; $P = .018$).

The remission rate for the entire cohort of 275 patients was 80% (69% type 1, 11% type 2), with an initial failure rate of 20% (Table 3). The 137 patients with microadenomas had a remission rate of 89% (81% type 1, 8% type 2) and a failure rate of 11%. Of the 35 patients with macroadenomas, 66% were in remission

TABLE 1. Patient Age and Sex for Entire Study Cohort[a]

	No. Patients	Average Age, y	Standard Deviation
Overall	275	39.9	14.78
Female	215 (78%)	41.3	14.4
Male	60 (22%)	34.7	14.9

[a]Student t test, $P = .003$.

TABLE 2. Preoperative Imaging Results by Patient Sex[a]

Imaging	No. Patients	Female	Male
Overall, n (%)	275	215 (78)	60 (22)
Microadenoma, n (%)	137 (50)	112 (82)	25 (18)
Macroadenoma, n (%)	35 (13)	32 (91)	3 (9)
Negative, n (%)	103 (37)	74 (72)	29 (28)

[a]Micro/macroadenoma vs negative × female vs male: χ^2 test, $P = .018$. Microadenoma vs macroadenoma × female vs male: χ^2 test, $P = .193$.

(54% type 1, 12% type 2) and 34% had treatment failures. The 103 patients with negative imaging had a remission rate of 71% (58% type 1, 13% type 2) and a failure rate of 29%. The surgical technique for exploring patients with negative imaging involved first opening the capsule of the pituitary on the side of the positive IPSS. If careful exploration within the gland on that side did not reveal an adenoma, then the same procedure was performed on the opposite side. If no abnormal tissue could be identified, then half of the gland on the side of positive petrosal sampling was resected.

Patients with microadenomas were more likely go into remission than patients with macroadenomas or negative imaging ($P = .001$). Patients with negative imaging were more likely to have treatment failure than patients with microadenomas or macroadenomas ($P = .013$). Patients with microadenomas were more likely to undergo type 1 remission than patients with macroadenomas or negative imaging ($P = .039$).

Because it was thought that the size of a macroadenoma might predict remission rate, we correlated the preoperative diameter of the 30 macroadenomas in which the exact size was available to surgical outcome (Table 4). The average size of macroadenomas in each outcome group was virtually identical. Those patients with macroadenomas and type 1 remission had an average tumor diameter of 13.6 mm. Those with a type 2 remission had an average tumor diameter of 14 mm, and those who did not have a remission had an average tumor diameter of 13.8 mm. Thus, there was no correlation between tumor size over 10 mm and outcome ($P = .370$).

Pathological tissue analysis, including immunohistochemical staining, obtained in the 137 microadenomas showed a typical ACTH-secreting adenoma in 82% of cases, hyperplasia in 8%, and negative pathology in 10% (Table 5). There were no cases in which a tumor was identified but did not stain for ACTH. Of the 35 macroadenomas found on imaging, all showed ACTH-secreting adenoma on tissue analysis. The 103 operations performed following negative imaging resulted in 43% with ACTH-secreting adenoma, 10% with hyperplasia, and 48% with negative tissue pathology. Thus, a surgeon is more likely to obtain abnormal tissue in patients with positive imaging (92% of 172 patients). Although negative imaging is associated with negative pathology ($P = .001$), patients with negative imaging still had pathological tissue identified in 54 of 103 cases. There was no statistically significant relationship between the diagnosis of microadenoma or macroadenoma and the pathological finding of adenoma or hyperplasia. The overall incidence of hyperplasia was 21 of 275 patients (8%).

The findings of both negative pathology and hyperplasia correlated with treatment failure (Table 6; $P = .001$). There was a trend toward the pathological finding of microadenoma predicting a type 1 remission, but this did not reach statistical significance ($P = .07$). In the 10 patients with hyperplasia in whom remission was not achieved, one underwent radiation therapy, 4 underwent bilateral adrenalectomy, and 2 underwent repeat surgery with total hypophysectomy. Six of these 7 experienced a remission. Follow-up was not available for 3 patients.

We noted that, in the group of 103 patients with negative imaging, of the 74 that were in remission, 43 (58%) had a pathologically proven adenoma. In the 29 patients who did not have a remission, only 4 (14%) had an adenoma pathologically. The identification of an adenoma on pathology in patients with negative imaging is strongly predictive of remission ($P = .001$).

Of the total 218 patients in remission, there was a 17% recurrence rate with an average time to recurrence of 4.0 years (Table 7). Follow-up was an average of 6.7 years, ranging from 1 to 29 years. The 188 patients with a type 1 remission had a 13% recurrence rate at an average of 4.5 years after surgery. Follow-up

TABLE 3. Remission Rates by Preoperative Imaging Results for Entire Study Cohort[a]

Imaging	No. Patients	Total Remissions	Type 1[b] Remission	Type 2[c] Remission	Remission Failure
Overall, n (%)	275	219 (80)	190 (69)	29 (11)	56 (20)
Microadenoma, n (%)	137 (50)	122 (89)	111 (81)	11 (8)	15 (11)
Macroadenoma, n (%)	35 (13)	23 (66)	19 (54)	4 (12)	12 (34)
Negative, n (%)	103 (37)	74 (71)	60 (58)	14 (13)	29 (29)

[a]Micro/macroadenoma vs negative × remission vs failure: χ^2 test, $P = .013$. Microadenoma vs macroadenoma × remission vs failure: χ^2 test, $P = .001$. Microadenoma vs macroadenoma/negative × type 1 vs type 2: χ^2 test, $P = .039$.
[b]Type 1, subnormal postoperative cortisol levels.
[c]Type 2, normal postoperative cortisol levels.

TABLE 4. Remission Type by Preoperative Macroadenoma Size[a]

Remission Type	No. Patients	Average Size, mm
Overall	30	13.7
Type 1[b]	18	13.6
Type 2[c]	4	14.0
Failure	8	13.8

[a]Student *t* test, $P = .370$.
[b]Type 1, subnormal postoperative cortisol levels.
[c]Type 2, normal postoperative cortisol levels.

for this group averaged 6.5 years with a range of 1 to 29 years. The 30 patients with type 2 remissions had a 50% recurrence rate at an average of 2.9 years. Their average follow-up was 8.5 years with a range of 1 to 19 years. Thus, it is clear that the type 2 patients had a higher recurrence rate and a shorter time to recurrence ($P = .001$).

Repeat surgery for failure of remission was performed in 33 patients. This resulted in remission in 15 patients and continued failure in 18 patients.

There were 19 children aged 17 years or under included in the study (Table 8). Of these, 53% were female, and the average age of the children was 13.5 years, ranging from 8 to 17 years.

Preoperative imaging of the children showed 58% with microadenomas, 5% with macroadenomas, and 37% with negative imaging. Although similar to the overall group, these data are insufficient to allow statistical comparison.

The overall remission rate in the 19 children was 84% (74% type 1, 11% type 2) (Table 9). The 11 patients with microadenomas had a remission rate of 82% (all type 1), and the 1 patient with a macroadenoma had a type 1 remission. The 7 patients with negative imaging had an 86% remission rate (57% type 1, 29% type 2). Once again, these numbers are insufficient to compare statistically with the overall group, but these remission rates are at least as good as those in adults.

TABLE 5. Preoperative Imaging Results vs Pathological Findings for Entire Study Cohort[a,b]

Imaging	No. Patients	ACTH-Secreting Adenoma	Hyperplasia	Negative
Overall, n (%)	275	192 (70)	21 (8)	62 (23)
Microadenoma, n (%)	137 (50)	113 (82)	11 (8)	13 (10)
Macroadenoma, n (%)	35 (13)	35 (100)	0 (0)	0 (0)
Negative, n (%)	103 (37)	44 (43)	10 (10)	49 (48)

[a]ACTH, adrenocorticotropic hormone.
[b]Micro/macroadenoma vs negative imaging × adenoma/hyperplasia vs negative imaging: χ^2 test, $P = .001$. Microadenoma vs macroadenoma × adenoma + hyperplasia vs negative imaging: χ^2 test, $P = .058$. Microadenoma vs macroadenoma × adenoma vs hyperplasia: Fisher exact test, $P = .124$.

TABLE 6. Pathological Findings vs Remission Rates for Entire Study Cohort[a,b]

Pathology	No. Patients	Remission Type 1[c]	Remission Type 2[d]	Remission Failure
Overall, n (%)	275	190 (69)	29 (11)	56 (21)
ACTH-secreting adenoma, n (%)	192 (70)	157 (82)	14 (7)	21 (11)
Hyperplasia, n (%)	21 (8)	8 (38)	3 (14)	10 (48)
Negative, n (%)	62 (23)	25 (40)	12 (19)	25 (40)

[a]ACTH, adrenocorticotropic hormone.
[b]Adenoma/hyperplasia vs negative × remission vs failure: χ^2, $P = .001$. Adenoma vs hyperplasia × remission vs failure: χ^2, $P = .001$. Adenoma vs hyperplasia × type 1 vs type 2: Fisher exact test, $P = .07$.
[c]Type 1, subnormal postoperative cortisol levels.
[d]Type 2, normal postoperative cortisol levels.

Pathology results for the children's group were similar to the overall group (Table 10). The 11 patients with microadenoma on imaging resulted in 82% with ACTH-secreting adenomas, 18% with hyperplasia, and none with negative findings. The 1 macroadenoma found on imaging was an ACTH-secreting adenoma, and the 7 patients with negative imaging resulted in 43% with ACTH-secreting adenoma, 29% with hyperplasia, and 29% with negative pathology. Only 1 recurrence was documented in the 19 children. This occurred 44 months after the initial surgery and was treated successfully with repeat surgery.

There were no postoperative deaths in the entire series of patients. Three deaths were documented during follow-up: 1 death occurred 20 years after surgery from stroke, 1 occurred 8 years after surgery from unknown cause, and 1 occurred 4 years after surgery from a bilateral adrenalectomy.

Postoperative complications included 1 patient with pneumonia and 1 patient with meningitis, both successfully treated with antibiotics. One patient had CSF rhinorrhea and was treated successfully with spinal drain. There were 5 patients with hyponatremia within the first week after surgery and all were treated without adverse sequelae. There were 2 cases of long-term diabetes insipidus. Transient diabetes insipidus occurred 5% of the time, but is considered a side effect rather than a complication.

Main Results

The overall remission rate for the 275 consecutive patients was 80%. When imaging suggested a microadenoma, the remission rate was 89%; when a macroadenoma was imaged, the remission rate was 66%; and when the imaging was negative, the remission rate was 71% (Figure). Patients with negative imaging were found to have pathological tissue in 52% of cases. Patients with microadenomas were more likely to experience adrenal insufficiency postoperatively and have a more durable remission. Overall, patients who experienced early postoperative adrenal insufficiency had a lower recurrence rate and a longer time to recurrence. The results in children were identical to those in adults.

TABLE 7. Recurrence Rates for Patients in Remission[a]

Remission Type	No. Patients	Recurrence Rate, %	Average No. Years to Recurrence	Average No. Years Follow-up	Range of Follow-up, yr
All	218	17	4.0	6.7	1-29
Type 1[b]	188 (87%)	13	4.5	6.5	1-29
Type 2[c]	30 (14%)	50	2.9	8.5	1-19

[a]Recurrence vs remission × type 1 vs type 2: χ^2 test, $P = .001$.
[b]Type 1, subnormal postoperative cortisol levels.
[c]Type 2, normal postoperative cortisol levels.

DISCUSSION

Key Results

The results of this review confirm that transsphenoidal surgical exploration and removal of ACTH-secreting tumors is an effective and safe method for the initial treatment of Cushing disease. The strengths of this series are that the patients were all operated on with the use of the same transsphenoidal microscopic approach at the same institution by 1 surgeon. Although this is not a prospective study, data on these patients were carefully monitored throughout the entire time of the study. The total number of patients is large for this diagnosis, although the number of children is small owing to the nature of the disease. The follow-up for patients is relatively long, although further follow-up to look for recurrences is very important.

Limitations

Weaknesses of this study include the fact that the early imaging (1980-1988) was done with CT scanning. Because we determined that the remission rate was the same (71%) in both the CT- and MRI-negative imaging patients, we thought it appropriate to include the CT-imaged patients in the study. Another minor weakness of the study is that we used mainly the initial postoperative morning cortisol levels to determine remission. In fact, if within a month of the surgery the patient was found by additional testing to not be in remission, they were considered to be a remission failure. We are confident that all labeling of the patients as remission or failure is accurate. Subdivision of our patients in remission into type 1 or type 2 is arbitrary, but provides a useful way to look for a predictor of recurrence.

TABLE 8. Preoperative Imaging Results by Sex for Children

Imaging	No. Patients	Female	Male
Overall, n (%)	19	10 (53)	9 (47)
Microadenoma, n (%)	11 (58)	5 (45)	6 (55)
Macroadenoma, n (%)	1 (5)	1 (100)	0 (0)
Negative, n (%)	7 (37)	4 (57)	3 (43)

Interpretation

The finding that 78% of our patients were female is consistent with previous reports for the diagnosis of pituitary-dependent hypercortisolism.[7-12] Our finding that males were significantly younger than females at diagnosis has not been frequently reported, but is often not analyzed.[7,8,11,12]

Children comprised 7% of our consecutive patients. Descriptions of Cushing disease usually state that this syndrome is "rare" in children. Although it is uncommon, we do not think it should be considered rare, and pediatricians need to be watchful for this diagnosis in children.

Our finding that 37% of the study cohort had high-quality modern imaging negative for pathology is consistent with previous reports.[8,13,14] Microadenomas in 50% of cases and macroadenomas in 13% are also typical findings. It should be noted that the absolute rate of microadenomas would be higher, because 71% of the negative imaging patients were in remission with surgery, presumably often of microadenomas. There was no statistical difference in the female:male ratio in any of these subgroups.

Our early postoperative remission rate of 89% in patients with microadenomas should be considered high and is in the range of 59% to 98% reported in large series.[7,9,10,13,15-20] The lower remission rate of 66% in the macroadenoma group is to be expected. Most series report remissions of less than 65% for macroadenomas.[16] Our analysis showed that the size of the macroadenoma did not correlate with the remission rate. Our remission rate of 71% in the negative imaging group demonstrates that even with negative imaging, a high percentage of patients can be placed in remission by surgery. We believe that an experienced neurosurgeon with a commitment to patients with pituitary disorders will lead to these optimal outcomes.

Our finding that patients with microadenomas were more likely to experience a type 1 remission compared with patients with macroadenomas or negative imaging is not surprising, because both microadenoma and adrenal insufficiency are known predictors of a long-lasting remission.[4,7,10,11,13,16,21] Because type 1 remissions were achieved in 54% and 58% of macroadenomas and negative imaging, respectively, this argues for an aggressive surgical approach in all patients with Cushing disease.

TABLE 9. Preoperative Imaging Results vs Remission Rates for Children

Imaging	No. Patients	Total Remissions	Type 1[a] Remission	Type 2[b] Remission	Remission Failure
Overall, n (%)	19	16 (84)	14 (74)	2 (11)	3 (16)
Microadenoma, n (%)	11 (58)	9 (82)	9 (82)	0	2 (18)
Macroadenoma, n (%)	1 (5)	1 (100)	1 (100)	0	0
Negative, n (%)	7 (37)	6 (86)	4 (57)	2 (29)	1 (14)

[a]Type 1, subnormal postoperative cortisol levels.
[b]Type 2, normal postoperative cortisol levels.

The pathological analysis of tissue obtained at surgery, including immunohistochemical staining, showed that 100% of macroadenomas were ACTH-secreting adenomas and 82% of microadenomas were ACTH-secreting adenomas. The actual rate in microadenomas may be higher, because there are clearly situations involving microadenomas in which the tumor is so small that nothing is available for the pathologist to recognize. These are the microadenomas that have "gone up the sucker."

Of the 103 patients with negative imaging, 43% had proven ACTH-secreting adenomas. Of these 103 patients, the 74 who were in remission postoperatively showed a 58% rate of adenomas, and the 29 who did not have a remission showed only a 14% rate of finding an adenoma. Thus, it is clear that finding an adenoma increases the chances of achieving a remission (Table 6). We believe that IPSS contributed significantly to the overall 71% remission rate in these patients with negative imaging.

The incidence of hyperplasia was 8%, and this finding predicted a higher rate of failure to achieve remission (Table 6). Cushing disease caused by corticotroph hyperplasia, usually nodular, is a rare but well-documented phenomenon.[22,23] Any role of hypothalamic corticotropin-releasing hormone in corticotroph hyperplasia remains unclear. Those with the diagnosis of hyperplasia and failure of remission underwent radiation therapy, bilateral adrenalectomy, or total hypophysectomy.

Recurrences in patients with Cushing disease have always been considered to be higher than for other types of pituitary adenomas, but reports range from 3% to 66%.[4,7-13,16,21] We found an overall recurrence rate of 17% in our 218 patients initially in remission. The average time to recurrence was 4.0 years with an average follow-up of 6.7 years ranging from 1 to 29 years. As we predicted, the recurrence rate was higher (50% vs 13%) and earlier (2.9 vs 4.5 years) in type 2 remissions than in type 1

TABLE 10. Preoperative Imaging Results vs Pathological Findings for Children[a]

Imaging	No. Patients	ACTH-Secreting Adenoma	Hyperplasia	Negative Pathology
Overall, n (%)	19	13 (68)	4 (21)	2 (11)
Microadenoma, n (%)	11 (58)	9 (82)	2 (18)	0
Macroadenoma, n (%)	1 (5)	1 (100)	0	0
Negative, n (%)	7 (37)	3 (43)	2 (29)	2 (29)

[a]ACTH, adrenocorticotropic hormone.

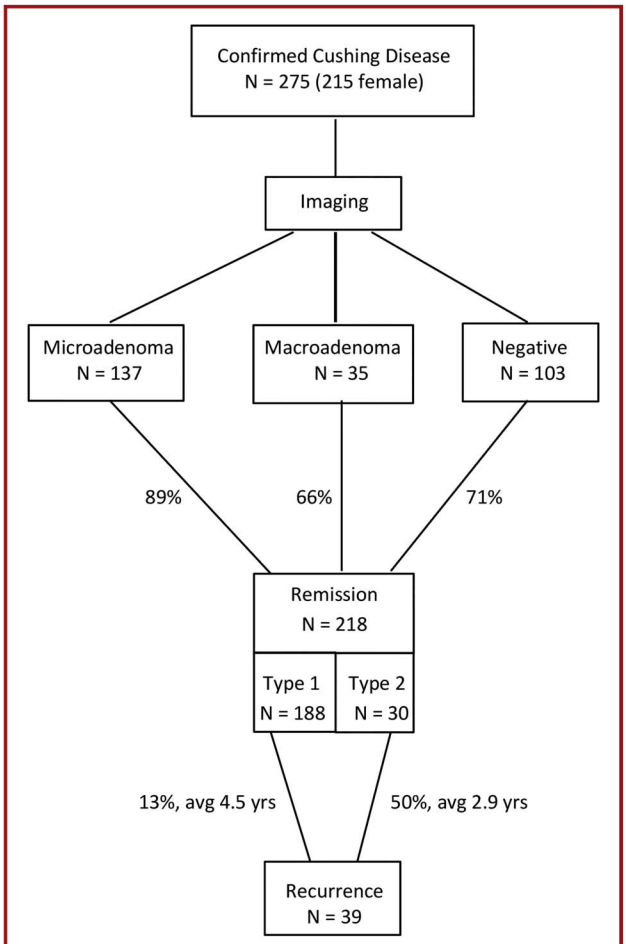

FIGURE. *Flow diagram demonstrating remission by imaging type and recurrence by remission type. Type 1 indicates adrenal insufficiency and type 2 indicates serum and urinary cortisols in the normal range.*

remissions. In our series, initial adrenal insufficiency predicted a favorable long-term outcome. Several other authors have identified a lower recurrence rate associated with an initial low postoperative cortisol level.[4,7,10,11,13,16,21,24] We used a morning cortisol level of 3 μg/dL or less within the first week of surgery as an indication of adrenal insufficiency. Several authors used 2 μg/dL or less as the cutoff,[10,12,13,16] but a consensus statement in 2008 noted that the recurrence rates were the same at 5 μg/dL and below as 2 μg/dL and below.[10,16] It is important to recheck morning cortisol levels in patients with elevated levels immediately after surgery, because occasionally they will drop to adrenal insufficiency levels over several weeks. We have only seen this phenomenon of delayed remission 3 times and confirmed the remissions with urinary free cortisol levels. It is also important to keep in mind that in every reported series, even with initial remission and adrenal insufficiency, patients experience a recurrence at least 10% of the time.[21]

Although the 19 children (aged 17 years and under) included in this study are a sizable number for a report on Cushing disease, the number in the various subgroups discussed above is insufficient for meaningful statistical analysis. The average age was 13.5 years, which is in line with other reports of children with Cushing disease.[1,3,4,13]

As in the adults in our series, 37% of the children had negative imaging for a specific tumor and 58% showed microadenomas. With an 82% remission rate in the 11 children with microadenomas and an 86% remission rate in the 7 with negative imaging, the overall remission rate of 84% was at least as favorable as for the 256 adults. This remission rate for children is well within the range of 60% to 98% reported by others.[1-4,13,25] Pathology for the children's group paralleled that seen in the adult group in every category. There were no technical difficulties in the surgery of children compared with adults. Although earlier patients were operated on via a sublabial approach, the direct transnasal route worked well in every patient after switching to this approach in 1989.

The death and complication rate in this series is consistent with expectations for an experienced surgeon.[12,26,27] There were no postoperative deaths and only a few treatable complications. With only 3 deaths during the long follow-up in this large series of patients, it is not possible to relate these to remission or recurrence. Hassan-Smith et al[9] found a lower long-term mortality in patients that experienced long-term remission. Swearingen et al[27] found normal 5- and 10-year mortality rates in patients with remission.

Generalizability

We believe that these results are generalizable to any experienced pituitary neurosurgeon. This experience applies to surgeons using either the operating microscope or endoscope, or a combination of the 2 techniques. There is evidence that with every surgical procedure the experience of the surgeon is important, but we also believe that working with an experienced endocrinologist is important in the overall remission rates.

CONCLUSION

This large series involving transsphenoidal surgery as the initial treatment for Cushing disease demonstrates that a high rate of remission can be achieved safely. Patients with microadenomas confirmed on imaging have the highest remission rates, but patients with macroadenomas and negative imaging also have acceptable rates of remission. Men were younger at diagnosis, and children had the same remission rates as adults. When pathological analysis showed hyperplasia or no pathology, remission was less likely than when an ACTH-positive adenoma was found. Recurrences were documented in 17% of patients and were least likely when a very low morning cortisol was found 2 days after surgery. It is important to remember that, with Cushing disease, a remission is not necessarily a cure and life-long surveillance for recurrence is mandatory.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

This is an important series in a large number of patients of outcomes of pituitary surgery for Cushing disease. Also important is the message that pituitary surgery for Cushing disease (and by inference, all types of pituitary lesions) that pituitary surgery should be conducted by neurosurgeons who have both experience and expertise with this procedure.

Mary Lee Vance
Charlottesville, Virginia

This is an interesting series with good long-term follow-up on a large number of patients with Cushing Disease. The results are good and demonstrate the need to concentrate these difficult cases in experienced hands. It also shows the need for long-term follow-up to see the true incidence of recurrence after what appears to be long-term remission. Five and ten year follow-up is not adequate to understand the true difficulty with this disease.

Kalmon D. Post
New York, New York

This is an important contribution to our knowledge on the efficacy of transsphenoidal surgery for the treatment of Cushing disease. The large cohort of patients and the fact that all the operations were done by the same neurosurgeon make this study homogenous and more meaningful. The rate recurrence of Cushing disease after surgery is not uniform among different series and this study adds an important data on this matter with 17% recurrence rate. This recurrence rate is larger than in my personal experience with a similar cohort of patients over 25 years. There is no information on the management of patients with recurrent disease which is important to inexperienced surgeons. I think that inclusion of pre MRI imaging (CT) in the negative imaging group has a bias on the rate of remission in negative imaging patients. Transient DI was not considered a complication. However, in my experience with a slightly similar cohort the rate of transient DI and SIADH were much higher than in this series.

Moshe Hadani
Tel Aviv, Israel

In this article the outcome of a large number of adults and children who underwent transsphenoidal surgery for Cushing disease are reviewed. Although, some of the findings are confirmative to previous literature the article adds to the knowledge of this rare disease. Clinical reports like this are always of great interest and importance.

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