

## Long-Term Mortality after Transsphenoidal Surgery for Cushing Disease

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**Background:** Untreated Cushing disease historically has a high mortality rate, but the long-term survival of patients with Cushing disease after transsphenoidal surgery has not been reported.

**Objective:** To determine long-term mortality rate in patients who are treated for Cushing disease with current management techniques.

**Design:** Retrospective case series.

**Setting:** Tertiary care center.

**Patients:** 161 patients (32 men and 129 women; mean age, 38 years) who were treated for Cushing disease between 1978 and 1996.

**Intervention:** Transsphenoidal adenomectomy and as-needed adjunctive therapy.

**Measurement:** Record review with follow-up interview.

**Results:** The cure rate for patients with microadenomas who had no previous therapy was 90% (123 of 137). No perioperative deaths occurred (0 of 193 procedures [95% CI, 0.0% to 1.9%]). Follow-up data (mean, 8.7 years) were obtained for 99% of patients (159 of 161). Six patients died. The 5- and 10-year survival rates were 99% (CI, 97% to 100%) and 93% (CI, 88% to 99%), respectively. Survival was similar to that seen in an age- and sex-matched sample that was based on U.S. population data (standardized mortality ratio, 0.98 [CI, 0.44 to 2.2];  $P > 0.2$ ).

**Conclusion:** Survival of patients treated for Cushing disease with current management techniques between 1978 and 1996 was better than the poor survival historically associated with this disorder.

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Little is known about the mortality rate associated with Cushing disease when this disease is treated with current management techniques. In Cushing's original series, the mean duration from presentation to death was 4.7 years (1), and a 1952 review of the natural history of Cushing disease (2) reported a 5-year survival rate of 50%. Despite advances in diagnosis and treatment, the mortality rate of patients with Cushing disease after resolution of hypercortisolemia remains uncertain. To determine this, we obtained follow-up data on 161 patients with Cushing disease who had undergone transsphenoidal surgery.

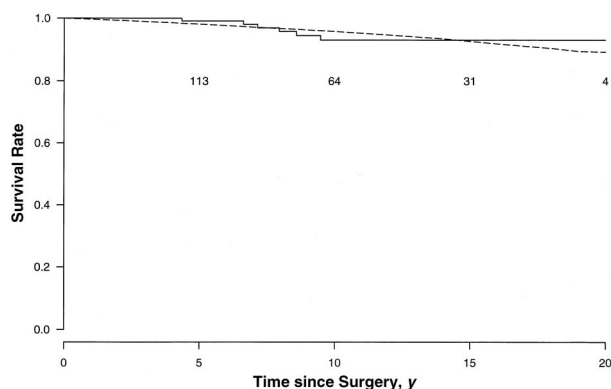
### Methods

#### Patients

Records were reviewed for all patients whose transsphenoidal surgery for Cushing disease was performed by the neurosurgeon authors between 1978 and 1996. We attempted to interview all surviving patients. Deaths were confirmed by death certificates, report of immediate family members or treating physicians, or hospital records. The Massachusetts General Hospital Subcommittee on Human Studies approved the study.

#### Endocrine Evaluation

All patients had both clinical and biochemical evidence of Cushing disease: a normal or elevated plasma adrenocorticotrophic hormone level and results of suppression testing that were consistent with pituitary disease (3). All patients were evaluated for cure within 10 postoperative days. Cure required both fasting serum cortisol levels less than 138 nmol/L and urine free cortisol excretion less than 55 nmol/d. Postoperative pituitary insufficiency was defined by patient reports of use of hormone replacement therapy; we did not correct for previous requirements or independent repeated assay. Recurrence was determined for surviving patients on the basis of questionnaire response and results of routine endocrine reevaluation, without independent repeated assay. Time to recurrence was defined as the interval between the first curative procedure and the date at which treatment for recurrence began. Entry into the study was the date of surgery. Long-term survival was defined as the interval between study entry and the date of interview or death.



**Figure 1.** Survival in 159 patients with long-term follow-up who underwent transsphenoidal surgery for Cushing disease compared with survival in the U.S. population. The solid line represents the Kaplan-Meier plot of survival for study patients; the dashed line represents the expected survival rate of an age- and sex-matched sample based on U.S. population data. The standardized mortality ratio was 0.98 (95% CI, 0.44 to 2.2;  $P > 0.2$ ). Numbers indicate patients at risk.

### Statistical Analysis

Kaplan-Meier product-limit estimation with 95% CIs was used to analyze survival (4). For multivariate Cox analysis, a forced regression model was used. Cure was considered a single event, and cure rates are given per patient even if multiple procedures were performed. For comparison between survival in the patient group and in the age- and sex-adjusted sample of the U.S. population, the person-years Poisson regression method was used to calculate a standardized mortality ratio with 95% CIs (5, 6). We did not correct for ethnicity. For graphic display, the Kaplan-Meier estimate of survival in the patient group is shown with a conditional survival estimate for an age- and sex-matched sample from the U.S. population, calculated by Verheul's conditional survival method (7). Statistical computations were performed by using S-PLUS software (Version 3.3, MathSoft, Seattle, Washington) (6).

### Results

Between 1978 and 1996, 161 patients (32 men and 129 women) had 193 transsphenoidal procedures for Cushing disease. The mean age at surgery was 38 years (median, 38 years [range, 8 to 76 years]).

#### Surgical Results

Of the 161 patients, 154 (96%) had no previous treatment and underwent transsphenoidal surgery as their primary treatment. Eighty-nine percent of these patients (137 of 154) had microadenomas (maximum tumor diameter  $< 1$  cm), and 90% (95% CI, 85% to 95%) of these patients (123 of 137) were cured. The remaining 17 patients without previous therapy (17 of 154 [11%]) had macroadenomas (maximum tumor diameter, 1 cm); 11 of these 17 patients (65% [CI, 38% to 86%]) were surgically

cured. Four percent of the patients (7 of 161) had undergone previous treatment (radiation therapy or transsphenoidal surgery); 3 of these 7 patients (43%) were cured. The cure rate for all patients was 85% (137 of 161). Twenty-eight patients required multiple procedures (10 of 18 patients had successful repeated surgery after an initial unsuccessful surgery, and 3 of 10 patients had successful repeated surgery for recurrence).

Follow-up interviews were completed by 152 of 161 patients. Six of the 9 patients who did not complete a follow-up interview had died, and 2 (1 who lived outside the state and 1 who was a foreign national) could not be contacted or proved to have died; these two patients were therefore excluded from analysis. Survival in an additional patient was inferred without contact on the basis of an active unlisted telephone number, a current address, and recent laboratory data that excluded the possibility of recurrence. Deaths were confirmed by death certificate (2 patients), immediate family (1 patient), treating physicians (2 patients), and hospital records (1 patient).

#### Survival

Survival data were obtained for 99% of patients (159 of 161), with a median follow-up of 8 years (mean, 8.7 years [range, 1 to 20 years]). Six patients (62 to 81 years of age) died at intervals of 4 to 9 years after surgery. Causes of death were cardiovascular events (2 patients), stroke (2 patients), lymphoma (1 patient), and trauma (1 patient). Five of these six patients had been surgically cured, although no data were available to confirm continued cure at time of death. One deceased patient (traumatic death) had received radiation and ketoconazole therapy to control persistent hypercortisolism. Survival in the patient group seems similar to that in an age- and sex-matched sample from the U.S. population (Figure 1). The standardized mortality ratio was 0.98 (CI, 0.44 to 2.2;  $P > 0.2$ ), the 5-year survival rate was 99% (CI, 97% to 100%), and the 10-year survival rate was 93% (CI, 88% to 99%).

#### Recurrence

Among the 136 cured patients with long-term follow-up, disease recurred in 10 patients (7%) (postoperative interval, 1 to 11 years [median, 4 years; mean, 5.7 years]). Seven patients had microadenomas (7 of 125 [6%]), and 3 patients had macroadenomas (relative risk, 5.1 [CI, 0.4 to 40]). The 5-year cure rate for patients who had microadenomas compared with patients who had macroadenomas was 96% compared with 91%; the 10-year cure rate for these patients was 93% compared with 55% (Figure 2).

## Surgical Mortality and Morbidity

No perioperative deaths resulted from the transsphenoidal procedure (0 of 193 patients [CI, 0% to 1.9%]) or from the subsequent adrenalectomy performed in 20 patients (0 of 20 [CI, 0% to 17%]). Five cases of cerebrospinal fluid rhinorrhea required repair (5 of 193 procedures [2.6%]). Three cases of meningitis (3 of 193 patients [1.5%]) and one case of severe epistaxis (1 of 193 patients [0.5%]) occurred. No patients experienced visual compromise or intrasellar hemorrhage. The most common complication was persistent sinus congestion (15 of 159 patients [9%]). Two patients required repeated surgery for refractory sphenoid sinusitis; organisms included actinomyces (one patient) and aspergillus (one patient).

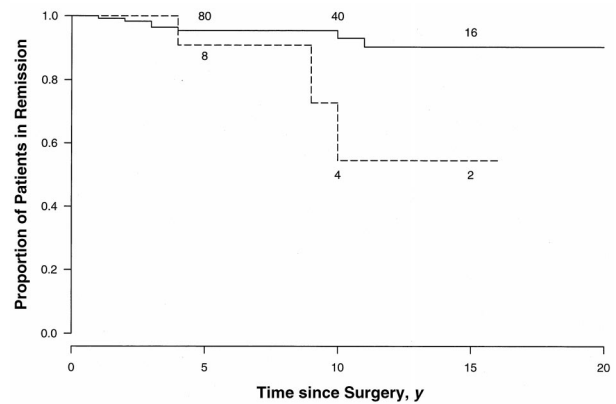
Of patients with no previous therapy who were cured after a single transsphenoidal procedure and followed for at least 1 year, 41% (47 of 115) were deficient in at least one hormone axis (glucocorticoid, 31% [36 of 115]; thyroid, 23% [26 of 115]; and gonadal steroid, 14% [16 of 115]). The occurrence of permanent diabetes insipidus was 6% [7 of 115].

## Management of Surgical Failures

Hypercortisolemia has resolved in all patients with persistently elevated cortisol levels despite transsphenoidal surgery. Of the 29 surviving patients who underwent unsuccessful transsphenoidal surgery (initially or after recurrence), 20 had adrenalectomy, 8 were treated with radiation or medical therapy, and 1 had curative surgery at another treatment center. Cushing disease in the deceased patient who was not cured at surgery was being controlled with medication at time of death. Hypercortisolemia that was not resolved by transsphenoidal surgery (as opposed to adjunctive techniques) did not adversely affect survival. In a Cox multivariate model incorporating age, sex, and cure after transsphenoidal surgery, patient age was the only predictor of survival ( $P < 0.01$ ): Younger patients lived longer.

## Discussion

This analysis demonstrates that survival for patients with Cushing disease has improved dramatically over the years. We report a 5-year survival rate of 99% (CI, 97% to 100%). Although the source of hypercortisolemia in earlier series was sometimes unclear, the 5-year survival rate for patients with Cushing syndrome in 1952 was reported as 50% before the introduction of cortisol replacement (2). In Cushing's original report, the duration from presentation to death was 4.7 years (1). In 1971, Orth and Liddle (8) treated 90 patients with radiation or



**Figure 2.** Duration of cure in Cushing disease after transsphenoidal surgery in 136 patients with long-term follow-up, stratified by tumor size. The solid line represents 125 patients with microadenomas; the dotted line represents 11 patients with macroadenomas. Five- and 10-year cure rates were 96% and 93%, respectively, for patients with microadenomas and 91% and 55% for patients with macroadenomas. The difference in recurrence rates (relative risk, 5.1) was significant ( $P > 0.03$ ). Numbers indicate patients at risk.

adrenalectomy and reported three deaths at variable follow-up intervals; in contrast, a 5-year survival rate after adrenalectomy of 86% was reported in 1994 (9).

Survival for patients in our study seems similar to that in an age- and sex-matched control sample; we report a standardized mortality ratio of 0.98. The CI (0.44 to 2.2;  $P > 0.2$ ) is wide, however, and the actual mortality rate could conceivably range from half of to more than twice the rate in the normal population. Another study reported decreased survival despite therapy, with a standardized mortality ratio of 3.8 (CI, 2.5 to 17.9) (10). At least 12% of patients in that series had ongoing hypercortisolemia; in contrast, none of our patients had persistent cortisol excess. Because we have not independently done repeated assays for persistent cure, undocumented recurrent hypercortisolemia may have developed in some patients. If this occurred in any of the deceased patients, we may have underestimated the true mortality rate related to Cushing disease. In addition, undetected disease-related morbidity may persist despite normalization of cortisol levels. The primary causes of death in the early series (2) were bacterial infection (46%) and cardiac failure (30%). In our study, cardiovascular events and stroke accounted for four of six deaths. No deaths were caused by infection. Increasingly sophisticated methods of managing infections in the immunocompromised host may have helped to improve survival.

Perioperative mortality after transsphenoidal surgery for Cushing disease is minimal (0% to 4%) in series reported from treatment centers with expertise in pituitary surgery (11–16). No treatment-related deaths occurred in our series, and major morbidity was uncommon. The recurrence rate was low overall but was clearly higher in patients who had mac-

roadenomas (relative risk, 5.1), perhaps because of increased potential for proliferation of these tumors (17, 18).

Transsphenoidal surgery by experienced neurosurgeons provides immediate resolution of hypercortisolemia with minimal morbidity. When transsphenoidal surgery was combined with modern techniques of endocrine management in patients treated between 1978 and 1996, survival was better than that reported in historical series. Cured patients may now have survival rates no different from those of the general population. Despite improvements in survival, however, the possibility of long-term morbidity resulting from years of chronic hypercortisolemia merits further investigation.

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