



# Durable Biochemical Remission After Transsphenoidal Surgery for Cushing's Disease: A 13 Year Single Institution Experience



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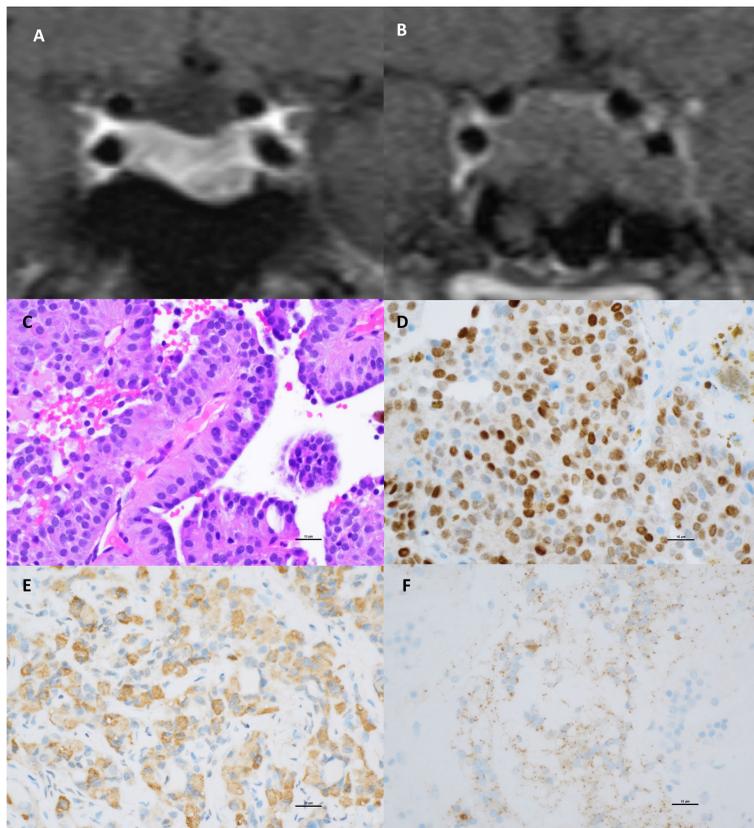
## Introduction

Transsphenoidal surgery remains the first line treatment for Cushing's disease; however, reported remission and recurrence rates vary widely.<sup>1,2</sup> We aim to assess postoperative remission and recurrence rates at our institution following transsphenoidal surgery for Cushing's disease. These patients are evaluated and treated in our multidisciplinary clinic involving neurosurgery, endocrinology, otolaryngology, and radiation oncology.

## Methods

A retrospective review was performed of 300 consecutive adult patients who underwent transnasal transsphenoidal surgery by skull base faculty from 2012 to 2025. 27 patients with biochemical evidence of Cushing's disease were included – 23 had confirmed corticotroph-lineage pituitary neuroendocrine tumor (PitNET) with ACTH and/or T-PIT immunostaining and 4 had indeterminate surgical pathology.

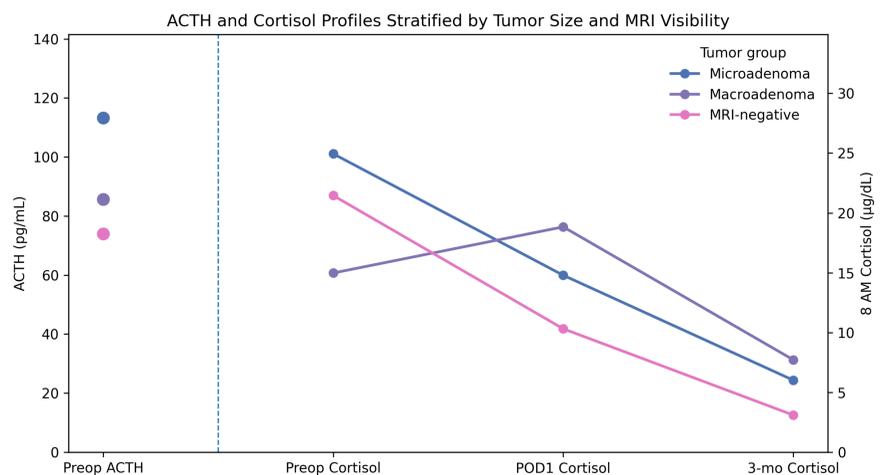
Clinical, operative, radiographic, and endocrine data were reviewed. The primary outcome was biochemical remission within 1 year from surgery, defined by development of adrenal insufficiency (AI) requiring steroid replacement or normalization of late-night salivary cortisol and 24-hour urine cortisol levels. Extent of resection (EOR) was assessed on 3-month postoperative MRI in patients with MRI-visible adenomas and categorized as gross total resection (GTR) or subtotal resection (STR).



**Figure 1. Cushing's Disease representative MRI imaging and histology.** Preoperative contrasted coronal MRI of the sellar region shows an inferiorly located hypoenhancing microadenoma (A), as compared to a macroadenoma with left sided cavernous sinus invasion (B). H&E stain (400x magnification) shows pituitary neuroendocrine tumor with foci of papillary architecture (C). T-PIT immunostain shows diffuse immunopositive staining in neoplastic cells (D). ACTH immunostain shows neoplastic cells with cytoplasmic granules filled with ACTH protein in the densely granular subtype (E) versus the sparsely granular subtype (F).

## Conclusions

In this single-institution series, transsphenoidal surgery for Cushing's disease achieved biochemical remission in 85% of patients. While limited by small sample size, remission rates for MRI-negative disease (83%) and macroadenomas (88%) compared favorably with published series.<sup>3-4</sup> Operative metrics were efficient, with low blood loss, short length of stay, and minimal postoperative morbidity. Kaplan–Meier analysis demonstrated durable freedom from additional treatment, with only one delayed recurrence 9 years postoperatively. Endocrine findings underscored the biological heterogeneity of corticotroph-lineage PitNETs and the limitations of relying solely on early postoperative cortisol thresholds to define remission. Overall, these outcomes support the effectiveness of transsphenoidal surgery for Cushing's disease within a multidisciplinary pituitary program.



Tumor group	Preop ACTH (pg/mL)	Preop 8 AM cortisol (µg/dL)	POD1 8 AM cortisol (µg/dL)	3-mo 8 AM cortisol (µg/dL)	GTR rate	AI or remission by 1 year
Microadenoma	113.2	24.9	14.8	6.0	83.3%	84.6%
Macroadenoma	85.7	15.0	18.8	7.7	57.1%	87.5%
MRI-negative	74.0	21.5	10.3	3.1	N/A	83.3%

**Figure 2: Biochemical and surgical outcomes stratified by tumor size and visibility on preoperative MRI.** Macroadenomas demonstrated lower preoperative 8 AM cortisol levels and less frequent early postoperative cortisol suppression, yet many achieved delayed biochemical remission. Values shown as means. Extent of resection not applicable in MRI-negative disease. One-year cortisol values excluded due to limited availability.

## Results

27 patients with Cushing's disease (9 male, median age 44.0) were analyzed. On preoperative MRI, 48% (13/27) had microadenomas, 30% (8/27) macroadenomas, and 22% (6/27) did not have an identifiable lesion and underwent inferior petrosal sinus sampling (IPSS). Median preoperative ACTH was 65 pg/ml (IQR 47.5-103.5) and serum 8 AM cortisol was 17.8 µg/dl (IQR 13.3-24).

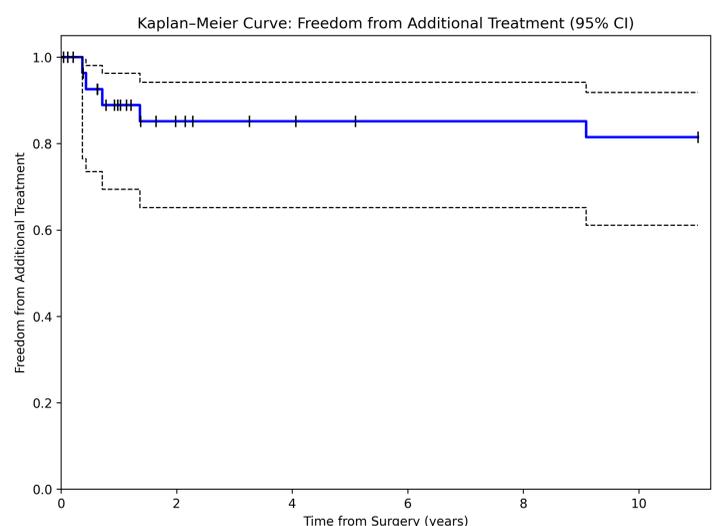
Most cases (93%) were performed microscopically. Median estimated blood loss was 25 cc, operative time 71 minutes, and length of stay 2 days. Intraoperative CSF leak was encountered in 22% of cases and was addressed intraoperatively. One patient subsequently experienced a postoperative leak necessitating re-exploration and cerebrospinal fluid diversion.

A stringent early postoperative biochemical response criterion (8 AM cortisol <2 µg/dL within 72 hours) was met in 41% (11/27), with a median postoperative day 1 cortisol of 10.8 µg/dL (IQR 2.0–20.8). 85% percent of patients were discharged on oral steroids. Transient inpatient diabetes insipidus occurred in 30%, with one case of permanent DI.

85% (23/27) experienced biochemical remission within one year after surgery. Excluding MRI-negative disease, 74% (14/19) achieved GTR – 83% (10/12) of microadenomas and 57% (4/7) of macroadenomas. Among patients in remission with ≥1 year follow-up, 39% (7/18) remained on steroid replacement for AI at last endocrine follow-up (median 2.0 years).

Among four patients with persistent disease after surgery, three underwent stereotactic radiosurgery (SRS) and one underwent repeat resection followed by non-localizing IPSS and long-term medical therapy. One patient with initial remission (POD1 cortisol <1.0 µg/dL) developed delayed recurrence 9 years later and underwent repeat surgery with adjuvant SRS. Kaplan–Meier analysis of time to additional treatment is presented in Figure 3.

On univariate statistical analysis, age, sex, and lesion size were not associated with need for further treatment. EOR showed a non-significant trend toward remission, limited by sample size. In patients without need for further treatment, early postoperative cortisol <2 µg/dL was associated with increased likelihood of long-term steroid dependence (OR 15.0, p = 0.04).



**Figure 3: Kaplan–Meier curve demonstrating freedom from additional treatment following transsphenoidal surgery for Cushing's disease (n = 27).** Events were defined as repeat surgical resection (n = 2) or SRS (n = 3). One delayed recurrence occurred 9 years postoperatively. Dashed lines represent the 95% confidence interval; censoring reflects last endocrine follow-up.

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