

Transsphenoidal surgery for Cushing's disease: a review of success rates, remission predictors, management of failed surgery, and Nelson's Syndrome

DANIEL F. KELLY, M.D.

Neuro-Endocrine Tumor Center, John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, California

✓Cushing's disease is a serious endocrinopathy that, if left untreated, is associated with significant morbidity and mortality rates. After diagnostic confirmation of Cushing's disease has been made, transsphenoidal adenomectomy is the treatment of choice. When a transsphenoidal adenomectomy is performed at experienced transsphenoidal surgery centers, long-term remission rates average 80% overall, surgical morbidity is low, and the mortality rate is typically less than 1%. In patients with well-defined noninvasive microadenomas, the long-term remission rate averages 90%. For patients in whom primary surgery fails, treatment options such as bilateral adrenalectomy, stereotactic radiotherapy or radiosurgery, total hypophysectomy, or adrenolytic medical therapy need to be carefully considered, ideally in a multidisciplinary setting. The management of Nelson's Syndrome often requires both transsphenoidal surgery and radiotherapy to gain disease control. (DOI: 10.3171/FOC-07/09/E5)

KEY WORDS • adrenocorticotrophic hormone • cortisol • Cushing's disease • Nelson's Syndrome • remission • transsphenoidal surgery

ENDOGENOUS Cushing's syndrome is caused by an ACTH-secreting pituitary adenoma (Cushing's disease) in approximately 70% of cases.^{1,6,53,54} Cushing's disease is a serious endocrinopathy that, if untreated, greatly increases morbidity and carries a four-fold increased risk of mortality, largely related to associated cardiovascular complications and abnormal glucose metabolism.^{22,26,40,47,58} In addition to hypertension and diabetes mellitus, other problems resulting from excess cortisol include hyperlipidemia, metabolic syndrome, coagulopathy, osteoporosis, depression, anxiety, and cognitive impairment, all of which may further debilitate patients.^{1,54} Given the multiple deleterious effects of Cushing's disease, treatment to achieve normal cortisol levels is indicated for all patients. Effective treatment decreases morbidity (such as hypertension and diabetes mellitus) and mortality and results in age- and sex-adjusted survival rates similar to those of the general population.^{25,26,45,58,71} Once the diagnosis of Cushing's disease is confirmed by a thorough endocrinological evaluation, transsphenoidal adenomectomy is considered the treatment of choice. In this review article, the success rates of first-time transsphenoidal surgery, repeat

surgery, and transsphenoidal surgery for Nelson's Syndrome are discussed.

Success Rate of Transsphenoidal Surgery for Cushing's Disease

The Early Years

For almost three decades, transsphenoidal adenomectomy has been shown to offer patients the best chance for a sustained remission of Cushing's disease. Adenomectomy for Cushing's disease was first performed by Hardy in the early 1960s.^{2,3,27,28} In the 1970s, other groups including Salassa and Laws⁶³ and Tyrrell and Wilson⁷² also began to adopt this approach for Cushing's disease with similar encouraging results. In these three reports of transsphenoidal microsurgery for Cushing's disease in a total of 63 patients, the clinical remission rate ranged from 68 to 89%, with no deaths.^{28,63,72} During the same period, use of hypophysectomy as an effective treatment for patients with Cushing's disease was reported by Lüdecke et al. in 1976⁴³ and Carmalt and associates in 1977¹¹ with remission rates of 50 and 85%, respectively. In subsequent years, there have been numerous reports describing outcomes after transsphenoidal surgery for Cushing's disease performed

Abbreviations used in this paper: ACTH = adrenocorticotrophic hormone; MR = magnetic resonance.

using the sublabial, transseptal endonasal, and direct endonasal routes with the operating microscope. More recently, the purely endonasal endoscopic approach⁵² and the microscopic approach with endoscopic assistance have been employed.

Contemporary Transsphenoidal Microsurgery for Cushing's Disease

In 18 retrospective reports published since 1995 involving more than 3000 patients, all with a minimum of 40 patients and a minimum 6-month follow-up, the remission rate ranged from 69 to 98% (simple [unweighted] average 79%), the recurrence rate from 3 to 17% (simple average 10%), and the acute surgical mortality rate from 0 to 1.9% (Table 1). Of the series' conducted at single centers, the smallest study included 41 patients⁶² and the largest included 310 patients.³⁷ Of the studies addressing transsphenoidal surgery as the primary treatment, long-term remission rates ranged from 69 to 98% (simple average 83%), recurrence rates from 5 to 11.5% (simple average 8%), and mortality rates from 0 to 1.9%.^{20,24,26,37,61,62,67,70,76} The best long-term remission rates, ranging from 86 to 98%, are found in patients with noninvasive microadenomas treated with primary transsphenoidal tumor removal.^{4,10,16,20,24,26,61,67,70} In contrast, lower remission rates are noted in patients with macroadenomas (range 31–83%) or invasive adenomas (range 22–65%).^{4,10,26,61,67,70}

Long-term postoperative surveillance of successfully treated patients with Cushing's disease is important because late recurrences occur; the median interval of disease recurrence ranges from 2.3 to 7.2 years after surgery and can be as late as 10 years after surgery.^{15,26,56,70} Similar rates of remission (range 56–98%) have been noted for pediatric patients with Cushing's disease treated using transsphenoidal surgery.^{9,18,19,33,39,46,55,64} The recurrence rate may be somewhat higher, however, as noted in several pediatric series.^{18,38,39,55}

Selective Adenectomy Compared with Hypophysectomy

In the patient series cited earlier, the initial goal of surgery was generally to remove an adenoma selectively. If no adenoma was found, in most instances a partial or total hypophysectomy was performed. In these patient series, the type of operation performed (selective adenectomy and partial or total hypophysectomy) did not appear to have a significant effect on the long-term remission rate.^{5,15,26,61} With increased removal of pituitary gland tissue, however, there is an increased rate of anterior and posterior pituitary failure.^{26,61} In two earlier patient series in which total hypophysectomy was the goal, new pituitary failure was seen in 79 to 95% of patients; however, using hemihypophysectomy, the rate of new failure was considerably lower.^{7,15,71}

New Pituitary Failure and Other Complications

The overall rate of anterior pituitary failure in the 19 patient series cited in Table 1 and published since 1995 ranged from 2 to 41%, but was typically less than 20% in most series; the incidence rate of permanent diabetes insipidus ranged from 3 to 9%. This relatively high rate of hypopituitarism associated with adenectomy appears to be directly related to the use of partial or complete hy-

pophysectomy required in a substantial minority of patients to maximize the chance of remission. In one recent report of using a purely endoscopic approach in 35 consecutive patients with Cushing's disease, the overall remission rate was 83%; however, the rate of new hypopituitarism, excluding isolated hypoadrenalism, was relatively high (48%).⁵² Other surgical complications in most transsphenoidal series are generally uncommon, including: cerebrospinal fluid leaks (0–8%), meningitis (0–3%), new neurological deficits (0–2%), postoperative hematomas (0–6%, generally < 1%), thromboembolic events (0–4%), and wound or nasoseptal complications (0–4%).^{15,20,26,65}

Early Reoperations for Persistent Cushing's Disease

After an unsuccessful initial operation for Cushing's disease, early reoperation within 60 days after the original surgery can result in a sustained remission in 38 to 67% of patients.^{14,37,42,60} If obvious adenoma was left within the gland at the first operation, this tumor may be visible on postoperative MR imaging; however, in most instances there is little utility in repeating MR imaging in these patients. In contrast, petrosal sinus sampling using corticotropin-releasing hormone stimulation appears useful for confirming the need for repeated surgery, if not performed prior to the initial procedure.⁴² In most reports, patients underwent a hemihypophysectomy or total hypophysectomy after a more limited initial operation. Second operations, however, are associated with a higher rate of postoperative cerebrospinal fluid leaks and hypopituitarism.^{14,37,42,60} Thus, it is reasonable to consider early reoperation only if residual adenoma is thought to reside in the gland and not within the cavernous sinus or skull base bone, which are factors that reduce the likelihood of achieving a remission rate to less than 50%.^{4,10,16,26}

Predicting Long-Term Remission after Transsphenoidal Surgery

Several methods of assessing early remission have been used to predict long-term remission from Cushing's disease. Provocative tests include the overnight low-dose dexamethasone suppression test and the corticotropin-releasing hormone stimulation test. Nonprovocative tests include assessment of serum cortisol and ACTH levels and 24-hour urinary free cortisol concentrations within the early postoperative period. Recent studies indicate that both provocative and nonprovocative tests have a similar high rate of predicting remission in Cushing's disease. For example, Chen and colleagues¹⁵ showed that a morning cortisol level on postoperative Day 3 of 3 µg/dl or less after an overnight 1 mg dexamethasone suppression test was predictive of sustained remission in 93% of patients. In the subset of 116 patients with microadenomas, the remission rate at 5 years after surgery was 96.5%.

In contrast, in three recent reports in which glucocorticoids were withheld in the early postoperative period until hypocortisolemia was evident, subnormal but not necessarily undetectable serum cortisol levels within 72 hours of surgery were highly predictive of sustained remission.^{20,62,68} In the report by Simmons and associates,⁶⁸ cortisol levels were measured every 6 hours for as long as 3 days after surgery, with a "low serum cortisol" cutoff value of 10 µg/dl (275.9 nmol/L); 21 patients (78%) met this cutoff cri-

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TABLE 1
Summary of studies of contemporary transsphenoidal microsurgery for Cushing's disease*

Author & Year	No. of Pts (% F)	Evidence Class†	Mean Age (range in yrs)	FU (yrs)	Remission (%)	- Recur (%)	Time to Recur (yrs)	Mortality (%)
Bochicchio et al., 1995‡§	668 (77)	III	38 (8–84)	2 (mean)	76, prim & sec	13	0.5–8.7	1.9
Knappe & Lüdecke, 1996	310 (NA)	III	NA	3.6 (mean)	85, all prim	11	w/in 10	0.6
Sonino et al., 1996§	103 (77)	II	37 (11–71)	7 (med)	77, all prim	19, 26	5, 10	NA
Blevins et al., 1998	106 (NA)	III	38	5.2 (mean)	91, micro 67, macro (prim vs sec NA)	12 36	NA	NA
Invitti et al., 1999	236 (83)	III	36 (11–72)	2.3	69	17	NA	NA
Swearingen et al., 1999‡§	161 (80)	III	38 (8–76)	8 (med)	85, prim & sec 90, prim micro 65, prim macro 70 (prim vs sec NA)	7	4 (med) 1–11 (range)	0
Cavagnini et al., 2001	300 (83)	III	NA	NA	79, prim & sec	15	NA	NA
Chee et al., 2001‡§	61 (74)	III	37 (12–69)	7.3 (med)	77, all prim	14.6	1.8–13 (range)	0
Rees et al., 2002§	54 (78)	III	41 (14–73)	6 (med)	86, intrasellar 40, extrasellar	5	1.1–3 (range)	1.9
Shimon et al., 2002‡§	82 (87)	III	39 (8–72)	4.2 (mean)	78, prim 62, sec 79, micro 33, macro	5	NA	0
Yap et al., 2002§	97 (80)	III	39 (14–82)	7.7 (mean)	69, all prim	11.5	0.7–6 (range)	1
Chen et al., 2003§	174 (68)	III	8–57	≥ 5 (min)	74 (prim vs sec NA)	7	2.3 (med)	0
Flitsch et al., 2003	147 (76)	III	35	NA	98, all prim	5.5	NA	0
Pereira et al., 2003‡§	78 (80)	III	37 (12–81)	7 (med)	72, prim & sec	9	7.2 (med) 2–20 (range)	1.2
Hammer et al., 2004	289 (83)	III	37 (18–72)	11.1 (med)	82, all prim 86, micro 83, macro 65, invasive	9 (of 150 pts)	1.7 (1 pt)	1
Rollin, et al., 2004‡§	41 (73)	II	38 (12–62)	4.8 (mean)	87.5, all prim	5	NA	NA
Esposito et al., 2006	40 (93)	III	39 (21–70)	2.7 (mean)	79.5, all 93, prim 45, sec	3	1.7 (1 pt)	1 pt
Hoffman & Fahlbusch, 2006	100 (NA)	III	NA	NA	75	4.8	NA	0

* FU = follow-up; macro = macroadenoma; med = median; micro = microadenoma; NA = not available; pt = patient; prim = primary; recur = recurrent; sec = secondary.

† Evidence Class II are prospective nonrandomized case series; Evidence Class III are retrospective case series.

‡ In six series including patients treated with surgery both as primary and secondary therapy (repeat transsphenoidal surgery), the percentage of patients undergoing a second procedure ranged from 4 to 26%.

§ In 10 series, pediatric patients were included.

|| Refers to reference 37.

terion and 100% of these 21 patients were in remission after a mean follow-up period of 27 months.⁶⁸ In the report by Rollin and coworkers,⁶² cortisol levels were obtained at 6, 12, and 24 hours postoperatively; of 21 patients (81%) in remission at a median follow-up of 34 months, serum cortisol levels 24 hours after surgery averaged $4.7 \pm 6.8 \mu\text{g/dl}$ (range 0.5–30 $\mu\text{g/dl}$). In the recent patient series reported by Esposito et al.,²⁰ in the 32 patients achieving early remission, the average morning cortisol nadir was $2.05 \pm 1.2 \mu\text{g/dl}$. In this study, a morning cortisol level of 5 $\mu\text{g/dl}$ or less on postoperative Day 1 or 2 was predictive of sustained remission in 97% of patients.

Regarding the absolute cortisol criterion establishing early remission, it appears that use of a more traditional value of nondetectable serum cortisol (< 50 nmol/L, or < 1.8 $\mu\text{g/dl}$) is excessively stringent given that more than 50% of patients who achieved remission in these three studies had a nadir cortisol level above this threshold with-

in 3 days of surgery.^{20,62,68} It should be noted that these studies also show that up to 4.5% of patients who achieve remission will not be identified within the first 72 postoperative hours and instead will have a delayed decrease in their cortisol values.^{20,62,68} Regarding the predictive value of early ACTH levels, only one-third of the patients in our recent series had a subnormal ACTH level during this early postoperative period, indicating that absolute ACTH level is a poor predictor of sustained remission.²⁰

There are several advantages of using early postoperative serum cortisol levels to assess early remission. First, this method requires no provocative testing and it gives an early and relatively reliable answer as to whether the patient is in remission, typically within 48 hours of surgery and prior to patient discharge home. Second, although patients with a successful operation without glucocorticoid replacement often develop symptoms of hypocortisolemia, manifestations of an adrenal crisis have not been reported.

Finally, this paradigm allows early identification of patients who initially had an unsuccessful first surgery, who may be candidates for a second operation within days of the first operation.^{20,42}

Management of Cushing's Disease after Failed Transsphenoidal Surgery

After a failed transsphenoidal surgery for Cushing's disease, treatment options include: 1) repeated transsphenoidal surgery; 2) bilateral adrenalectomies; 3) radiation therapy; 4) pharmacological therapy; or 5) a combination of these measures. The treatment options of bilateral adrenalectomy and radiation therapy are discussed in detail.

Bilateral Adrenalectomy

Bilateral adrenalectomy for the treatment of Cushing's disease became popular in the 1950s. As perioperative management and steroid replacement became widely available, patient mortality and immediate morbidity rates as a result of the operation were greatly reduced. Primary or secondary bilateral adrenalectomy for Cushing's disease has a very high success rate in reversing hypercortisolism, ranging from 88 to 100%. Over time, however, there is a significant risk of patients' developing Nelson's Syndrome. In patient series published since 1983 with adequate follow-up, the rate of Nelson's Syndrome ranged from 15 to 46%.^{8,23,29,32,34,48,50,57,69} Only one study that addressed the role of radiation therapy demonstrated that prior radiation therapy reduced the risk and delayed the onset of developing Nelson's Syndrome; however, this potential beneficial effect of radiotherapy remains understudied.⁵⁰ The average interval between a bilateral adrenalectomy and the development of Nelson's Syndrome is approximately 5 to 10 years, but may be as short as 6 months and as long as 24 years.^{32,34,50} The long-term risk of developing Nelson's Syndrome after a bilateral adrenalectomy is at least 25 to 30%, and there is a significant risk of major pituitary tumor enlargement, particularly in those patients with visible adenomas on MR imaging or computed tomography. Therefore, use of bilateral adrenalectomy as a first-line therapy is generally contraindicated.⁶⁹ Furthermore, as described later, the ACTH-secreting adenomas associated with Nelson's Syndrome tend to be invasive and relatively aggressive in their growth pattern, further complicating their management.

Radiation Therapy

Although radiation therapy was widely used as a first-line therapy for Cushing's disease from the 1940s to the early 1980s, it is typically used now as a secondary treatment after failed transsphenoidal surgery. In the largest series of patients undergoing secondary external radiation therapy after failed transsphenoidal surgery, remission rates ranged from 53 to 83%, and recurrence rates from 0 to 17%.^{21,31,73} The study results of Sonino and colleagues⁶⁹ indicate that prior unsuccessful surgery is a predictor of long-term success for external radiation therapy. In their study, all nine patients (100%) with prior transsphenoidal surgery had sustained remission after undergoing external radiation therapy, whereas only seven (50%) of 14 patients who

received radiation as a primary treatment had sustained remission.

In the two largest series of patients who underwent secondary radiosurgery using the Gamma knife (single fraction therapy), remission rates were 63%⁶⁶ and 73%.⁵⁹ The recurrence rate was 11% in the study of Sheehan and co-workers,⁶⁶ resulting in a control rate of 52%. A more recent report of 40 patients treated using Gamma knife radiosurgery as either a primary (in 11 patients) or secondary therapy (in 29 patients) demonstrated a 42% remission rate after a mean follow-up of 22 months.¹² Both external beam and stereotactic radiation therapy appear to result in similar rates of radiation-induced pituitary failure, ranging from 16 to 57%; the rates of hypopituitarism appear to increase with longer follow-up periods.^{17,21,41,49,57,69}

Overall, these studies indicate that radiation therapy is an effective secondary treatment for patients with Cushing's disease who have undergone unsuccessful surgery. Currently, however, given the relatively higher long-term remission rates in transsphenoidal adenomectomy, radiation therapy should be considered a first-line therapy only in cases of uncontrolled Cushing's disease with severe medical complications. In such patients who are medically unstable and in whom induction of anesthesia poses high risks, radiotherapy is a reasonable treatment option when performed in conjunction with adrenolytic medical therapy to achieve a relatively rapid lowering of cortisol levels.

Treatment of Nelson's Syndrome

As previously noted, after a patient with Cushing's disease undergoes bilateral adrenalectomy, the risk of developing Nelson's Syndrome is relatively high, ranging from 15 to 46%.^{8,23,29,32,34,48,50,57,69} The neurosurgical management of Nelson's Syndrome is challenging, due to the aggressive and often invasive nature of these ACTH-secreting adenomas. In five patient series published from 1982 to 2002, surgery was effective in improving or restoring vision and reducing the degree of hyperpigmentation in the great majority of patients. The ACTH levels normalized in fewer than 50% of patients, however, and additional radiation therapy was required in 20 to 30% of such patients to help control tumor growth.^{35,36,44,74,75}

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Address correspondence to: Daniel F. Kelly, M.D., John Wayne Cancer Institute at Saint John's Health Center, 2200 Santa Monica Blvd, Santa Monica Boulevard, California 90404. email: kellyd@jwci.org.