Late Recurrences of Cushing's Disease after Initial Successful Transsphenoidal Surgery

Chirag G. Patil, Daniel M. Prevedello, Shivanand P. Lad, Mary Lee Vance, Michael O. Thorner, Laurence Katznelson, and Edward R. Laws, Jr.

Department of Neurosurgery (C.G.P., S.P.L., L.K., E.R.L.), Stanford University School of Medicine, Stanford, California 94305; Department of Neurological Surgery (D.M.P.), University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania 15213; and Department of Internal Medicine-Endocrinology (M.L.V., M.O.T.), University of Virginia Health System, Charlottesville, Virginia 22908

Context: Few studies have systematically analyzed the long-term recurrence rates of Cushing's disease after initial successful transsphenoidal surgery.

Setting: This was a retrospective review of patients treated at the University of Virginia Medical Center.

Patients: A total of 215 subjects with Cushing's disease who underwent initial transsphenoidal surgery for resection of a presumed pituitary microadenoma from 1992–2006 were included.

Main Outcome Measures: Remission and recurrence rates of Cushing's disease were examined. Recurrence was defined as an elevated 24-h urine free cortisol with clinical symptoms consistent with Cushing's disease.

Results: Of the 215 patients who underwent transsphenoidal surgery for Cushing's disease, surgical remission was achieved in 184 (85.6%). The mean length of follow-up was 45 months. Actuarial recurrence rates of Cushing's disease after initially successful transsphenoidal surgery at 1, 2, 3, and 5 yr were 0.5, 6.7, 10.8, and 25.5%, respectively. Among the 184 patients who achieved remission, 32 (17.4%) patients followed for more than 6 months ultimately had a recurrence of Cushing's disease. The median time to recurrence was 39 months. Immediate postoperative hypocortisolemia (serum cortisol $\leq$ 2 μg/dl within 72-h surgery) was achieved in 97 (45.1%) patients. Patients who had postoperative serum cortisol of more than 2 μg/dl were 2.5 times more likely to have a recurrence than patients who had serum cortisol less than or equal to 2 μg/dl (odds ratio = 2.5; 95% confidence interval 1.12–5.52; $P = 0.022$).

Conclusions: A quarter of the patients with Cushing's disease who achieve surgical remission after transsphenoidal surgery, recur with long-term follow-up. This finding emphasizes the need for continued biochemical and clinical follow-up to ensure remission after surgery. (***J Clin Endocrinol Metab*** **93: 358–362, 2008)**

First described by Harvey Cushing in 1932, Cushing's disease results from overproduction of glucocorticoids due to excessive corticotropin (ACTH) secretion by a tumor of the pituitary gland's corticotroph cells (1, 2). Cushing's disease is uncommon, with an incidence between 0.7 and 2.4 cases per million per year (3). Cushing's disease results in obesity, diabetes mellitus, hypertension, muscle wasting, osteoporosis, depression, and cognitive deficits, and the 5-yr cardiovascular mortality for untreated disease is up to 50% (4, 5).

Successful long-term management of patients with Cushing's disease remains a challenge. Currently, the treatment of choice for patients with Cushing's disease is transsphenoidal microadenomectomy (6, 7). Other treatments used after failure of initial surgical therapy include repeat transsphenoidal surgery, medical

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Abbreviations: H&E, Hematoxylin and eosin; MRI, magnetic resonance imaging; UFC, urine free cortisol.

therapy to block adrenal cortisol production, bilateral adrenalectomy, and radiotherapy/radiosurgery. With the advances in transsphenoidal microsurgery, recent series have reported immediate postoperative remission rates of 59–88% (8–16). However, long-term follow-up with actuarial 3- and 5-yr recurrence rates has rarely been reported (13, 17). In this study we report on the recurrence rates in a series of patients with Cushing's disease who underwent initial successful transsphenoidal surgery. We compare the risk of recurrence in patients with postoperative hypocortisolemia (serum cortisol ≤ 2 μg/dl) to those with serum cortisol more than 2 μg/dl. In addition, a comparison of long-term recurrence rates of patients with pathology confirmed ACTH-staining tumor to patients without pathological confirmation is presented.

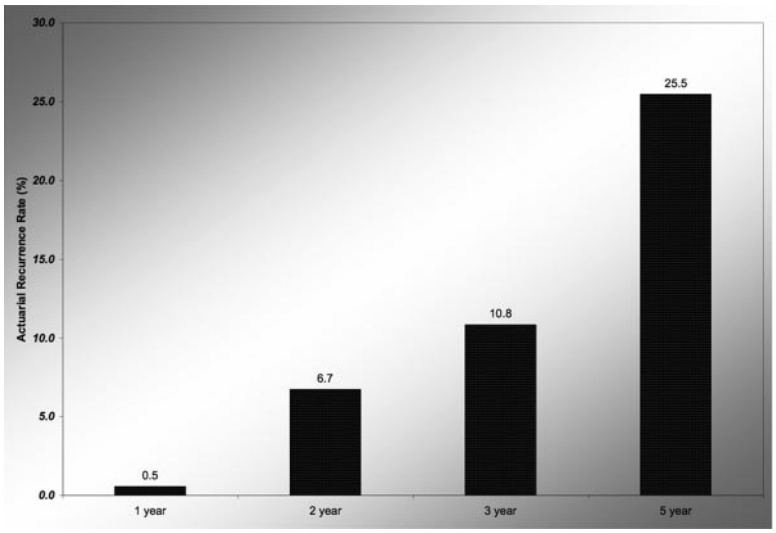

FIG. 1. Actuarial recurrence rates of Cushing's disease after initial successful transsphenoidal surgery.

Patients and Methods

Inclusion criteria

Patients with Cushing's disease who underwent transsphenoidal resection of a presumed pituitary microadenoma at the University of Virginia Medical Center between 1992 and 2006, and who had at least a 6-month clinical follow-up were included in the current analysis. Patients with previous surgery for Cushing's disease or with a macroadenoma were excluded. Microadenoma was defined as a pituitary tumor with a diameter of less than 1 cm in any dimension on magnetic resonance imaging (MRI). Institutional review board approval was obtained before initiation of this study.

Diagnostic criteria

Cushing's disease was diagnosed using previously described and currently accepted standard criteria (18, 19). At least two elevated 24-h urine free cortisol (UFC) levels were used to establish hypercortisolemia in all patients. MRI evidence of a pituitary microadenoma, inferior petrosal sinus sampling, or high-dose dexamethasone suppression tests were used to establish pituitary dependence.

Surgical management

All operations were performed by a single neurosurgeon (E.R.L.). The surgical technique and strategy used have been previously described in detail (18). Briefly, resection of all presumed microadenomas was performed via the transsphenoidal approach. After the sella was exposed and the dura incised, the entire pituitary gland was carefully examined, and all abnormal tissue was submitted to pathology. In patients with no clear abnormal tissue, depending on age, history, and severity of disease, a hemi-hypophysectomy, subtotal hypophysectomy, or, rarely, a total hypophysectomy was performed. Aggressiveness of surgery was individualized considering patient characteristics, preoperative morbidity, severity of clinical symptoms, and patient preference.

Specimen handling and histological analysis

The resected specimens were immediately placed on a moist piece of Telfa (Kendall Co., Mansfield, MA), bagged, and submitted in their entirety to the neuropathologist (18). 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 (18).

Endocrine follow-up and remission criteria

A senior neuroendocrinologist supervised the endocrine evaluation in all patients.

Preoperatively and intraoperatively, patients did not receive exogenous glucocorticoid. Postoperatively, patients were administered hydrocortisone only after adrenal insufficiency was confirmed. Postoperatively, serum cortisol measurements were obtained every 6 h until serum cortisol was less than 2 μg/dl or until 72 h after surgery. Adrenal insufficiency was defined by a serum cortisol of less than 5 μg/dl and/or onset of addisonian symptoms. If serum cortisol was less than 5 μg/dl, hydrocortisone supplementation was initiated.

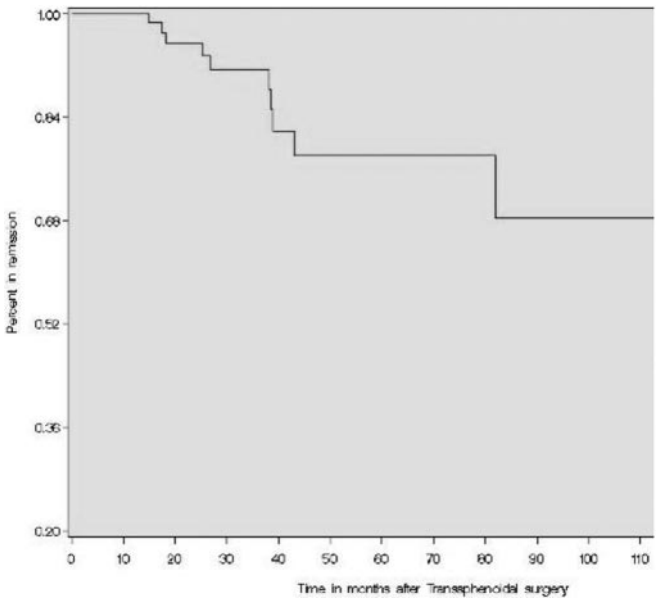

FIG. 2. Kaplan-Meier curve showing freedom from recurrence of Cushing's disease in patients with successful initial transsphenoidal surgery.

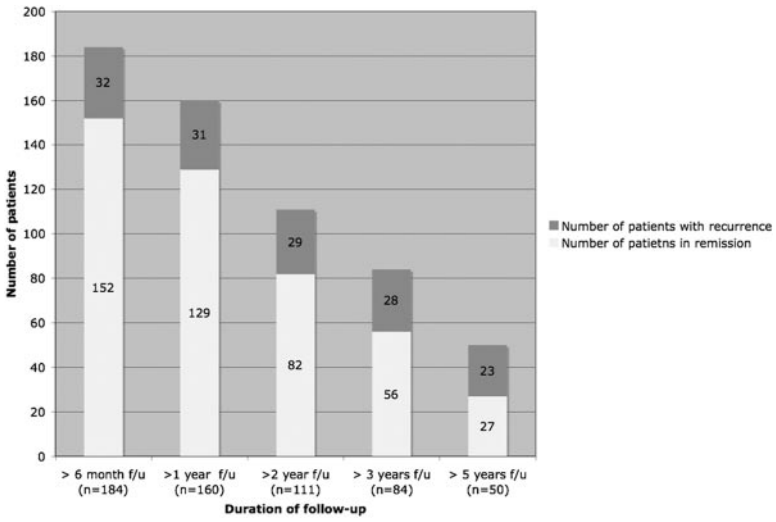

Fig. 3. Proportion of patients with recurrence after initial successful transsphenoidal surgery for Cushing's disease. Number of patients who had surgery more than 1, 2, 3, and 5 yr from the end of data collection were 184, 174, 154, and 112, respectively. f/u, Follow-up.

Remission at follow-up was defined as a normal postoperative 24-h UFC or continued need for corticosteroid replacement after transsphenoidal surgery. The first postoperative evaluation was performed 6–8 wk after surgery. Patients were seen in clinic, off hydrocortisone replacement for 2 d, and serum cortisol levels were measured. If cortisol levels were low (<5 μg/dl), patients resumed hydrocortisone replacement. Other patients underwent a one sample, 24-h UFC to establish remission status. Recurrence was defined as an elevated 24-h UFC with clinical symptoms consistent with Cushing's disease.

Statistical analysis

Descriptive statistics, including mean age, mean length of follow-up, and median time to recurrence, were tabulated. Proportion of patients who ultimately suffered a recurrence after a follow-up duration of greater than 6 months, and 1, 2, 3, and 5 yr was ascertained. Kaplan-Meier analysis for recurrence was performed using the product-limit method. Actuarial 1, 2, 3, and 5-yr recurrence rates were determined from the Kaplan-Meier analysis. Differences in recurrence rates between patient groups (postoperative cortisol ≤ 2 μg/dl *vs.* > 2 μg/dl and pathology positive *vs.* pathology negative, preoperative MRI positive *vs.* MRI negative) were assessed using χ^2 analysis. A P value of less than 0.05 was considered significant. Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

Results

A total of 307 patients who underwent first-time transsphenoidal surgery for a confirmed or presumed pituitary microadenoma between 1992 and 2006, were identified. Of these, 215 patients who had a follow-up of more than 6 months were included in this analysis.

Patient characteristics

The mean age of patients at transsphenoidal surgery was 39.6 ± 15 yr, and 77.7% of the patients were women. The average duration of symptoms before diagnosis was 43 months (median 36, range 2–244). A pituitary protocol MRI scan, with and without contrast, was obtained in all patients. Of patients, 61% had preoperative MRI findings consistent with a pituitary microadenoma. In 39% of subjects, the MRI scan was equivocal for a tumor, and inferior petrosal sinus sampling revealed a central to peripheral ACTH gradient consistent with a pituitary source for the ACTH overproduction. The mean preoperative 24-h UFC and serum ACTH were 393 μg/24 h (range 51–4000) and 74 pg/ml (range 7–272), respectively.

Surgical resection and histopathological findings

Of patients, 81% underwent a selective adenomectomy, 7% a subtotal hypophysectomy, and 7% a hemi-hypophysectomy. A total hypophysectomy was performed on a small number of patients (3%) who were clinically ill and in whom a microadenoma was not found during initial systematic exploration of the pituitary gland. Of patients, 75% were found to have an ACTH-staining adenoma, 14% had no abnormality, 7% had Crooke's hyaline change, and 2% had two adenomas: ACTH and prolactin staining.

Recurrence

Of the 215 patients that underwent transsphenoidal surgery, 184 (85.6%) achieved remission as defined by a normal postoperative UFC or continued need for corticosteroid replacement after surgery. The mean length of follow-up was 45 months (median 33, range 6–166). Actuarial recurrence rates of Cushing's disease after initial successful transsphenoidal surgery at 1, 2, 3, and 5 yr were 0.5, 6.7, 10.8, and 25.5%, respectively (Fig. 1). Kaplan-Meier analysis of recurrence of Cushing's disease after initial successful transsphenoidal surgery is depicted in Fig. 2. Overall, Cushing's disease recurred in 17.4% of patients with initial successful transsphenoidal surgery. The median duration to recurrence was 39 months (range 3–134). Of the 84 patients with postoperative remission followed for greater than 3–13 yr, 28 (33.3%) ultimately had a recurrence (Fig. 3). Of patients followed for greater than 5–13 yr (n = 50), 46% ultimately recurred.

A total of 97 patients (45.5%) fulfilled a stricter immediate postoperative remission criterion of a decrease in serum cortisol to less than or equal to 2 μg/dl within 72-h transsphenoidal surgery. Patients who had postoperative serum cortisol of more than 2 μg/dl were 2.5 times more likely to have a recurrence than patients who had a serum cortisol less than or equal to 2 μg/dl within 72-h surgery (odds ratio = 2.5; 95% confidence interval 1.12–5.52; $P = 0.022$). The 1, 2, 3, and 5-yr actuarial recurrence rates for patients with postoperative cortisol of more than 2 μg/dl were 1.1, 10.4, 14.1, and 28.5%, respectively. In comparison, the 1, 2, 3, and 5-yr actuarial recurrence rates for patients with postoperative cortisol of less than or equal to 2 μg/dl were 0, 3.0, 7.0, and 20.6%, respectively (Fig. 4).

In patients with confirmed postoperative remission, there was

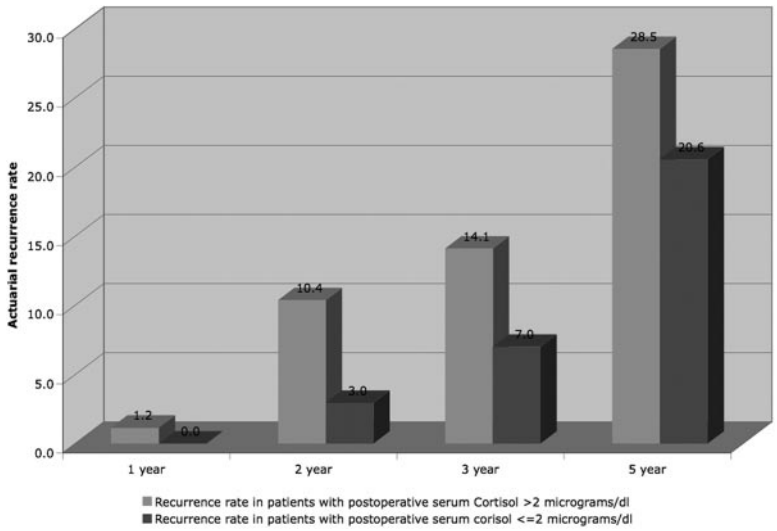

Fig. 4. Comparison of actuarial recurrence rates of patients with postoperative cortisol more than 2 μg/dl and less than or equal to 2 μg/dl.

no difference in recurrence rates between patients with pathology confirmed ACTH tumors (17.8%) and patients with negative pathology (17.8 *vs.* 15.8%, respectively; $P = 0.78$). Similarly, in patients with confirmed postoperative remission, there was no difference in recurrence rates between patients with a preoperative MRI confirmed microadenoma and patients with negative MRI (19.5 *vs.* 13.6%, respectively; $P = 0.32$).

Discussion

In our series, remission of Cushing's disease after initial transsphenoidal surgery (defined as a normal postoperative 24-h UFC or continued need for glucocorticoid replacement) was achieved in 85.6% of patients with a microadenoma. Large clinical series have reported remission rates of 59–90% (10, 12, 13, 20–25). Our remission rate falls at the higher end of this range in part due to the exclusion of patients with macroadenomas. The rationale for our exclusion of patients with a macroadenoma was to report recurrence rates in a homogeneous group of patients that represented the most common presentation of Cushing's disease.

Leinung *et al.* (17) reported a 50% recurrence rate in pediatric Cushing's disease after initial successful transsphenoidal surgery with a mean follow-up of 6.7 yr. This and other pediatric series have suggested that ACTH secreting tumors may have a high propensity for recurrence (26, 27). Several small studies have published short-term relapse rates of 0–13% with a median follow-up of less than 2 yr (28–30). Larger studies with longer follow-up have reported overall recurrence rates of 5–27% with a median time to recurrence of 33–59 months (11, 13, 16, 20, 21, 24, 31, 32). In our study the overall recurrence rate of Cushing's disease after initial successful transsphenoidal surgery was a comparable 17.4%. However, we found higher recurrence rates with prolonged follow-up, and it is likely that the methodology used to describe recurrence in prior studies underestimates the true 5-yr recurrence rate. For example, the actuarial 5-yr recurrence rate in our study as determined from the Kaplan-Meier analysis was 25.5%. Therefore, although our overall recurrence rate (17.4%) appears to be acceptable and consistent with previous reports, it disguises the true 5-yr actuarial recurrence rate of 25.5%.

The 1-, 3-, and 5-yr actuarial recurrence rates for Cushing's disease after initial successful transsphenoidal surgery are rarely reported in the literature. Chen *et al.* (13) reported a 5-yr recurrence rate of 27%. In our series, the 5-yr actuarial recurrence rate was a comparable 25.5%. Future studies with prospective designs and long-term follow-up with no (or minimal) attrition are necessary to characterize the true long-term recurrence rates. Nonetheless, our study highlights that with appropriate and prolonged follow-up, the recurrence of Cushing's disease is common. Strategies to manage these recurrences are necessary for the successful long-term management of patients with Cushing's disease. The options for managing recurrence include repeat transsphenoidal surgery, medical therapy with adrenal blockade, bilateral adrenalectomy, and radiation therapy (conventional or stereotactic radiosurgery) (25).

We defined postoperative remission as a normal 24-h UFC or continued need for glucocorticoid replacement. Some of the variability in recurrence rates between published studies can be attributed to the different criteria used to define remission. Therefore, we wanted to assess the impact of a different, stricter remission criterion (decrease in serum cortisol to ≤ 2 μg/dl within 72-h surgery) on long-term recurrence rates. Of the 215 total patients, 97 (45.5%) fulfilled this remission criterion. Patients who had postoperative serum cortisol of more than 2 μg/dl were two and half times more likely to have a recurrence than patients who had a postoperative serum cortisol less than or equal to 2 μg/dl. The 3-yr actuarial recurrence rates of patients with postoperative cortisol of more than 2 μg/dl and less than or equal to 2 μg/dl were 14.1 and 7.0%, respectively. Thus, patients that had a decrease in serum cortisol to less than or equal to 2 μg/dl after transsphenoidal surgery were less likely to recur. However, given that only 45% of our patients fulfilled this remission criterion, the disadvantage of using this criterion is that it excludes many patients who will go on to have long-term remission of their Cushing's disease.

Lack of pathological confirmation has been associated with lower remission rates. Invitti *et al.* (33) reported significant differences in remission rates related to the histological confirmation of an adenoma but reported no significant differences in recurrence rates. Similarly, we found that in patients who achieve postoperative remission, there was no difference in recurrence rates between patients with and without pathological confirmation of ACTH-staining tumor.

The long-term recurrence rate for other benign secreting tumors of the pituitary gland such as GH secreting tumors is only

about 2–6% (34, 35). Thus, ACTH secreting tumors appear to have a much higher recurrence rate and, presumably, a different biology that makes them resistant to surgical cure. Further investigation into the biology of these tumors is necessary to elucidate the mechanisms underlying the frequent recurrences and to improve the long-term outcomes of patients with Cushing's disease.

Acknowledgments

Address all correspondence and requests for reprints to: Chirag G. Patil, M.D., Stanford Hospital, Department of Neurosurgery, 300 Pasteur Drive, Room R281 MC5327, Stanford, California 94305. E-mail: chiragpatil@gmail.com.

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References

1. **Cushing H** 1932 The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism). Bull Johns Hopkins Hosp 50:137–195
2. **Lanzino G, Maartens NF, Laws Jr ER** 2002 Cushing's case XLV: Minnie G. J Neurosurg 97:231–234
3. **Lindholm J, Juul S, Jorgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, Hagen C, Jorgensen J, Kosteljanetz M, Kristensen L, Laurberg P, Schmidt K, Weeke J** 2001 Incidence and late prognosis of Cushing's syndrome: a population-based study. J Clin Endocrinol Metab 86:117–123
4. **Dekkers OM, Biermasz NR, Pereira AM, Roelfsema F, van Aken MO, Voormolen JH, Romijn JA** 2007 Mortality in patients treated for Cushing's disease is increased, compared with patients treated for nonfunctioning pituitary macroadenoma. J Clin Endocrinol Metab 92:976–981
5. **Orth DN** 1995 Cushing's syndrome. N Engl J Med 332:791–803
6. **Laws ER, Reitmeyer M, Thapar K, Vance ML** 2002 Cushing's disease resulting from pituitary corticotrophic microadenoma. Treatment results from transsphenoidal microsurgery and gamma knife radiosurgery. Neurochirurgie 48(2–3 Pt 2):294–299
7. **Reitmeyer M, Vance ML, Laws Jr ER** 2002 The neurosurgical management of Cushing's disease. Mol Cell Endocrinol 197:73–79
8. **De Tommasi C, Vance ML, Okonkwo DO, Diallo A, Laws Jr ER** 2005 Surgical management of adrenocorticotropic hormone-secreting macroadenomas: outcome and challenges in patients with Cushing's disease or Nelson's syndrome. J Neurosurg 103:825–830
9. **Vignati F, Berselli ME, Loi P** 1994 Early postoperative evaluation in patients with Cushing's disease: usefulness of ovine corticotropin-releasing hormone test in the prediction of recurrence of disease. Eur J Endocrinol 130:235–241
10. **Pieters GF, Hermus AR, Meijer E, Smals AG, Kloppenborg PW** 1989 Predictive factors for initial cure and relapse rate after pituitary surgery for Cushing's disease. J Clin Endocrinol Metab 69:1122–1126
11. **Rees DA, Hanna FW, Davies JS, Mills RG, Vafidis J, Scanlon MF** 2002 Long-term follow-up results of transsphenoidal surgery for Cushing's disease in a single centre using strict criteria for remission. Clin Endocrinol (Oxf) 56:541–551
12. **Sheehan JM, Lopes MB, Sheehan JP, Ellegala D, Webb KM, Laws Jr ER** 2000 Results of transsphenoidal surgery for Cushing's disease in patients with no histologically confirmed tumor. Neurosurgery 47:33–36
13. **Chen JC, Amar AP, Choi S, Singer P, Couldwell WT, Weiss MH** 2003 Transsphenoidal microsurgical treatment of Cushing disease: postoperative assessment of surgical efficacy by application of an overnight low-dose dexamethasone suppression test. J Neurosurg 98:967–973
14. **Boggan JE, Tyrrell JB, Wilson CB** 1983 Transsphenoidal microsurgical management of Cushing's disease. Report of 100 cases. J Neurosurg 59:195–200
15. **Chandler WF, Schteingart DE, Lloyd RV, McKeever PE, Ibarra-Perez G** 1987 Surgical treatment of Cushing's disease. J Neurosurg 66:204–212
16. **Ram Z, Nieman LK, Cutler Jr GB, Chrousos GP, Doppman JL, Oldfield EH** 1994 Early repeat surgery for persistent Cushing's disease. J Neurosurg 80:37–45
17. **Leinung MC, Kane LA, Scheithauer BW, Carpenter PC, Laws Jr ER, Zimmerman D** 1995 Long term follow-up of transsphenoidal surgery for the treatment of Cushing's disease in childhood. J Clin Endocrinol Metab 80:2475–2479
18. **Pouratian N, Prevedello DM, Jagannathan J, Lopes MB, Vance ML, Laws Jr ER** 2007 Outcomes and management of patients with Cushing's disease without pathological confirmation of tumor resection after transsphenoidal surgery. J Clin Endocrinol Metab 92:3383–3388
19. **Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, Fava GA, Findling JW, Gaillard RC, Grossman AB, Kola B, Lacroix A, Mancini T, Mantero F, Newell-Price J, Nieman LK, Sonino N, Vance ML, Giustina A, Boscaro M** 2003 Diagnosis and complications of Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab 88:5593–5602
20. **Bochicchio D, Losa M, Buchfelder M** 1995 Factors influencing the immediate and late outcome of Cushing's disease treated by transsphenoidal surgery: a retrospective study by the European Cushing's Disease Survey Group. J Clin Endocrinol Metab 80:3114–3120
21. **Utz AL, Swearingen B, Biller BM** 2005 Pituitary surgery and postoperative management in Cushing's disease. Endocrinol Metab Clin North Am 34:459–478
22. **Barbetta L, Dall'Asta C, Tomei G, Locatelli M, Giovanelli M, Ambrosi B** 2001 Assessment of cure and recurrence after pituitary surgery for Cushing's disease. Acta Neurochir (Wien) 143:477–481
23. **Sonino N, Zielezny M, Fava GA, Fallo F, Boscaro M** 1996 Risk factors and long-term outcome in pituitary-dependent Cushing's disease. J Clin Endocrinol Metab 81:2647–2652
24. **Hammer GD, Tyrrell JB, Lamborn KR, Applebury CB, Hannegan ET, Bell S, Rahl R, Lu A, Wilson CB** 2004 Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. J Clin Endocrinol Metab 89:6348–6357
25. **Locatelli M, Vance ML, Laws ER** 2005 Clinical review: the strategy of immediate reoperation for transsphenoidal surgery for Cushing's disease. J Clin Endocrinol Metab 90:5478–5482
26. **Kane LA, Leinung MC, Scheithauer BW, Bergstralh EJ, Laws Jr ER, Groover RV, Kovacs K, Horvath E, Zimmerman D** 1994 Pituitary adenomas in childhood and adolescence. J Clin Endocrinol Metab 79:1135–1140
27. **Kanter AS, Diallo AO, Jane Jr JA, Sheehan JP, Asthagiri AR, Oskouian RJ, Okonkwo DO, Sansur CA, Vance ML, Rogol AD, Laws Jr ER** 2005 Single-center experience with pediatric Cushing's disease. J Neurosurg 103:413–420
28. **Bigos ST, Somma M, Rasio E, Eastman RC, Lanthier A, Johnston HH, Hardy J** 1980 Cushing's disease: management by transsphenoidal pituitary microsurgery. J Clin Endocrinol Metab 50:348–354
29. **Salassa RM, Laws Jr ER, Carpenter PC, Northcutt RC** 1978 Transsphenoidal removal of pituitary microadenoma in Cushing's disease. Mayo Clin Proc 53:24–28
30. **Arnott RD, Pestell RG, McKelvie PA, Henderson JK, McNeill PM, Alford FP** 1990 A critical evaluation of transsphenoidal pituitary surgery in the treatment of Cushing's disease: prediction of outcome. Acta Endocrinol (Copenh) 123:423–430
31. **Atkinson AB, Kennedy A, Wiggam MI, McCance DR, Sheridan B** 2005 Long-term remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance. Clin Endocrinol (Oxf) 63:549–559
32. **Oldfield EH** 2003 Cushing disease. J Neurosurg 98:948–951
33. **Invitti C, Pecori Giraldi F, de Martin M, Cavagnini F** 1999 Diagnosis and management of Cushing's syndrome: results of an Italian multicentre study. Study Group of the Italian Society of Endocrinology on the Pathophysiology of the Hypothalamic-Pituitary-Adrenal Axis. J Clin Endocrinol Metab 84:440–448
34. **Freda PU, Wardlaw SL, Post KD** 1998 Long-term endocrinological follow-up evaluation in 115 patients who underwent transsphenoidal surgery for acromegaly. J Neurosurg 89:353–358
35. **Kreutzer J, Vance ML, Lopes MB, Laws Jr ER** 2001 Surgical management of GH-secreting pituitary adenomas: an outcome study using modern remission criteria. J Clin Endocrinol Metab 86:4072–4077