

ORIGINAL

Recurrence of Cushing's disease after primary transsphenoidal surgery in a university hospital in Korea

Jung Hee Kim¹⁾, Chan Soo Shin¹⁾, Sun Ha Paek²⁾, Hee Won Jung²⁾, Sang Wan Kim^{1), 3)} and Seong Yeon Kim¹⁾

¹⁾ Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea

²⁾ Department of Neurosurgery, Seoul National University College of Medicine, Seoul, South Korea

³⁾ Division of Endocrinology and Metabolism, Seoul Metropolitan Government Boramae Medical Center, Seoul, South Korea

Abstract. Successful long-term management of patients with Cushing's disease (CD) remains a challenge. To date, studies on the long-term outcome of patients with CD have been conducted mainly in Caucasians. Our objective was to assess the recurrence rate in patients who underwent transsphenoidal surgery (TSS) in the management of CD and to identify predictive markers for the long-term outcomes of CD in Korea. The long-term outcome in 54 patients who underwent TSS for the treatment of CD from 1984 to 2010 was retrospectively reviewed. Recurrence was defined as an elevated serum cortisol or an elevated 24 hour urine free cortisol or a suppressed serum cortisol by dexamethasone higher than 138 nmol/L. Mean age at diagnosis was 35.8 ± 12.8 years and median follow-up duration was 50.7 months. Initial successful TSS was obtained in 38 patients (70.4%). Among these 38 patients, 18 (47.4%) patients had a recurrence of CD. Preoperative serum cortisol level was significantly associated with recurrence. Pathologic confirmation of an adenoma was marginally associated with lower risk of recurrence. Positive results of imaging study and presence of microadenoma were not associated with risk of recurrence. Recurrence rate of CD after initial successful TSS was 32.4% at 5 years and 54.6% at 10 years, respectively. Following initial successful TSS, close long-term endocrine surveillance is mandatory as the recurrence rate increases with time. Preoperative serum cortisol level and pathologic confirmation of an adenoma may have a predictive value for recurrence of CD after TSS.

Key words: Cushing's disease, Transsphenoidal surgery, Recurrence, Cortisol

CUSHING'S DISEASE (CD) is a very rare disorder with an estimated incidence of 3-4 cases per 1,000,000 individuals [1]. However, CD is the most common cause of spontaneous Cushing's syndrome, occurring in 60% to 70% of Cushing's patients. CD patients have a mortality rate four times higher than age- and gender-matched subjects [2, 3]. The majority of the complica-

tions experienced by patients are cardiovascular complications including coronary heart disease, congestive heart failure, and cerebrovascular events [3]. Lindholm *et al.* reported that 6 of 20 patients with persistent hypercortisolism after initial transsphenoidal surgery (TSS) died; however, only 1 of 45 patients who had been cured through TSS died [2]. Therefore, early diagnosis and successful treatment of CD are warranted.

Generally, remission is obtained in 65% to 85% of patients with Cushing's disease [4-8], depending upon the size and location of the tumor, surgical expertise, length of follow-up, and the biochemical criteria for remission [9]. However, successful long-term management of patients with CD remains a challenge as the recurrence rate is 5% to 10% at 5 years and 10% to 20% at 10 years [4, 5, 7, 10-13]. Moreover, the risk does not seem to plateau even after 20 years, and a 2- to 3-fold increase in mortality affects those patients in

Submitted Mar. 14, 2012; Accepted Jun. 1, 2012 as EJ12-0109
Released online in J-STAGE as advance publication Jun. 22, 2012

Correspondence to: Sang Wan Kim, Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul National University College of Medicine, Seoul Metropolitan Government Borame Medical Center, Seoul 156-707, South Korea.

E-mail: swkimmd@snu.ac.kr

Correspondence to: Seong Yeon Kim, Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul 110-744, South Korea.

E-mail: seongyk@plaza.snu.ac.kr

whom initial cure was not obtained [6, 10, 14, 15]. In this respect, to identify favorable predictive markers for the recurrence of CD might be useful.

Favorable predictors associated with successful adrenalectomy include detection of the microadenoma by magnetic resonance imaging (MRI), a well-defined tumor that is not invading either the basal dura or cavernous sinus, histological confirmation of an ACTH-secreting tumor, low postoperative serum cortisol levels, and long-lasting adrenal insufficiency. Nevertheless, none of them have shown consistent results [6, 15-18].

To date, studies on the long-term outcome of Cushing's disease patients have been conducted mainly in Caucasians. The available studies on the long-term recurrence of CD in Asian population are very limited [19, 20]. The aim of the present study was to assess the recurrence rate of CD in the Korean population over a long period. In addition, we wished to identify predictive markers for the long-term outcomes of CD patients.

Methods and Materials

A retrospective study of 54 patients (13 men; 41 women) who had undergone TSS for the treatment of CD at Seoul National University Hospital between January 1984 and December 2010 was performed. In the same period, 1,664 cases of pituitary tumors were operated in our hospital. Patients who had received previous treatment (*i.e.*, surgery or radiotherapy to the pituitary or adrenal glands) or were less than 6 months post-TSS were excluded.

All patients had symptoms consistent with hypercortisolism, which was verified by increased 24-hour urinary free cortisol (UFC) excretion and lack of suppression of the serum cortisol response (serum cortisol > 50 nmol/L) during a low-dose dexamethasone suppression test (0.5 mg every 6 hours for 48 hours). The diagnosis of pituitary-dependent Cushing's disease was suggested by analysis of ACTH, the response to high-dose dexamethasone suppression test (2 mg every 6 hours for 48 hours) (> 50% suppression of plasma cortisol from the basal value), pituitary imaging, and bilateral inferior petrosal sinus sampling (BIPSS). An ectopic source of ACTH secretion was also excluded when results were equivocal.

Pituitary adenomas not visible on magnetic resonance imaging (MRI) (Sigma, General Electric Medical Systems, Milwaukee, WI, USA) or computed

tomography (CT) (SOMATOM, Siemens, Forchheim, Germany) or adenomas <1 cm in diameter were classified as microadenomas. The positive finding on MRI was defined as visible tumor on MRI. BIPSS was performed if no adenoma was present on imaging. Basal petrosal sinus-to-peripheral plasma ACTH ratio ≥ 2.0 and post-corticotrophin-releasing hormone (CRH) stimulation ratio ≥ 3.0 were used to demonstrate pituitary ACTH hypersecretion. Resection of all presumed adenomas was performed *via* the transsphenoidal approach by one of three neurosurgeons at the same hospital.

Remission criteria included a normal postoperative 24-hour UFC or the continued need for corticosteroid replacement after TSS at the 6-month follow-up. Persistence criteria was defined by urinary free cortisol values >348 nmol/day or failure to suppress serum cortisol adequately after low-dose dexamethasone testing.

All patients were administered dexamethasone both intraoperatively and postoperatively. Therefore, the cortisol level within the first postoperative week was not included among the remission criteria.

Recurrence criteria included elevated serum cortisol, elevated 24-hour UFC, and serum cortisol >140 nmol/L following overnight dexamethasone suppression test after remission.

Plasma ACTH, serum cortisol, and 24-hour UFC excretion were measured using radioimmunoassay (Cis Bio, Gif sur Yvette, France) techniques.

Data are presented as mean \pm standard deviation (SD) or % (n) for descriptive statistics. *T*-test or Wilcoxon rank sum test were used for continuous variables, and the Fisher's exact or χ^2 test was used for nominal variables. Kaplan-Meier analysis for recurrence was performed using the product-limit method. Actuarial recurrence rates were determined from the Kaplan-Meier analysis. Receiver operating characteristic (ROC) curve analysis was used to figure out the cut point of the preoperative serum cortisol level for recurrence. Cox proportional hazards regression analysis was used for recurrence according to the preoperative cortisol level. All analyses were done using SPSS 16.0 for Windows (SPSS Inc, Chicago, IL). Two-sided *p* values <0.05 were considered evidence of statistical significance.

Results

The outcomes of the 54 patients are summarized in Fig. 1. Mean age at diagnosis was 35.8 ± 12.8 years, and median follow-up duration was 50.7 months (range,

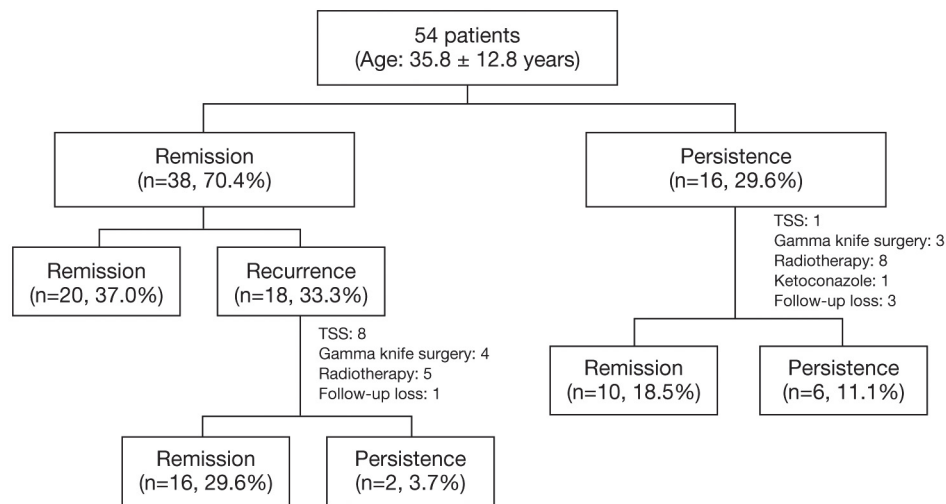


Fig. 1 Outcomes of 54 patients treated with transsphenoidal surgery for Cushing's disease
TSS, transsphenoidal surgery

Table 1 Comparisons of clinical, biochemical and radiological parameters between initial remission and persistence groups

Variables	Remission (n = 38)	Persistence (n = 16)	<i>P</i>
Age at diagnosis (year)	34.9 ± 12.6	38.4 ± 13.5	0.386
Female	81.6% (31)	62.5% (10)	0.478
ACTH before surgery (pmol/L)	17.9 ± 10.5 (37)	18.8 ± 17.3 (16)	0.700
Serum cortisol before surgery (nmol/L)	679.0 ± 229.1 (36)	808.4 ± 582.1 (16)	0.972
UFC before surgery (nmol /day)	1413.9 ± 818.9 (35)	2298.8 ± 1363.1 (16)	0.148
Microadenoma	93.3% (28/30)	93.3% (14/15)	0.840
MRI (positive finding) before surgery	86.1% (31/36)	87.5% (14/16)	0.986
Lateralization at BIPSS	80% (24/30)	61.5% (8/13)	0.631
Adenoma at pathology	96.7% (29/30)	87.5% (14/16)	0.098
ACTH after surgery (pmol/L)	4.98 ± 2.27 (21)	8.83 ± 4.95 (7)	0.092
Serum cortisol after surgery (nmol/L)	135.2 ± 138 (21)	441.6 ± 270.5 (6)	0.003
UFC after surgery (nmol /day)	85.3 ± 83.1 (20)	1083.6 ± 1481.6 (11)	<0.001
MRI (positive finding) after surgery	10% (1/10)	33.3% (2/6)	0.518
Follow-up duration (months)	106.7 ± 61.3	92.2 ± 57.2	0.320

Data are mean ± SD (n) or % (n); ACTH, adrenocorticotrophic hormone; UFC, urine free cortisol; BIPSS, bilateral inferior petrosal sinus sampling; MRI, magnetic resonance imaging

11.4-174.2 months). Sixteen patients did not achieve remission in the immediate postoperative period and required further therapy. Thirty-eight patients (7 men, 31 women) achieved remission and were followed for a long period. The initial success rate of TSS was 70.4%. The mean age at diagnosis for the 38 patients who achieved remission was 34.9 years (range, 16-71 years). Eighteen of the patients who achieved initial remission relapsed.

Comparisons of clinical, biochemical, and radiological parameters between the initial remission and persistence groups were shown in Table 1. There were no significant differences in the preoperative biochemical or radiological findings and the presence of adenoma at pathology between the initial remission and persistence groups.

Several parameters were also compared between the long-term remission and recurrence groups (Table 2).

Patients who remained in remission showed lower serum cortisol levels before surgery than patients with recurrence ($p < 0.05$). Pathologic confirmation of an adenoma was marginally associated with a lower risk of recurrence ($p = 0.057$). Positive findings on an imaging study and the presence of a microadenoma were not associated with a lower risk of recurrence. The duration of follow-up was longer in the recurrence group than in the remission group. Furthermore, no differences were identified between the remission and recurrence groups with respect to postoperative plasma ACTH, serum cortisol, and 24-hour UFC (Fig. 2).

Of the 16 patients who failed to achieve initial remission, 3 patients were lost to follow-up; 1 patient underwent TSS again; 3 patients underwent gamma knife surgery; 8 patients received radiotherapy; and 1 patient received oral ketoconazole. Ten of the remaining 13 patients achieved remission. Among 18 patients with recurrence, 8 patients whose adenomas were visible on MRI underwent secondary TSS; 4 patients in whom adenomas were suspected but not clearly identified on MRI were treated with gamma knife surgery; and 5 patients who were suspected clinically (without any MRI findings) underwent radiotherapy. Sixteen of 18 patients achieved remission again.

The probability of recurrence-free survival of patients in immediate remission after pituitary surgery was 86.1% at 24 months, 67.6% at 60 months, and

45.4% at 120 months. Median time to recurrence was 57.2 months (range 13.0-148.0 months) (Fig. 3).

Patients were split into two groups based on a cut point for the preoperative serum cortisol level of 635 nmol/L, which was derived from the ROC curve analysis (AUC, 0.678). Cox proportional hazards regression analysis was performed for recurrence according to the different levels of preoperative cortisol. However, patients with preoperative cortisol levels ≥ 635 nmol/L did not show an increased risk for recurrence for compared to patients with preoperative cortisol levels < 635 nmol/L (hazard ratio = 1.129, $p = 0.826$).

No patients died due to intra- or postoperative complications. One patient suffered meningitis, and 9 patients developed hypopituitarism.

Discussion

Thirty-eight of 54 patients (70.3%) who underwent TSS did achieve initial remission, and 18 of those patients with recurrence. The recurrence rate of CD after initial successful TSS was 32.4% at 5 years and 54.6% at 10 years. Preoperative serum cortisol level was different between persistent remission group and recurrence groups. The pathology confirmation of adenoma was correlated with a lower risk of recurrence. Tumor size, postoperative plasma ACTH level, serum cortisol level, presence of visible tumor on preopera-

Table 2 Comparisons of clinical, biochemical and radiological parameters between long-term remission and recurrence groups

Variables	Remission (n = 20)	Recurrence (n = 18)	<i>p</i>
Age at diagnosis (year)	37.1 \pm 13.5	33.5 \pm 12.1	0.529
Female	90% (18)	72.2% (13)	0.265
ACTH before surgery (pmol/L)	21.1 \pm 11.2 (19)	13.9 \pm 8.7 (18)	0.051
Serum cortisol before surgery (nmol/L)	612.7 \pm 242.9 (19)	745.2 \pm 190.4 (17)	0.048
UFC before surgery (nmol /day)	1413.9 \pm 818.9 (18)	1958.2 \pm 1378.1 (17)	0.303
Microadenoma	80.0% (16)	77.7% (14)	0.412
MRI (positive finding) before surgery	85.0% (17/20)	94.4%(17/18)	0.999
Lateralization at IPSS	83.3% (15/18)	63.6% (7/11)	0.434
Adenoma at pathology	95.0% (19/20)	66.6% (12/18)	0.057
ACTH after surgery (pmol/L)	5.0 \pm 1.9 (14)	6.7 \pm 4.3 (7)	0.255
Serum cortisol after surgery (nmol/L)	106.1 \pm 85.6 (15)	253.9 \pm 223.6 (5)	0.123
UFC after surgery (nmol /day)	79.5 \pm 82.5 (14)	246.2 \pm 281.8 (7)	0.138
MRI (positive finding) after surgery	0.0 % (0)	5.6% (1)	0.300
Follow-up (months)	78.5 \pm 53.6	133.7 \pm 56.1	0.006

Data are mean \pm SD (n) or % (n); ACTH, adrenocorticotrophic hormone; UFC, urine free cortisol; MRI, magnetic resonance imaging; IPSS, inferior petrosal sinus sampling

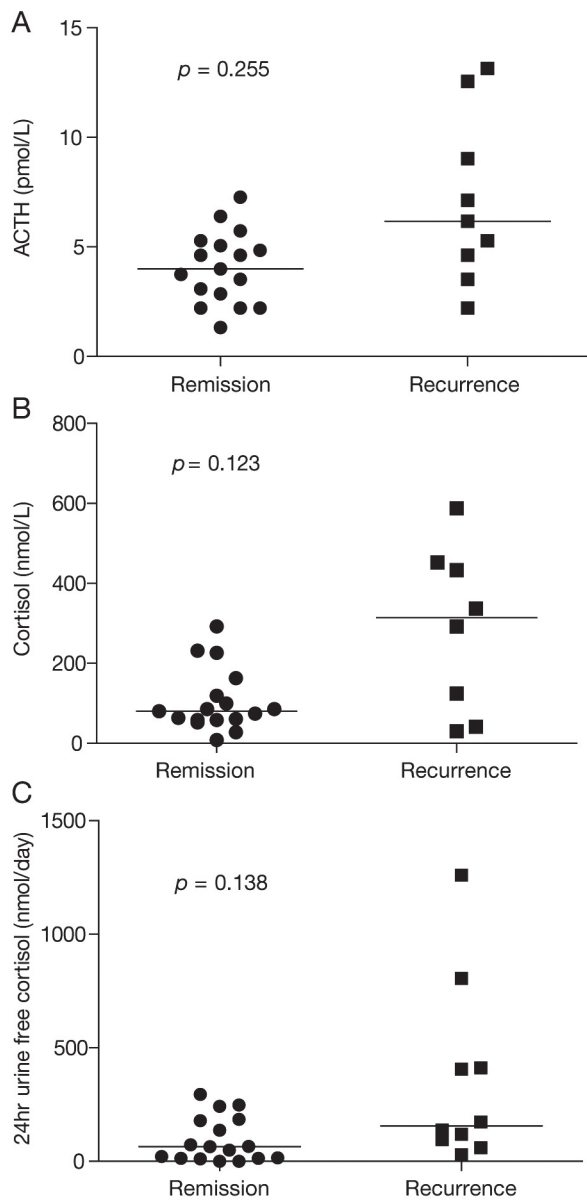


Fig. 2 Comparisons of postoperative (A) plasma adrenocorticotrophic hormone (ACTH), (B) serum cortisol, and (C) 24 hour urine free cortisol between remission and recurrence groups

tive imaging, and lateralization at BIPSS did not help predict recurrence.

Our initial success rate was similar to or slightly lower than that reported in other studies; however, the recurrence rate was higher than previous studies [4-9]. Atkinson *et al.* reported that the relapse rate was 22% (10/45) after a mean follow-up of 9.6 years. The median time to relapse was 5.3 years [10]. Swearingen *et al.* reported a much lower recurrence rate (7%) with a median time to recurrence of 5.7 years [13]. In

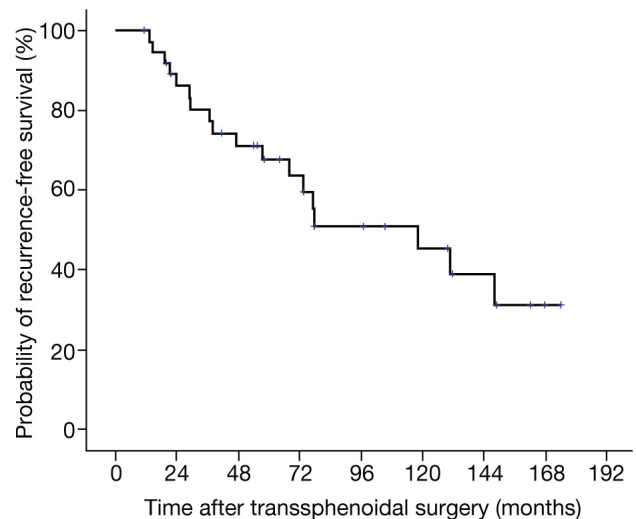


Fig. 3 Kaplan-Meier curve showing recurrence-free survival of patients with initial remission after transsphenoidal surgery for Cushing's disease

our study, the recurrence rate of patients in immediate remission after pituitary surgery was 13.9% at 24 months, 32.4% at 60 months, and 54.6% at 120 months. The median time to recurrence was 4.8 years. Several factors can be raised to explain difference between our and previous results. First, the criteria for remission or recurrence can attribute the variability of remission or recurrence rate. The morning serum cortisol levels as remission criteria varied such as less than 50, 55 or 138 nmol/L [15, 21-23]. Second, the duration of follow-up varied in each study. Prolonged follow-up leads to lower cure rates, as the incidence of recurrence increases with time. In our study, the median duration of follow-up was more than 4 years. Recurrence occurred >10 years after initially successful pituitary surgery in one patient, implying that lifelong follow-up of patients with CD is mandatory. Third, instead of higher recurrence rate, the complication rate was lower in our study than in previous studies [4]. The trend toward more conservative surgery in our center, focusing on preserving pituitary functions, resulted in a relatively higher recurrence rate. In the present study, the incidence of hypopituitarism following initial TSS, 16.7% (9/54), was lower than previous reports exceeding 25% [16]. In addition, the success rate of secondary TSS was higher than in other study [24].

The reason for the high recurrence rate for CD patients compared with conditions related to other benign secreting tumors of the pituitary gland (such as

growth hormone-secreting tumors) remains unknown [6]. CD patients might have a different biology that makes them resistant to surgical cure. Regardless of the initial outcome, all studies demonstrate that the risk of recurrence is relatively high and that this risk continues for many years [5, 7, 25].

In this study, preoperative serum cortisol level was significantly associated with recurrence. This result suggested that preoperative serum cortisol level might be related to the activity of CD. Though postoperative serum cortisol levels within the first postoperative week showed no difference between the long-term remission and recurrence groups in this study, low or undetectable postoperative serum cortisol levels has been suggested as one of the best biochemical predictor of long-term remission [5, 8, 15, 22, 23, 26]. Particularly, persistent postoperative morning serum cortisol levels <55 nmol/L are associated with remission and a recurrence rate of approximately 10% at 10 years [4, 10, 14, 15, 21, 22, 27, 28]. However, this is still a matter of debate. Yap *et al.* argued that undetectable postoperative cortisol levels did not always predict long-term remission in CD patients [23]. Moreover, occasionally serum cortisol level falls more gradually, possibly reflecting transient adrenal autonomy. For this reason, it is important to ensure that serum cortisol level has reached a nadir before considering further therapy. Recent study showed that delayed remission in 5.6 % of patients who had early elevated or normal UFC levels. These patients developed a delayed and persistent cortisol decrease after an average of 38 ± 50 postoperative days [9]. This observation suggested that serum cortisol levels 6 to 12 weeks after surgery may be more accurate in predicting long-term outcomes. Serum cortisol levels after 6 to 12 weeks were not included in our data. Thus, it is difficult to conclude that the postoperative serum cortisol level was not related to the recurrence of CD. Collectively, to determine the best time point to measure serum cortisol postoperatively requires further studies.

Our study revealed that pathologic confirmation of an adenoma was marginally associated with lower risk of recurrence ($p = 0.057$). Pathological confirmation of an

adenoma has been associated with a lower recurrence rate [21, 29]. As well, identification of a tumor preoperatively by CT or MRI was generally seen as a good prognostic indicator [5]. The morphology of the pituitary tumor based on the Knosp grade was assessed in the available 22 cases, but the outcome was not different according to the Knosp grade (data not shown) [30]. Intriguingly, in the study by Chee *et al.*, when histological and radiological confirmation of a tumor was assessed in combination, positive findings predicted a good outcome.

In our study, the preoperative plasma ACTH level was marginally associated with recurrence. The reason for the result is unclear and technical factors may underlie this unexpected finding, which has been observed by others [31, 32].

The retrospective nature and the small sample size were major limitations in our study. However, due to the very low incidence of CD, several studies were conducted retrospectively. In addition, the protocol was not consistent in the early years, and data were missing for some study subjects. Also, the specific histology types of pituitary adenomas were not described by pathologists in our hospital.

Few published studies are available regarding the long-term outcome of patients with CD after TSS. Nevertheless, most of studies included Caucasian. This study investigated long-term outcomes and predictive parameters of CD patients among Asians. Additionally, many predictive indicators, such as biochemical parameters and both radiological and pathological findings were assessed.

In conclusion, high preoperative cortisol levels and the absence of adenoma at pathology might predict recurrence of CD after primary TSS. Lifelong follow-up is required for patients with CD since the recurrence rate increases with time.

Appendix

The authors have no conflicts of interest.

This research was supported by the grant from Seoul National University Hospital (No. 0420070150).

References

1. Ross NS (1994) Epidemiology of Cushing's syndrome and subclinical disease. *Endocrinol Metab Clin North Am* 23: 539-546.
2. Lindholm J, Juul S, Jorgensen JO, Astrup J, Bjerre P, et al. (2001) Incidence and late prognosis of cushing's syndrome: a population-based study. *J Clin Endocrinol*

- Metab* 86: 117-123.
3. Etxabe J, Vazquez JA (1994) Morbidity and mortality in Cushing's disease: an epidemiological approach. *Clin Endocrinol (Oxf)* 40: 479-484.
 4. Hammer GD, Tyrrell JB, Lamborn KR, Applebury CB, Hannegan ET, et al. (2004) Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. *J Clin Endocrinol Metab* 89: 6348-6357.
 5. 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.
 6. Patil CG, Prevedello DM, Lad SP, Vance ML, Thorner MO, et al. (2008) Late recurrences of Cushing's disease after initial successful transsphenoidal surgery. *J Clin Endocrinol Metab* 93: 358-362.
 7. Sonino N, Zielesny 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.
 8. Biller BM, Grossman AB, Stewart PM, Melmed S, Bertagna X, et al. (2008) Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 93: 2454-2462.
 9. Valassi E, Biller BM, Swearingen B, Pecori Giraldi F, Losa M, et al. (2010) Delayed remission after transsphenoidal surgery in patients with Cushing's disease. *J Clin Endocrinol Metab* 95: 601-610.
 10. 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.
 11. Knappe UJ, Ludecke DK (1996) Persistent and recurrent hypercortisolism after transsphenoidal surgery for Cushing's disease. *Acta Neurochir Suppl* 65: 31-34.
 12. Shimon I, Ram Z, Cohen ZR, Hadani M (2002) Transsphenoidal surgery for Cushing's disease: endocrinological follow-up monitoring of 82 patients. *Neurosurgery* 51: 57-61; discussion 61-62.
 13. Swearingen B, Biller BM, Barker FG, 2nd, Katznelson L, Grinspoon S, et al. (1999) Long-term mortality after transsphenoidal surgery for Cushing disease. *Ann Intern Med* 130: 821-824.
 14. Rees DA, Hanna FW, Davies JS, Mills RG, Vafidis J, et al. (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.
 15. Pereira AM, van Aken MO, van Dulken H, Schutte PJ, Biermasz NR, et al. (2003) Long-term predictive value of postsurgical cortisol concentrations for cure and risk of recurrence in Cushing's disease. *J Clin Endocrinol Metab* 88: 5858-5864.
 16. Hofmann BM, Hlavac M, Martinez R, Buchfelder M, Muller OA, et al. (2008) Long-term results after microsurgery for Cushing disease: experience with 426 primary operations over 35 years. *J Neurosurg* 108: 9-18.
 17. Alwani RA, de Herder WW, van Aken MO, van den Berge JH, Delwel EJ, et al. (2010) Biochemical predictors of outcome of pituitary surgery for Cushing's disease. *Neuroendocrinology* 91: 169-178.
 18. Steffensen C, Bak AM, Rubeck KZ, Jorgensen JO (2010) Epidemiology of Cushing's syndrome. *Neuroendocrinology* 92 Suppl 1: 1-5.
 19. Lee YY, Kim JS, Mun BS, Shin CS, Kim SY, et al. (1997) The Results of transsphenoidal microsurgery for pituitary microadenoma in Cushing's disease. *Korean J Med* 53: 811-816 (In Korean).
 20. Arita K, Kurisu K, Tominaga A, Uozumi T (1998) A questionnaire study on outcome of transsphenoidal surgery for Cushing's disease in Japan. *Endocr J* 45: 805-806.
 21. Chee GH, Mathias DB, James RA, Kendall-Taylor P (2001) Transsphenoidal pituitary surgery in Cushing's disease: can we predict outcome? *Clin Endocrinol (Oxf)* 54: 617-626.
 22. Estrada J, Garcia-Uria J, Lamas C, Alfaro J, Lucas T, et al. (2001) The complete normalization of the adrenocortical function as the criterion of cure after transsphenoidal surgery for Cushing's disease. *J Clin Endocrinol Metab* 86: 5695-5699.
 23. Yap LB, Turner HE, Adams CB, Wass JA (2002) Undetectable postoperative cortisol does not always predict long-term remission in Cushing's disease: a single centre audit. *Clin Endocrinol (Oxf)* 56: 25-31.
 24. Benveniste RJ, King WA, Walsh J, Lee JS, Delman BN, et al. (2005) Repeated transsphenoidal surgery to treat recurrent or residual pituitary adenoma. *J Neurosurg* 102: 1004-1012.
 25. Dekkers OM, Biermasz NR, Pereira AM, Roelfsema F, van Aken MO, et al. (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.
 26. Trainer PJ, Lawrie HS, Verhelst J, Howlett TA, Lowe DG, et al. (1993) Transsphenoidal resection in Cushing's disease: undetectable serum cortisol as the definition of successful treatment. *Clin Endocrinol (Oxf)* 38: 73-78.
 27. Chen JC, Amar AP, Choi S, Singer P, Couldwell WT, et al. (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.
 28. Esposito F, Dusick JR, Cohan P, Moftakhar P, McArthur D, et al. (2006) Clinical review: Early morning cortisol levels as a predictor of remission after transsphenoidal surgery for Cushing's disease. *J Clin Endocrinol Metab* 91: 7-13.
 29. Tindall GT, Herring CJ, Clark RV, Adams DA, Watts

- NB (1990) Cushing's disease: results of transsphenoidal microsurgery with emphasis on surgical failures. *J Neurosurg* 72: 363-369.
30. Knosp E, Steiner E, Kitz K, Matula C (1993) Pituitary adenomas with invasion of the cavernous sinus space: a magnetic resonance imaging classification compared with surgical findings. *Neurosurgery* 33: 610-617; discussion 617-618.
31. 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.
32. Findling JW, Doppman JL (1994) Biochemical and radiologic diagnosis of Cushing's syndrome. *Endocrinol Metab Clin North Am* 23: 511-537.