Outcomes of Primary Transsphenoidal Surgery in Cushing Disease: Experience of a Tertiary Center

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■ BACKGROUND: **To report the initial and long-term remission rates and related factors, secondary treatments, and outcomes of a series of patients with Cushing disease (CD).**

■ METHODS: **We included 147 consecutive adult patients with CD who underwent primary transsphenoidal surgery (TSS) between 1998 and 2014 in this study. Eighty-two were followed up in the Cerrahpasa Medical Faculty Endocrinology and Metabolism outpatient clinic. Patients were requested to attend a long-term remission assessment; 55 could be contacted, and data for the remaining 27 patients' last visit to the outpatient clinics were reviewed for early and late remission. Six patients were excluded from the study. Magnetic resonance imaging (MRI) findings and pathologic results including mitosis, Ki-67 levels, and P53 in immunostaining of all patients were evaluated.**

■ RESULTS: **Data of 82 patients with CD with an average age of 36 years [interquartile range: 29–47] were analyzed with a mean follow-up of 7.5 years [interquartile range: 5–10]. Overall initial remission rates were 72.3% after TSS. Among the 82 patients, 16 patients had Gamma Knife radiosurgery and 7 patients underwent adrenalectomy. After these additional treatments, the long-term remission rate was found as 69.7%. The highest remission rates were with microadenomas. Recurrence was most frequently seen in patients without tumor evidence on MRI. Patients with high Ki-67 levels had higher recurrence rates in long-term follow-up ($P = 0.02$).**

■ CONCLUSION: **Life-long follow-up for patients with CD seems essential. Undetectable tumors on MRI before TSS and high Ki-67 immunopositivity were found as risk factors for tumor recurrence.**

INTRODUCTION

Cushing disease (CD) is the most common cause of endogenous hypercortisolism induced by a pituitary adrenocorticotropic hormone (ACTH)-secreting adenoma.[1,2]

Hypercortisolemia is associated with increased morbidity and mortality. Untreated patients with CD have a fivefold increased risk of cardiovascular mortality compared with patients in remission.[3,4] In contrast, patients who achieve normal cortisol levels with treatment have decreased mortality compared with those after long-term exposure to hypercortisolemia.[2,5] Therefore early diagnosis and treatment are of crucial importance. In addition, identification of patients at risk for treatment failure is essential.

The current first-line therapeutic approach for CD is transsphenoidal adenomectomy.[6] The goal of surgery is complete tumor removal while preserving pituitary function and avoiding complications. Although remission rates in the early postoperative period range from 55%–85%,[7,8] there are no obvious criteria for early remission. Different studies have considered early remission as undetectable or very low

Key words
- Cushing disease
- Remission
- Surgery

Abbreviations and Acronyms
ACTH: Adrenocorticotropic hormone
Cc: Crooke cell
CD: Cushing disease
CSS: Cavernous sinus sampling
DST: Dexamethasone-suppression testing
LDDST: Low-dose dexamethasone-suppression testing
MRI: Magnetic resonance imaging
RT: Radiotherapy
TSS: Transsphenoidal surgery
UFC: Urinary free cortisol

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Citation: World Neurosurg. (2017) 106:374-381.
http://dx.doi.org/10.1016/j.wneu.2017.07.014

*Journal homepage: **www.WORLDNEUROSURGERY.org***

*Available online: **www.sciencedirect.com***

postoperative cortisol levels,[2,9,10] whereas others defined remission as resolution of clinical signs, subnormal or undetectable levels of serum cortisol in serum or 24-hour urinary free cortisol (UFC), and normalization of circadian rhythm.[3,11]

Predictors of remission and recurrence rates are still controversial. Long-term relapse has been reported as up to 46%.[12] In the literature, remission rates are correlated with neurosurgical expertise; size, location, and invasion of tumor; methodology; biochemical criteria used in postoperative assessments; histologic characteristics; remission definition; and duration of follow-up.[3,4,13-15]

After the first surgery, a second surgery is recommended in patients with evidence of incomplete resection or pituitary lesion on imaging.[16] Radiotherapy (RT)/radiosurgery, medical treatment, and bilateral adrenalectomy are adjuvant therapies in resistant CD.

We aimed to assess the outcomes of patients with CD shortly after transsphenoidal surgery (TSS) and after long-term follow-up in our tertiary center. We also analyzed the remission and recurrence rates of CD and potential contributory factors for remission. Additionally, we defined adjuvant therapies and the results of these secondary treatments used after recurrence of CD over a long follow-up period.

MATERIALS AND METHODS

Patients

The study included 147 patients with CD who underwent TSS as a first-line treatment for CD in the Department of Neurosurgery at Cerrahpasa Medical Faculty between 1998 and 2014. All procedures were performed by the senior surgeon (NG). The general number of pituitary surgeries in this period for the same surgeon was 844. All patients were invited to the outpatient clinics of Endocrinology and Metabolism for prospective analysis of CD status. Eighty-two of the patients could be contacted, 55 of whom could attend the prospective analyses. The remaining 27 who lived outside the city could not attend new screening tests. Their final assessment was from their last records. Twenty one were eligible for this study. The remaining 6 patients did not have recent control, and their data were not completed. They were not taken into consideration. The time of operation, number and types of surgeries, period of disease, and demographic data of the patients were recorded.

Diagnosis of Cushing Disease

The diagnosis of CD was established using appropriate tests such as UFC, late-night plasma or salivary cortisol, and an overnight 1 mg dexamethasone suppression test (DST). Two positive tests from 3 patients were considered as hypercortisolism.[11] The classic 48-hour, low-dose 2 mg DST test was used to confirm the diagnosis. If the diagnosis was still controversial, a dexamethasone-CRH test was performed for a final decision. We performed ACTH, high-dose dexamethasone-suppression testing, 8 mg overnight DST, or intravenous CRH testing to confirm the diagnosis of CD. In the case of equivocal hormonal assessments, suspected pituitary imaging, and adenomas <6 mm, cavernous venous sinus sampling (CSS) with CRH stimulation was used to establish the central cause and to give an indication of lateralization. Post-CRH stimulation ratios of >3.0 were defined as an indication of the pituitary source of ACTH. Lateralization ratios were calculated by comparing ACTH levels simultaneously sampled from the right and left cavernous sinuses for each time point. The greatest lateralization ratio >1.4 at any point was used to predict the side of the pituitary adenoma.[17,18]

Radiologic Assessment

Before TSS, all patients underwent high-resolution 1.5 Tesla magnetic resonance imaging (MRI) of the pituitary-hypothalamic region. The presence of a hypointense lesion after intravenous injection of gadolinium indicated a pituitary adenoma. Adenomas with a diameter <1 cm were determined as microadenomas; those >1 cm were defined as macroadenomas. If the tumor was not clearly visualized on MRI, we defined it as an undetectable or suspected lesion.

Surgical Technique

The transsphenoidal microsurgical approach was the treatment method between 1998 and 2007. In 2007, we switched to endoscopic transsphenoidal surgery for pituitary lesions. The surgical technique consisted of selective resection of the adenoma if detected on MRI. Before surgery, all cases without evident pituitary adenoma underwent CSS. A gradient >1.4 for 1 side was considered lateralization. Selective adenomectomy was performed only if the adenoma could be found. If any suspicious lesion during the exploration could be detected, hemihypophysectomy was performed according to CSS lateralization. In the event that CSS was inconclusive, the whole gland was explored. If the suspect lesion on MRI was not located on the same side of the CSS lateralization, the suspect lesion was resected but the contralateral side was also explored. The adenoma was removed piecemeal or en bloc when feasible.

Histopathologic Assessment

Surgical specimens were collected for histopathologic analysis (standard hematoxylin-eosin, periodic acid—Schiff stain, and reticulin staining) and immunohistochemical staining for pituitary hormones, keratin, Ki-67, and p53. The result was considered positive if the presence of an ACTH-staining adenoma was confirmed. The pathology was considered as histology negative for a corticotropinoma if the adenoma staining was negative for ACTH. Ki-67 score, p53, and mitosis were reported, as well as the presence of Crooke hyalinization.

Initial Remission Assessment

Blood cortisol level below 2 mcg/L after TSS was considered early postoperative remission. We did not use steroid coverage during surgery. Steroid replacement was introduced when cortisol levels were below 2 mcg/L after the first day of surgery. Overall final remission was evaluated in the third month after surgery by basal cortisol, 24-hour UFC, midnight salivary cortisol, and overnight 1-mg DST suppression tests.

Long-Term Remission Assessment

For evaluating long-term remission, 55 patients were analyzed with prospective screening tests and 27 were screened using the records of their last visit in 2015 from our outpatient clinic's files. Six patients had inadequate data and were excluded. Basal cortisol, 24-hour UFC, midnight salivary cortisol, and overnight 1 mg