Research Article

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Evaluation of factors that affect remission and recurrence after endonasal endoscopic approach in Cushing disease

Cushing hastalığında endonazal endoskopik yaklaşım sonrası remisyon ve nükse etki eden faktörlerin değerlendirilmesi

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Abstract

Purpose: Clinical consequences of the endoscopic endonasal approach (EEA) for Cushing Diseases (CD) were investigated in a single-center series based on definitions and assessments of recurrence and remission.

Materials and methods: 825 patients were evaluated, including 64 patients with CD who underwent EEA at Ankara University Neurosurgery Department and were evaluated retrospectively between 2014 and 2021. Postoperative next-morning cortisol and adrenocorticotrophic hormone (ACTH) values were used to assess postoperative endocrinological remission.

Results: Twenty-two patients had macroadenoma, and 40 had microadenoma. In 2 patients, no lesions were detected in the sellar region, and a magnetic resonance imaging (-) CD diagnosis was done. Regardless of remission, the effect of the duration of glucocorticoid use after surgery on recurrence made examined. Glucocorticoid therapy was given in 46 patients (71%) after pituitary surgery. No recurrence was observed in 20 patients whose treatment was longer than one year. In 12 patients, the glucocorticoid therapy duration ranged from 6 months to 12 months, and four patients showed recurrence. The glucocorticoid therapy duration of >6 months predicted that recurrence would not occur (p<0.05).

Conclusion: The sustainability of hypocortisolemia is essential in the treatment of CD. The mainstay of CD treatment is appropriate postoperative follow-up and administration of the necessary medical and surgical interventions. Glucocorticoid therapy duration> six months after surgery predicts that recurrence will not occur. Long-term glucocorticoid therapy after surgery suggests surgical success.

Key words: Cushing disease, endonasal endoscopic approach, recurrence, remission.

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Öz

Amaç: Bu çalışmada, Cushing Hastalığı (CH) için endoskopik endonazal yaklaşımın (EEY) klinik sonuçları, remisyon ve nüks tanımları ve değerlendirmelerine dayalı olarak tek merkezli bir seride araştırıldı.

Gereç ve yöntem: Ankara Üniversitesi İbni Sina Hastanesi Nöroşirürji Anabilim Dalı'nda 2014-2021 yılları arasında EEY uygulanan 825 hasta arasında CH'lığı tanısı alan 64 hastanın verileri retrospektif olarak değerlendirildi. Postoperatif ertesi sabah kortizol ve adrenokortikotropik hormon (ACTH) değerleri postoperatif endokrinolojik remisyonu değerlendirmek için kullanıldı.

Bulgular: Yirmi iki hastada makroadenom ve 40 hastada mikroadenom saptandı. 2 hastada sellar bölgede lezyon saptanmadı, manyetik rezonans görüntüleme (-) CH tanısı kondu. Kırk hasta kadın, 12 hasta erkekti. Remisyondan bağımsız olarak ameliyat sonrası glukokortikoid kullanım süresinin nüks üzerine etkisi incelendi. Hipofiz cerrahisi sonrası 46 hastaya (%71) glukokortikoid tedavisi verildi. Tedavi süresi 1 yıldan uzun olan 20 hastada nüks gözlenmedi. 12 hastada glukokortikoid tedavi süresi 6 ay ile 1 yıl arasında değişmekteydi ve 4 hastada nüks görüldü. 6 aydan uzun glukokortikoid tedavi süresinin nüksün olmayacağını saptadığı öngörüldü (p<0,05).

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Sonuç: Hipokortizoleminin sürdürülebilirliği CH tedavisinde önemlidir. Ameliyattan sonra 6 aydan fazla glukokortikoid tedavi süresi, nüksün olmayacağını öngörmede yardımcıdır. CH tedavisinin temel dayanağı uygun postoperatif takip ve gerekli medikal ve cerrahi girişimlerin uygulanmasıdır.

Anahtar kelimeler: Cushing hastalığı, endoskopik endonazal yaklaşım, rekürrens, remisyon.

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Introduction

Cushing disease (CD) is the consequence of hypercortisolism that occurs in a pituitary corticotroph adenoma that releases adrenocorticotropic hormone (ACTH), and CH is a prevalent cause of endogenous Cushing syndrome (CS). As such, CD accounts for 75% of all cases of CS, with an incidence of 1.2-1.7 per million population and a prevalence of 39-940/ per million [1]. Furthermore, the CD is highly related to mortality, which is reported approximately twice that compared to the general population. However, the mortality rate of patients with CD who are in remission after treatment tends to be lower than that of patients not in remission [2].

CD treatment aims to achieve disease remission and long-term control without recurrence. Transsphenoidal surgery (TSS) is the first-line therapy for CD for tumor removal; microscopic or endoscopic TSS may be used. However, the remission and recurrence rates after the first TSS in patients with CD were reported to vary considerably, whereas high remission rates have been reported after endoscopic TSS [3].

A lifetime follow-up by endocrinologists is required after surgery for CD. Several factors may influence the outcomes after TSS, including the adenoma size, dural invasion, localization on preoperative imaging, intraoperative tumor visualization, preoperative ACTH level, urinary free cortisol (UFC)' levels, and histological confirmation of corticotroph adenomas. Hormone values should be measured after TSS, based on which the patient should be followed up. The main goal of the treatment of CD is to reduce cortisol production, which leads to clinical manifestations without causing a new hormone deficiency. Medical adrenalectomy, radiosurgery, and radiotherapy can be chosen in patients without remission after TSS.

This paper will discuss whether postoperative glucocorticoid therapy duration predicts recurrence and the effect of sex, Ki-67 index, and adenoma size on tumor gender.

Materials and methods

The study was designed in a reference center for pituitary surgery, of the 825 patients who received TSS between 2014 and 2021. Sixty-four patients diagnosed with CD were included in the study. Diurnal variation in ACTH and cortisol levels, 24-hour UFC measurement, and overnight or longer LDDST (2 mg/day for 48 hours) were used to diagnose CD. Inferior petrosal sinus sampling (IPSS) was performed on seven patients.

The patients were given 1 mg of oral dexamethasone at 11 pm, and the serum cortisol level was examined at 8 am in the LDDST. In addition, overnight 8-mg DST was used to distinguish CD from ectopic ACTH secretion. It involved the administration of '2 mg of dexamethasone' every 6 hours or a 'single dose of 8 mg DST' at 11 pm, followed by serum cortisol measurement on the next day, at 8 am.

One of the reliable tests to differentiate CH from the ectopic or pituitary origin is IPSS. IPSS is performed in cases of resistant CS after TSS, incompatibilities between biochemical and radiological imaging findings, and the absence of pituitary lesions on imaging [4, 5]. A 'petrosal sinus-to-peripheral ACTH gradient ratio' of ≥2.0 at baseline or ≥3.0 after CRH administration in the setting of sustained hypercortisolemia suggests a pituitary source of ACTH.

The most common reasons for patients to apply to the outpatient clinic are headaches and visual field loss, which was diagnosed with CD after an endocrinological evaluation. Preoperative MRI was performed for all the patients, and experienced radiologists evaluated the results. Adenomas <1 cm in size were considered microadenomas, and those >1 cm in size were considered macroadenomas [6-8] (Figure 1, 2).

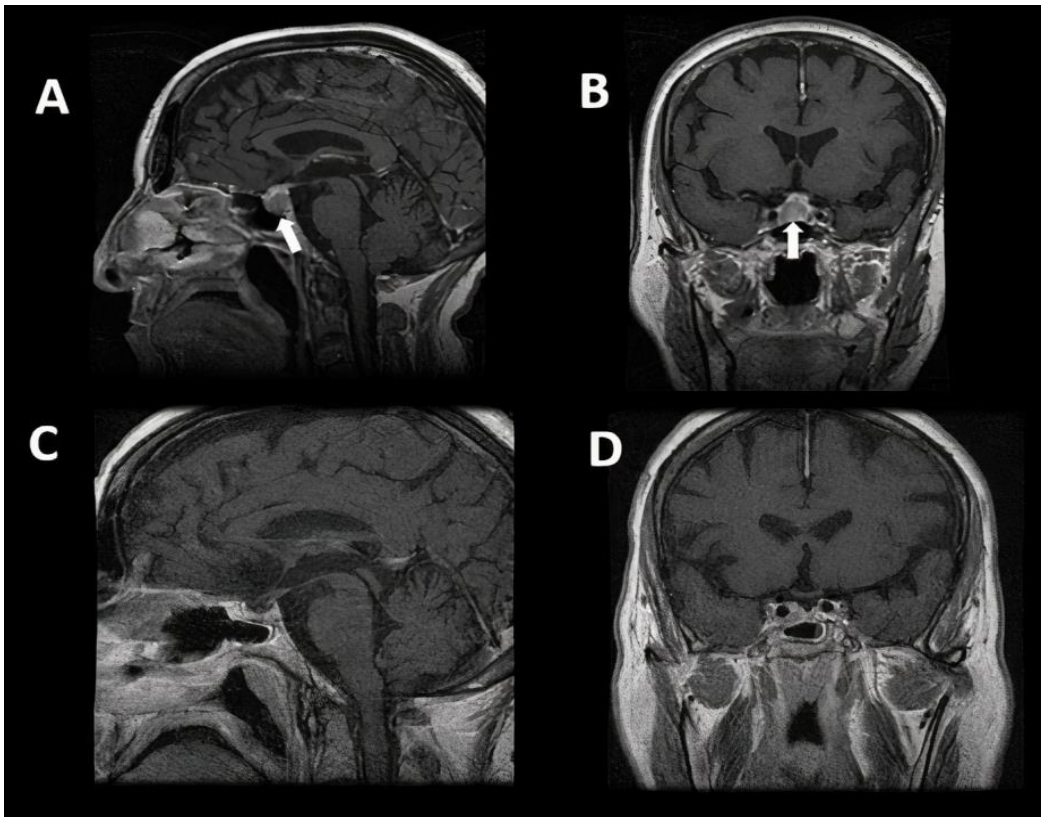

Figure 1. In contrast-enhanced pituitary MR images of a Cushing Disease with microadenoma

Pre-operative sagittal (A) and coronal (B) MRI sections showed the tumor (hypointense adenoma is indicated by a white arrow). Post-operative sagittal (C) and coronal (D) MRI sections no tumor is observed

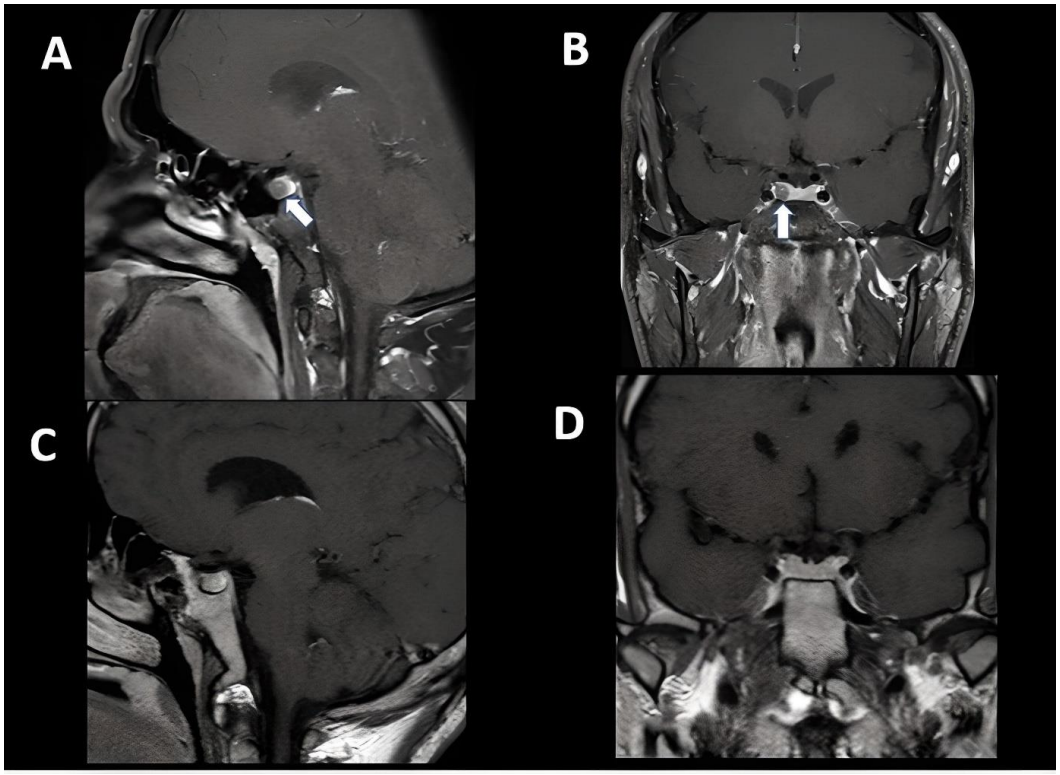

Figure 2. In contrast-enhanced pituitary MR images of a Cushing Disease with macro-adenoma

Pre-operative sagittal (A) and coronal (B) MRI sections showed the tumor (hypointense adenoma is indicated by a white arrow). Post-operative sagittal (C) and coronal (D) MRI sections no tumor is observed

The following day after the operation, all patients' cortisol and ACTH levels were measured. Our study evaluated remission based on the laboratory values obtained the following day after the surgery, with <2 µg/dl and <5 pg/ml as reference values, respectively. The postoperative duration of glucocorticoid use and the time to recurrence were investigated. Different morning cortisol cutoff values were used when remission was identified using biochemical tests, including 'morning cortisol levels.' Although these values ranged from 50 to 275.9 nmol/l, the cutoff of 50 nmol/l was most consistently used when morning serum cortisol level was measured without any other biochemical assay to define remission. In the pathological evaluation, the Ki-67 index values of the patients were also measured. Ki-67 index values <2% were evaluated as indicative of low mitotic activity [9-12]. Studies have evaluated whether the Ki-67 index affects tumor recurrence.

This study was approved by Ankara University Faculty of Medicine Human Arts Research Ethics Committee. No personal data or photographs were used against human and animal rights.

Statistical analysis

'IBM SPSS Statistics version 20 software (IBM Inc.)' was used for statistical analysis. The Pearson correlation analysis was used to test the relationship between age and recurrence. The Spearman correlation analysis was applied to test the relationship between glucocorticoid hormone therapy duration and recurrence. The chi-square test was applied to analyze the relationships of adenoma size, Ki-67 index, and next-morning ACTH value to recurrence.

Results

Sixty-four patients with CD who underwent EEA pituitary surgery at the referral clinic were included. Fifty patients (78%) were female, and 14 (22%) were male. The mean age was 41.6±12.68 (25-68) years, and the mean follow-up period of the patients was 25.5±8.24 (12-68) months. Twenty-two lesions were identified as macroadenomas, and 40, as microadenomas. Two patients had no lesions in the sellar region, so they were evaluated as having MRI (-) CD. (Table 1).

Of the patients, 34 (53%) were considered in remission biochemically for at least ≥1 year. Eleven patients (17%) developed panhypopituitarism. Nineteen patients (29%) did not achieve remission after TSS. Eight patients who had remission underwent reoperation because of tumor recurrence or relapse, of whom six again achieved remission after the reoperation. Twelve patients who did not achieve remission underwent reoperation, of

Table 1. Patients' distribution and laboratory values

	Microadenoma (n=40)	Macroadenoma (n=22)	MRI (-) CD (n=2)
Age, years	37 (19-61)	48 (23-70)	48 (43-54)
Female/male	37/3	14/8	1/1
Recurrent endoscopic TSS	16	3	1
Ki-67 index <2%	17 (5 with a tumor recurrence)	9 (3 with a tumor recurrence)	1
Serum cortisol value on the next day <2 µg/dl	14	1	1
Third-month control serum cortisol value <2 µg/dl	4 (Among 23 patients who underwent regular checkups)	1 (Among 18 patients who underwent regular checkups)	1
Serum ACTH value on the next day <5 pg/ml	11	3	1
Third-month control serum ACTH value <5 pg/ml	12 (Among 23 patients who underwent regular checkups)	4 (Among 18 patients who underwent regular checkups)	1
Panhypopituitarism after TSS	6	4	1
Persistent diabetes insipidus after TSS	3	2	
Cerebrospinal fluid rhinorrhea after TSS	2	2	1

TSS: transsphenoidal surgery, MRI: magnetic resonance imaging

whom 6 entered remission. During the repeated TSS (20 patients), 14 microadenomas, five macroadenomas, and 1 MRI (-) CD were found. Gamma knife surgery was performed in 1 patient with a microadenoma, and bilateral adrenalectomy was performed in 1 patient with a macroadenoma. After EEA, five patients (7.8%) had persistent central diabetes insipidus, and one patient (1.5%) had cerebral salt wasting. In 5 patients (7.8%), sellar floor repair was performed because of rhinorrhea.

The "Chi-Square Independence Test" was applied for a significant relationship between cortisol value on the first day after surgery and recurrence. The 24-h postoperative cortisol value was <2 µg/dl in 7 patients with microadenoma, <2 µg/dl in 1 patient with macroadenoma, and <2 µg/dl in 1 patient with MRI (-) CD. Of the patients with microadenoma who attended regular follow-up checkups, 9 and 5 were found to have 24-h postoperative cortisol values <2 and <5 µg/dl, respectively. Of those with macroadenomas who attended regular follow-up checkups, three had 24-h postoperative cortisol values <2 µg/dl <2 µg/dl in 2 patients with MRI (-) CD, which made regular control visits and in 1 patient with a recurrent microadenoma. There was no significant correlation between the cortisol value on the first day after surgery and recurrence (p=0.119).

The Ki-67 index was >10% in 5 patients, and four had a recurrence. In 17 patients, the Ki-67 index was <2%, and 2 had a recurrence. Of the patients with macroadenomas, 3 had Ki-67 index values >10%, and 2 had a recurrence. In 9 patients, the Ki-67 index was <2%, and one had a recurrence. One of the patients with MRI (-) CD had a Ki-67 index >2% and a recurrence. The "Chi-Square Independence Test" was applied for the Ki-67 index-affected recurrence. There was no significant correlation between the Ki-67 index and recurrence (p=0.640).

In 46 patients (71%), glucocorticoid administration was required after pituitary surgery. The postoperative glucocorticoid therapy duration was >1 year in 20 patients, of whom none had a recurrence. In 12 patients, the glucocorticoid therapy duration ranged from 6 to 12 months, and four patients showed recurrence. In 8 patients, the glucocorticoid therapy duration was <6 months, and four patients showed recurrence. In 6 patients, the glucocorticoid therapy duration was <1 month and four patients showed recurrence. "Spearman Correlation Analysis" was applied for the significant relationship between the duration of hormone use and recurrence. There was a significant correlation between the duration of hormone use and recurrence (p=0.003) (Table 2).

Table 2. Glucocorticoid therapy duration and time to recurrence

Relapse Patients		
Microadenoma (8)		
	GDT	**RT**
Patient 1	3 months	1st year
Patient 2	1 year	In the 3rd year
Patient 3	1 year	1st year
Patient 4	0	Within 18 months
Patient 5	6 months	In the 3rd year
Patient 6	0	Within 3 months
Patient 7	2 months	In the 6th year
Patient 8	3 weeks	In the 2nd year
Macroadenoma (3)		
	GDT	**RT**
Patient 1	3 months	In the 3rd year
Patient 2	6 months	Within 9 months
Patient 3	0	In the 5th year
MR - (1)		
	GDT	**RT**
Patient 1	0	Within 3 months

GDT: glucocorticoid therapy duration time, RT: recurrence time

Discussion

The glucocorticoid hormone therapy duration after surgery for CD has been reported to be a remission marker. Bochicchio et al. [22] reported that 5-year remission was achieved in 97% of the patients who received glucocorticoid replacement therapy for >1 year. Remission rates of 76% and 53% were reported in those who received glucocorticoid replacement therapy for <1 year and those without hormone replacement therapy. Bansal et al. [23] reported that continuing postoperative hypocortisolemia for >13 months predicted long-term remission at a mean follow-up of 74 months. Low postoperative cortisol level is an expected finding. Chronic hypocortisolemia after surgery can indicate remission [24]. Numerous studies are needed to predict short- or long-term remission. Alexandraki et al. [25] reported no improvement in the hypothalamic-pituitary-adrenal (HPA) axis over six months and one year and that predicts remission with specificity rates of 93% and 89%, respectively. Contrary to the findings of the other studies, Dimopoulou et al. [26] reported that long-term postoperative hypocortisolemia duration does not prevent CD recurrence. In our study, we discussed whether glucocorticoid therapy duration predicts recurrence, regardless of whether it affects hormonal remission. No recurrence was detected in the 28 patients who underwent glucocorticoid replacement therapy for >6 months during a mean follow-up of 5 years. Recurrence was observed in 12 patients who underwent replacement therapy for <1 year. In 4 patients, the need for hormone replacement was <2 weeks, which suggests surgical failure. However, postoperative glucocorticoid replacement therapy was not required in 8 patients, and recurrence was not detected in these patients. Our study's glucocorticoid therapy duration of >6 months predicted that recurrence would not occur (p<0.05). Postoperative hypocortisolemia can be affected by the amount of surgical resection, cortisol half-life, and reactive adrenal hyperplasia. These findings suggest the importance of repetitive hormone tests and correctly timing the need for replacement.

Cortisol and ACTH values measured on the next day after the operation can be used as early remission markers. Mayberg et al. [27] reported that in patients with cortisol levels <2.1 µg/dl in the first 72 hours after surgery, an 88% remission rate was achieved without a second surgery. This value could be used as a remission marker. In addition, low remission rates were found in patients with cortisol levels of 2.1-5.4 µg/dl (75%). Starke et al. [17] showed that low cortisol levels <5.4 µg/dl may be the best indicator of remission. However, Mayberg et al. [27] suggested that low cortisol levels the next day after the operation may be a short-term rather than a long-term remission marker. They attributed this to the continuation of cortisol production due to adrenal hyperplasia even if ACTH production was wholly stopped surgically. On the next day after surgery, they obtained a cortisol value of 74 nmol/l. In the literature, cortisol, and ACTH levels below a specific value have been evaluated as markers and predictors of hormonal remission. In our study, we examined whether cortisol and ACTH values predicted recurrence. The next day cortisol cutoff value was 2 µg/dl. Three of the 16 patients with cortisol levels <2 µg/dl on the following day had a recurrence one year later, and the cortisol value measured on the following day did not predict recurrence (p=0.119). Similarly, the cortisol values measured in the 42 patients who made a follow-up visit after 3 months did not predict recurrence (p=0.169). Ramm Pettersen et al. [28] reported that the probability of recurrence in patients with cortisol values >2 µg/dl in the first 72 hours after the operation is 2.5 times higher than in patients with cortisol values <2 µg/dl. However, the same study reported that 45% of the patients had cortisol values >2 µg/dl and did not include patients who were predicted to go into long-term remission.

The relationship between adenoma size and recurrence has been examined in many studies. In the study of Guaraldi et al. [13], patients with microadenoma benefited more from surgery. In addition, cavernous sinus invasion negatively affected the prognosis of macroadenomas. In the study of Clayton et al. [2], the remission rate was higher in patients with microadenomas. When only patients with macroadenomas were examined, the remission rate was higher in those who underwent endoscopic TSS. This can be explained by the surgeon's more expansive field of view in endoscopic surgery for invasive macroadenomas. Chandler et al. [14], Kaptain et al. [15], and Sarkar et al. [16] found that

the remission rate was higher in patients with microadenomas. In the study of Starke et al. [17], no significant difference was found between microadenomas and macroadenomas in terms of recurrence. The difference in recurrence rate according to adenoma size can be attributed to the experience of the surgical team and the choice of endoscopic or microscopic surgical approach. In our study, a proportionally higher recurrence rate was observed in the patients with macroadenomas than in those with microadenomas and macroadenomas, but the differences were not statistically significant (p=0.495).

Only a few studies have investigated the relationship between the Ki-67 index and CD recurrence. The cutoff Ki-67 index was 3% according to the 'World Health Organization classification,' and cases with Ki-67 index values above this cutoff were more aggressive and had poor prognoses [18]. A high Ki-67 index alone is not an indicator of poor prognosis. Liu et al. [19] reported that high Ki-67 index values did not significantly affect patients with recurrent CD. Kara et al. [20] reported a Ki-67 index >3%. They suggested its importance in CD cases with increasing tumor sizes, indicating invasion and aggressive prognosis. In the study of Keskin et al. [21], the Ki-67 index was 1.1%, and the high Ki-67 index was significant in CD recurrence. In our study, the cutoff Ki-67 index was 2%. In our series, Ki-67 index values >2 were not found to be significantly related to CD recurrence (p=0.640).

In conclusion, remission markers can change the frequency of patient follow-up or predict treatment response early. The most crucial aspect in treating CD is a proper follow-up after surgery and administration of the necessary medical and surgical interventions. In the treatment of CD, the sustainability of hypocortisolemia is essential. Glucocorticoid therapy duration> six months after surgery predicts no recurrence. Long-term glucocorticoid therapy after surgery also suggests surgical success. Postoperative cortisol and ACTH values did not predict recurrence in our study. This may be due to the amount of adenoma removed and variable compensatory mechanisms in the HPA axis.

Conflict of interest: No conflict of interest was declared by the authors.

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Authors' contributions to the article

M.C.K. and B.C.A. have constructed/constructed the main idea and hypothesis of the study. S.H. developed the theory and arranged/edited the material and method section. G.K. and C.M. have evaluated the data in the Results section. Discussion section of the article written by A.B.B., S.B. and M.A.U. M.C.K., B.C.A., S.H., G.K., A.B.B., C.M., and S.B. reviewed, corrected, and approved. In addition, all authors discussed the entire study and approved the final version.