Recurrent Cushing's Disease in Adults: Predictors and Long-Term Follow-Up

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ABSTRACT

Cushing's disease (CD) is characterized by endogenous hypercortisolism that is associated with increased mortality and morbidity. Due to high recurrence rates in CD, the determination of high-risk patients is of paramount importance. In this study, we aimed to determine recurrence rates and clinical, laboratory, and histological predictors of recurrence in a high volume single-center. This retrospective study included 273 CD patients operated in a single pituitary center between 1997 and 2020. The patients with early postoperative remission were further grouped according to recurrence status (recurrent and sustained remission groups). Demographic, radiologic, laboratory, pathologic, and follow-up clinical data of the patients were analyzed and compared between groups. The recurrence rate was 9.6 % in the first 5 years; however, the overall recurrence rate was 14.2 % in this study. Higher preoperative basal ACTH levels were significantly correlated with CD recurrence even with ACTH levels adjusted for tumor size, Ki-67 levels, and tumoral invasion. Recurrence rates were significantly higher in patients with ACTH levels higher than 55 pg/ml, tumor diameter > 9.5 mm, and if adrenal axis recovery was before 6 months. The severity of hypercortisolism, morbidities, and demographic factors except age were not predictive factors of recurrence. Based on our study data, younger age at diagnosis, a diagnosis of osteoporosis, higher preoperative ACTH levels, larger tumor size, invasive behavior, higher Ki 67 index, and early recovery of the adrenal axis during the postoperative period attracted attention as potential predictors of recurrent disease.

Introduction

Cushing's disease (CD) is an endocrine disorder characterized by overexpression of adrenocorticotropic hormone (ACTH) due to a pituitary adenoma and manifests with clinical and biochemical signs of endogenous hypercortisolism. Selective removal of pituitary adenoma has been the first treatment of choice in CD [1]. Remission rates after transsphenoidal surgery (TSS) in experienced centers vary from 70 to 90 % [2]. Persistent hypercortisolemia is associated with increased morbidity and mortality rates in patients with recurrent CD, therefore follow-up is crucial for early detection of any potential recurrence. Treatment options include repeat TSS, pituitary radiation therapy, medical therapy, and ultimately, adrenalectomy in recurrent or persistent CD; treatment should be tailored to each patient and prognostic markers should be taken into consideration when making treatment decisions [2].

Studies on surgical success and long-term follow-up of CD after transsphenoidal surgery have reported recurrence rates varying between 9 % and 25 % [3–5]. The reason of this variability in the remission rates is lack of either consensus or recommendation for criteria to define remission and recurrence in CD. A recent study conducted by Ferriere et al. included 25 studies, with each including ≥ 60 patients undergoing surgery, based on a standardized laboratory criterion for diagnosis. In this study, the mean recurrence rate was 18.5 %, and the mean time to recurrence was 47 months [6]. However, recurrence rates varied in a wide range from 6 to 44 %, in this analysis. Surgeon's experience with the procedure is another factor that can affect recurrence rates; recurrence rates were lower in TSS procedures performed by an experienced surgeon [5, 7]. Studies in the literature show that recurrence rates increase with the duration of follow-up [8–10]. CD displays wide heterogeneity in terms of diagnosis, treatment, and follow-up; therefore, it is very important to determine the risk of recurrence for disease management and prevention of mortality. Studies on recurrence risk have assessed several parameters including clinical features, histological and radiological features of the tumor, and post-operative remission but have reported conflicting results. In this retrospective study, we report a single-center experience, and aim to determine recurrence rates and clinical, laboratory, and histological predictors of recurrence.

Materials and Methods

Study design

Data from 300 patients with Cushing's disease were included in this retrospective study. Study patients were on follow-up at the Pituitary Center, Endocrinology and Metabolism Clinics of the Medical School of Kocaeli University, between 1997 and 2020. All patients had undergone a TSS surgery at the neurosurgery department same center. This study was approved by the Institutional Ethics Committee of the Medical School of Kocaeli University (14.01.2020-KOUGOKAEK-2020/11.29). Informed consent was not required given the retrospective design. Data on diagnoses, routine imaging studies, and laboratory workup during the pre/post-operative and follow-up periods were retrospectively retrieved from the hospital's outpatient files and health record system. Patients non-compliant with follow-up visits were called by phone to gather information about their current status. All preoperative diagnostic workup was reviewed, patients were assessed for potential recurrences and remission and post-operative disease activity was recorded.

Diagnosis of CD

Preoperative data including basal ACTH and cortisol levels, cortisol levels following low dose dexamethasone suppression test (DST), 24-hour urinary free cortisol levels, midnight salivary cortisol levels, and/or midnight blood cortisol levels were recorded for each patient. Fold changes from the upper limit of the reference range were recorded for 24-hour urinary-free cortisol measurements. Preoperative pituitary MRI scans and if available, postoperative follow-up MRI scans were evaluated. Pituitary adenomas < 10 mm in diameter on MRI scans were categorized as microadenomas and those ≥ 10 mm in diameter were categorized as macroadenoma. Furthermore, tumor size, tumoral invasion, and optic nerve compression were noted. Study investigators also evaluated reports from inferior petrosal sinus sampling (IPSS) studies performed in other medical centers (if any) to detect the location of any microadenoma in patients suspicious of Cushing's disease with negative MRI scans or adenomas less than 6 mm in diameter.

Standard treatment procedure and outcome measures

All patients underwent pituitary surgery performed by the same team led by the senior surgeon of the department of neurosurgery at the Pituitary Center of the Medical School of Kocaeli University. The same pathologist assessed the data from hematoxylin-eosin (HE) staining and immunohistochemical staining for cytokeratin, ACTH, p53, and Ki-67 of tumor samples obtained during the procedure. In most of cases an ACTH secreting adenoma was confirmed with distrupted reticular pattern and ACTH IHC staining positivity. In some cases a normal pituitary gland was found, showing a normal acinar reticular pattern. In such cases, the identification of Crooke's hyaline changes was used for histopathologic confirmation. However, there were still minor cases without pathological confirmation but had biochemical remission. Patients did not receive steroids before the surgical procedure. An early postoperative remission was considered if morning basal cortisol levels were < 5 µg/dl with signs of adrenal insufficiency or basal cortisol levels were < 2 µg/dl independently from the signs of adrenal insufficiency on the first postoperative day after the TSS procedure. Patients in remission were initiated on steroid replacement therapy. The time to recovery of the pituitary-adrenal axis was calculated based on the duration of steroid replacement therapy and/or results from ACTH stimulation tests. Subsequent therapies (repeat surgery, radiation therapy, or medical therapies) were recorded for patients who did not go into remission following surgery. Patients were reassessed for the existence of recurrence, following the recovery of the hypothalamic-pituitary-adrenal (HPA) axis and routinely once a year and also any timeline if the symptoms reappeared. Patients who underwent a low-dose DST and 24-hour urinary-free cortisol levels were measured for the follow-up. If these values were suggestive of recurrence, further confirmation of recurrence was done by nocturnal plasma/salivary cortisol measurements. Patients with biochemically-confirmed recurrence underwent a repeat pituitary MR imaging. Demographic and clinical features, comorbid conditions at the time of diagnosis laboratory findings, tumor size, tumoral invasion, pathological findings (Ki-67 levels, p53 staining), and time to HPA axis recovery in patients with recurrent disease were compared to those of patients in remission.

Statistics

An IBM SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA) software package was used for the statistical analysis. The normality of distribution was tested using the Kolmogorov–Smirnov test. Numerical variables were given as mean ± standard deviation and median (25th–75th percentiles) and frequencies (percentages). For non-normally distributed numerical variables, differences between the groups/materials were assessed using the Mann–Whitney U-test, while Fisher's Exact Chi-square test, Yates' Chi-square test, and Monte Carlo Chi-square test were used for categorical varia-

bles. The ROC curve was used to assess the diagnostic performance of the test. A p-value less than 0.05 was considered statistically significant for two-sided tests.

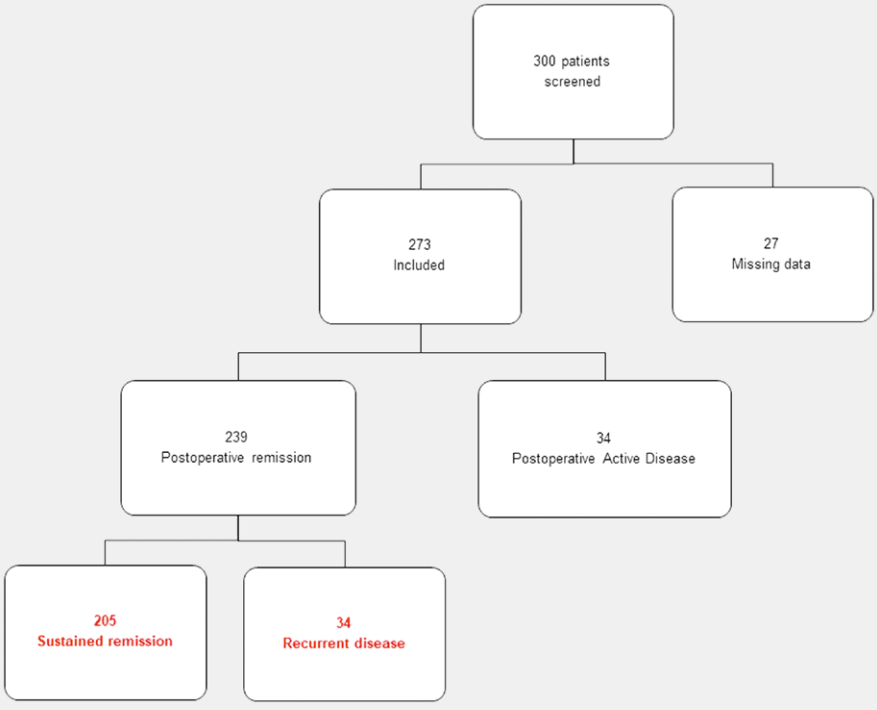
Results

This study included 300 patients diagnosed with CD and who underwent pituitary surgery in our hospital between 1997 and 2020. Out of 300 patients, 27 were excluded due to missing data. Out of 273 patients with available data, 34 patients had persistent disease and 239 patients (87.5 %) were in remission following an initial surgical procedure. Thirty-four patients (14.2 %) developed recurrence following initial remission and 205 patients remained in sustained remission. Therefore, the present study compared the clinical features of 205 patients in sustained remission to those of 34 patients with recurrent disease (a total of 239 patients) following initial pituitary surgery. The patient enrollment flowchart based on clinical outcomes is presented in ▶ **Fig. 1**.

Among 239 study patients, the mean age was 38.7 (31.0–47.0) years, and the median duration of follow-up was 41.3 months (22.7–71.1), 38 of the patients were males (15.9 %) and 201 (84.1 %) were females. No statistically significant gender difference was found between the group of patients with sustained remission and patients with the recurrent disease following initial remission (p = 0.646). Intergroup comparisons of age revealed that younger age at the time of diagnosis was associated with a higher rate of recurrences compared to older age [median 32.5 (23.7–50.0) years] (p = 0.027). Among the patients with available bone mineral density data, osteoporosis was detected in 25 % of 32 patients with recurrent disease and 9.3 % of 193 patients without recurrent disease and the difference was statistically significant (p = 0.017). Osteoporosis was defined as; BMD Z-score ≤ –2.0 in premenopausal women or men < 50 years or; BMD T-score ≤ –2.5 in premenopausal women or men > 50 years or any established fragility fracture. Although a history of thromboembolism, DM, or HT was more common among patients with recurrent disease, no statistically significant differences were found between the two groups, probably due to the small sample size (▶ **Table 1**).

Preoperative ACTH levels were significantly higher in patients who developed recurrences compared to those in sustained remission following surgical procedure, however preoperative cortisol levels were similar (p: 0.008 and p: 0.117; respectively) (▶ **Table 2**). The AUC of the receiver operating characteristic curve (ROC) for preoperative ACTH predicting recurrence was 0.644 (cutoff value = 55 ng/l, sensitivity 72.7 %, specificity 55.3 %). Recurrence rates were significantly higher in patients with ACTH levels higher than 55 pg/ml (p = 0.0029) (▶ **Fig. 2**). Preoperative dehydroepiandrosterone sulfate (DHEAS) levels were assessed in 156 patients with available data. The mean DHEAS levels were 332 µmol/l (± 326) in patients with recurrent disease and 268 µmol/l in patients in sustained remission. Although DHEAS levels were higher in the recurrent disease group, the intergroup difference did not reach statistical significance (p = 0.062). No significant intergroup differences were found in 24- midnight salivary cortisol levels, midnight blood cortisol level, and fold change from the upper limit of the reference range of 24-hour urinary cortisol (p: 0.60 p: 0.49 p: 0.55, and p: 0.28, respectively) (▶ **Table 2**).

Tumor size was larger in the recurrent disease group compared to the sustained remission group (p: 0.014). The receiver operating characteristic curve for tumor size predicting recurrence had



▶ **Fig. 1** Patient enrollment flowchart.

an AUC of 0.638 (cutoff value = 9.5 mm, sensitivity 61.2 %, specificity 65.7 %) (p = 0.013) (▶ **Fig. 2**). The tumoral invasion was detected in 31.3 % of patients with recurrent disease and 6.4 % of patients in sustained remission (p < 0.001) (▶ **Table 2**). In our study, the tumoral invasion was detected in a total of 23 patients. Forty-three percent of patients with tumoral invasion and 11 % of patients without tumoral invasion were in the recurrent disease group. In the overall study population, either from the recurrent disease group or sustained remission group, cavernous sinus invasion was detected in 19 patients and suprasellar invasion was detected in 6 patients. The recurrence rates were higher in those with macroadenoma and tumoral invasion. Pituitary MRI was negative for adenoma in 16 (7 %) of the patients and 9 of them was confirmed with IPSS, remaining 7 patients were surgically explored without IPSS. All these patients were pathologically confirmed and had postoperative early remission. IPSS data was available in 37 (15 %) of the patients, among them lateralization was seen in 40 % of the patients. The diagnostic accuracy rate could not be calculated due to small sample size.

Early postoperative cortisol levels were 4.2 (± 3.2) in the recurrent disease group and 3.6 (± 3.9) in the sustained remission group. Histological examination revealed that Ki-67 levels were higher in the recurrent disease compared to the sustained remission group (p = 0.014); however, p53 levels were similar between the two groups (p: 0.88) (▶ **Table 2**). In 223 patients with available Ki-67 data, recurrence rates were two times higher if the Ki-67 staining rate was ≥ 3 %, although no statistically significant intergroup difference was found due to the small sample size (p: 0.057) (▶ **Table 2**). The median time to adrenal axis recovery was 3.0 (1.0–4.0) months in patients with recurrent disease and 8.0 (3.0–13.0) months in patients without recurrent disease and the difference between the two groups was statistically significant (p < 0.001) (▶ **Table 2**). The time to adrenal axis recovery was 1 month at least and 24 months at most in 34 patients with recurrent disease, although adrenal axis recovery occurred within less than 3 months in 22 (64 %) out of these 34 patients. Adrenal axis recovery occurred as late as 69 months in patients without recurrent disease. Adrenal axis recovery occurred earlier in patients with the recurrent disease compared to patients with sustained remission.

Statistically significant correlations were found between preoperative basal ACTH levels and ACTH levels adjusted for tumor size, Ki-67 levels, and tumoral invasion (p: 0.004 p: 0.001 and p < 0.001,

▶ **Table 1** Demographic data of patients.

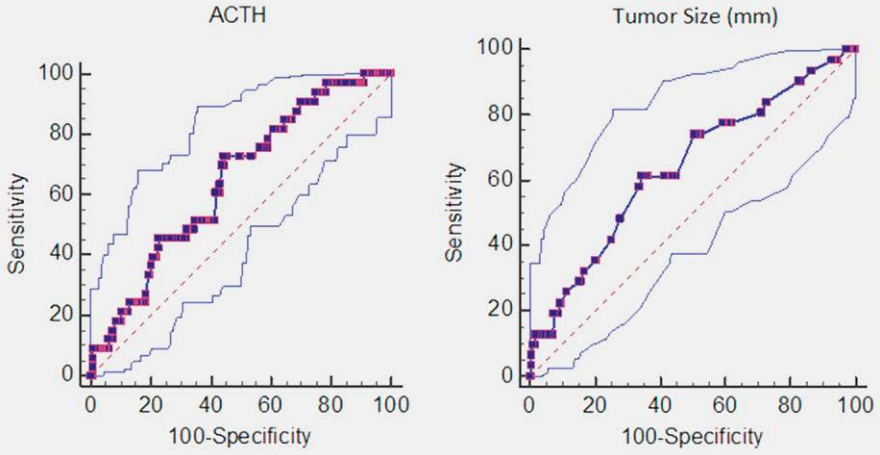
	Recurrent disease	Sustained remission	p-Value
Sex, n (%)			
Female	30 (88.2 %)	171 (83.4 %)	0.646
Male	4 (11.8 %)	34 (16.6 %)	
Age (years)	32.5 (23.75–50.0)	40.0 (32.5–49.0)	**0.027***
Osteoporosis (%)	25 %	9.3 %	**0.017***
Thromboembolism (%)	6.3 %	1.6 %	0.149
Mental disorders (%)	1.6 %	14.6 %	0.793
Diabetes mellitus (%)	61.8 %	43.7 %	0.078
Hypertension (%)	50.0 %	37.0 %	0.212

*p < 0.05 statistically significant.

▶ **Table 2** Preoperative and postoperative data.

	Recurrent disease	Sustained remission	p-Value
Preoperative period			
Basal ACTH (pg/ml)	67 (50.85–93.5)	53.2 (36.4–75.0)	**0.008***
Basal cortisol (µg/dl)	20.5 (16.12–25.36)	18.07 (14.02–22.8)	0.117
Midnight salivary cortisol (µg/dl)	0.46 (0.46–0.92)	0.50 (0.40–0.98)	0.600
Midnight plasma cortisol (mg/dl)	16.0 (11.0–19.31)	16.27 (13.0–21.01)	0.491
Urinary free cortisol/day (x ULN)	1.830 (1.23–3.22)	1.6 (1.0–2.72)	0.553
Tumor size (mm)	10 (7.0–16.0)	8 (5.0–11.750)	**0.014***
Tumor invasion n (%)	10 (31.3 %)	13 (6.4 %)	**< 0.001***
Optic nerve compression n (%)	4 (12.5 %)	14 (6.9 %)	0.282
Postoperative period			
Ki-67 (%)	2.0 (1.0–5.750)	1.0 (1.0–3.0)	0.014*
< 3 %	59 %	75 %	0.057
≥ 3 %	41 %	25 %	
p53 positivity	50 %	46.6 %	0.880
Time to adrenal axis recovery (m)	3.0 (1.0–4.0)	8.0 (3.0–13.0)	< 0.001*

*p < 0.05 statistically significant.



▶ **Fig. 2** Receiver operating characteristic (ROC) curve of preoperative ACTH levels and tumor size by the outcome of "recurrence."

▶ **Table 3** Comparisons of ACTH levels adjusted for tumor size, Ki-67 index and tumoral invasion.

	Recurrent disease	Sustained remission	p-Value*
Tumor size	76.00 (37.53–132)	36.82 (19.83–73.42)	0.004
Ki-67 index	86.04 (47.2–122.48)	51.55 (37.5–76.5)	0.001
Tumoral invasion	97.00 (57.4–154.75)	54,.00 (37.5–76.50)	<0.001

* $p < 0.05$ statistically significant.

respectively) (▶ **Table 3**). Therefore, higher preoperative basal ACTH levels were associated with higher recurrence rates independently from tumor size, Ki-67 levels, and tumoral invasion (▶ **Fig. 3**).

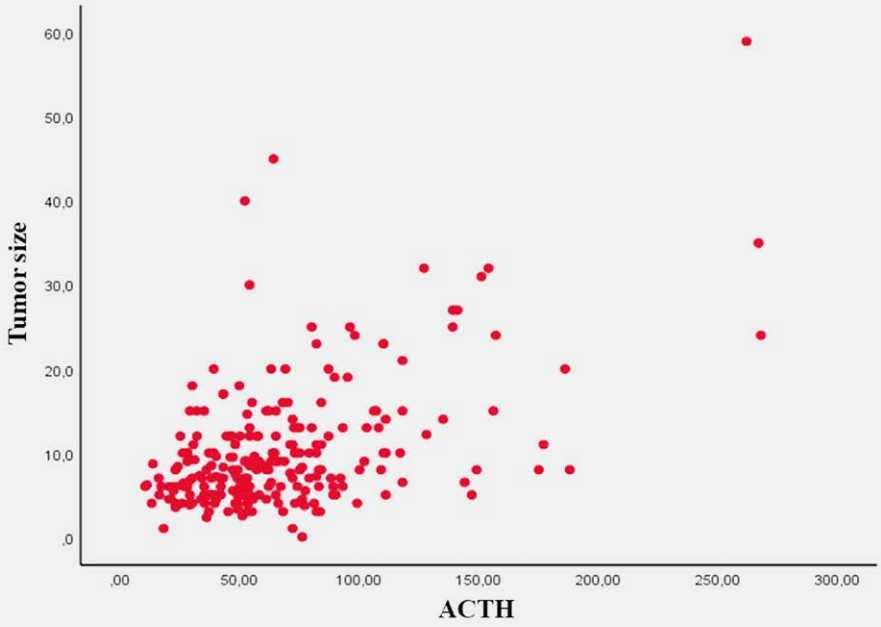
Discussion

Cushing's disease is fatal if left untreated and recurrence rates are high as shown in the present study. Thus, lifelong annual follow-up of clinical and biochemical parameters is of paramount importance. Recurrence rates reported in the literature are not consistent due to the heterogeneity of criteria used to define the recurrent disease. It would be more rational to define the situation as a persistent disease, in patients who present with hypercortisolemia within < 6 months after the surgery, although they have been considered to be in early postoperative remission. Recent Pituitary Society consensus recommends initiating the evaluation of any potential recurrence when the hypothalamic-pituitary-adrenal (HPA) axis recovers and then annually or sooner if they have clinical symptoms [2]. In the present study, remission was defined as hypocortisolism or ongoing eucortisolism lasting more than 6 months in patients with early recovery of the HPA axis. Criteria defining a recurrence are as important as the timing of the recurrence. Standard diagnostic criteria to be used to define Cushing's disease are also recommended to determine any recurrence, as we did in this study [5, 11, 12]. Recent studies that used homogenous data reported recurrence rates varying from 15 to 20 % while this rate was 15.4 % in the pediatric age group [5, 13, 14]. The recurrence rate was 14.2 % in this study and disease recurrence was seen even after 12 years in some cases. As stated by Guignat et al. recurrence rates increase with the duration of follow-up in the literature [5, 15]. In the present study, the recurrence rate was 9.6 % in the first 5 years, but it increased to 14.2 % with the longest follow-up of 12 years (data not shown). The analysis of the recurrences revealed that two-thirds of recurrences occurred during the first 5 years and one-third occurred ≥ 5 years after the initial surgery. With the accumulation of long-term data, we will be able to determine risk groups and develop different individual follow-up schedules for this disease requiring lifelong follow-up.

Preoperative predictors

As with many studies in the literature, the analysis of demographic characteristics revealed that gender did not affect recurrences. Although studies on the impact of age on disease recurrences reported conflicting results, patients with recurrent disease were younger in our cohort [3, 5, 8, 10]. During the course of chronic diseases, the probability of losing patients to follow-up increases as the duration of follow-up increases. Considering this fact, patients with a disease that requires lifelong follow -up such as CD, particularly those who are diagnosed at a younger age should be informed more clearly about the risk of recurrence and the requirement for follow-up. A timeline of recurrence adjusted to age can be determined in larger studies with > 10-year follow-ups.

Preoperative comorbidities were hardly ever evaluated in studies on disease recurrence. Our study evaluated possible associations between recurrences and comorbidities including osteoporosis, DM, HT, history of thromboembolism, and mental disorders,



▶ **Fig. 3** Correlations between tumor size and preoperative basal ACTH.

and no associations were found between recurrences and comorbidities other than osteoporosis. A diagnosis of osteoporosis was made based on bone mineral density measurements routinely performed on every patient with CD in our hospital. Although patients with recurrent disease are younger, osteoporosis was more common in this group of patients. This finding might be associated with the severity of hypercortisolemia; however, additional data including data on whether or not hypogonadism was present and current medications were required to determine whether osteoporosis was an independent predictor of recurrences. Longitudinal follow-up studies can be conducted for a detailed assessment of a potential association.

The evaluation of preoperative diagnostic workup, including basal and dynamic laboratory tests for CD did not reveal any significant difference between the groups with recurrences and without recurrences in parameters other than preoperative ACTH levels. Similarly, many studies in the literature did not find any association between recurrent disease and preoperative severity of hypercortisolemia or diagnostic tests [5, 11]. However, in retrospective studies, basal ACTH levels appear to be a potential predictor of disease recurrence [11, 16, 17]. In our study, basal ACTH levels were markedly higher in the group of patients with the recurrent disease compared to patients in sustained remission. The ROC analysis suggests that a preoperative basal ACTH level higher than 55 pg/ml can be a predictor of postoperative recurrences. In a study, Zhang et al. reported that a cutoff value of 67.3 pg/ml for ACTH levels may be predictive of recurrent disease although the sensitivity and specificity of this cutoff value were slightly lower than those of our study (72.7 % sensitivity, 55.3 % specificity vs. 60.9 % sensitivity and 49.5 % specificity, respectively) [16]. The correlation between tumor size and preoperative ACTH levels has been demonstrated in many studies [4, 12, 17, 18]. Therefore, as a predictor of recurrence, whether an increased ACTH level is an independent risk factor for recurrence or is associated with the tumor size, is a subject of debate. In our study, preoperative ACTH levels positively correlated with the Ki-67 index, tumor size, and tumoral invasion. In a regression analysis, the significant difference in ACTH levels between the recurrent disease group and the sustained remission group persisted even when adjusted for these parameters. Therefore, an elevated basal ACTH level was considered as an independent risk factor for recurrence. Another study reported that preoperative DHEA levels were higher in patients with recurrent disease and suggested that DHEA levels could be used as an additional parameter. In our study, preoperative DHEA levels were analyzed in 156 patients who had available data, and a statistically significant level for recurrence prediction was not reached ($p = 0.062$), but available data were quite limited [4].

Studies in the literature have been more precise regarding preoperative radiological findings: macroadenomas and invasive tumors were associated with a higher rate of recurrence in almost all studies [5, 11, 16, 18]. Tumor size was also bigger in recurrent cases compared to those in sustained remission in our study. Based on the ROC analysis, a tumor diameter of > 9.5 mm was considered as a parameter to be used to predict recurrences with a sensitivity of 61.2 % and a specificity of 65.7 %. Macroadenomas are associated with disease recurrence because, in addition to their size, a macroadenoma can also be invasive [11, 16, 19]. In our study, recurrences were also more common with invasive tumors, particularly in the presence of cavernous sinus invasion (data not shown). However, optic nerve compression was not associated with recurrences.

In addition to providing remission, a surgeon's experience can also predict recurrences in Cushing's disease [5, 20]. In our study, all surgical interventions were performed by the same surgical

team. This team performs more than 300 transsphenoidal procedures per year and is very experienced in pituitary surgery. One of the strengths of our study is the homogeneity of patients in terms of surgical experience. Furthermore, these patients were diagnosed and treated based on standardized criteria in a single center; therefore, confounding factors were minimized.

Postoperative predictors

Early postoperative cortisol level is a valuable parameter in determining remission; however, its role in predicting recurrence is controversial. In our study, early postoperative morning cortisol levels in patients with recurrent disease were similar to those in sustained remission therefore this parameter was not considered a significant parameter in predicting recurrence. In the literature, there are studies demonstrating that desmopressin- or CRH-induced peak cortisol and ACTH levels were more utile than early postoperative morning cortisol levels in predicting recurrence [21, 22]. In the study, Ambrogio et al. reported that these stimulation tests might predict the presence of residual tumor tissue or recurrence during the postoperative first months and throughout clinical follow-up [5, 21]. Unfortunately, these tests are not included in our routine postoperative protocols. Therefore, these parameters were not assessed in this retrospective study and this was one of the limitations of this study.

In several studies, histological confirmation of an ACTH-secreting adenoma was found to be associated with a lower risk of recurrence [5, 11, 12]. In the present study, the presence of an adenoma was histologically confirmed in > 95 % of patients in both groups; therefore, we did not perform an analysis to detect intergroup differences in this study. Routine histological assessments included Ki-67 staining and the percentage of Ki-67-positive cells was higher in the recurrent disease group compared to the sustained remission group. The rate of Ki-67-positive cells was more than 3 % in 40 % of patients in the recurrent disease group whereas this rate was 25 % in the sustained remission group. A high Ki-67 index is known to be associated with invasion and aggressive clinical course in pituitary tumors [23, 24]. This association has also been shown in corticotropic adenomas; however, data on a potential association between the Ki-67 index and disease recurrence are conflicting. Similar studies on remission and recurrences in CD reported that matrix metalloproteinase-9, pituitary tumor transforming gene, somatostatin receptor subtypes ubiquitin-specific protease 8 gene expression could be additional parameters to be assessed in adenoma tissue [12, 24, 25]. Associations between these parameters and recurrent disease have been demonstrated and we believe that they may also guide prospective studies.

Follow-up predictors

Hypocortisolism is an expected outcome following the successful removal of an ACTH-secreting adenoma. The recovery of the HPA axis can take several weeks or even months, and rarely, hypocortisolism can be permanent [8]. In our study, glucocorticoid replacement was initiated for patients who developed hypocortisolism following surgery, and HPA axis recovery was assessed with intervals of 1–3 months beginning from the first month after the surgery and in case of the presence of any symptoms of recurrence. The time to HPA axis recovery was determined based on morning cortisol measurements or ACTH stimulation test without any glucocorticoid use at least for 48 hours. Once the recovery of the HPA axis occurred, patients underwent standard assessments for recurrence monitoring. In line with the literature, the time to HPA axis recovery was longer in the sustained remission group than in the recurrent disease group. 20 % of patients in the recurrent disease group never received replacement therapy postoperatively, whereas replacement therapy was discontinued at postoperative month 6 or earlier in > 85 % of patients who were on replacement therapy. Two patients developed permanent hypocortisolism and 35 % of patients received steroid replacement therapy for more than one year in the sustained remission group (data not shown). Bansal et al., concluded that adrenal insufficiency lasting more than 13 months was a predictor of sustained remission whereas Alexandraki et al., reported that no recurrence was observed during 15 years postoperatively in patients who suffered from HPA axis dysfunction for more than 3 years [10, 26]. These data suggest that patients may be at higher risk of recurrence if eucortisolemia is present, particularly during the early postoperative period or if it takes 6 months or less to wean off steroids.

Our study included a homogenous patient group who underwent testing in line with standard guidelines on the diagnosis, follow-up, and determination of recurrences of Cushing's disease and had a transsphenoidal surgery performed by the same experienced surgical team. Although the study sample is larger than many studies, data from longer follow-ups and larger sample-sized studies are still needed. The retrospective nature of the study prevented the assessment of data obtained by technics recently introduced into the field of histology such as transcription factor and somatostatin receptor subtype immunochemistry. Another limitation of this study was that every study patient did not routinely undergo an ACTH stimulation test. Prospective studies should include an assessment of the desmopressin/ACTH- stimulation test that appears to be valuable in predicting recurrences.

Conclusion

Cushing's disease recurs in 15 % of patients following a successful surgery. Although recurrences mostly occur within the first 5 years after the surgery, they may still occur during the long-term follow-up. The determination of patients at risk of recurrence is crucial for early detection and a more rational disease management plan for a lifelong disease such as Cushing's disease. Based on our study data, younger age at diagnosis, a diagnosis of osteoporosis, higher preoperative ACTH levels (> 55 pg/ml), larger tumor size (> 9.5 mm), invasive behavior, higher Ki 67 index, and early recovery (< 6 months) of the adrenal axis during the postoperative period attracted attention as potential predictors of recurrent disease. There is an unmet need for prospective studies with longer follow-ups and additional genetic, pathological, and biochemical findings.

Author contributions

AS and MU had the idea for the article and drafted it, performed the literature search, data analysis, writing process as well as revised the work. BC, ZC, BCa, IA, and SC did literature search, data

interpretations, and discussions. EG, MS, and DK did data collection, analysis, and revision. All authors approved the final draft.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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