



Original Article

Retrospective analysis of the outcomes of endoscopic transsphenoidal surgery for Cushing's disease

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ABSTRACT

Background: The first-line surgical management of an adrenocorticotropic hormone (ACTH)--secreting pituitary adenoma causing Cushing's disease (CD) is endoscopic transsphenoidal resection of the tumor. This study was performed to assess postoperative (postop) complications and remission in endoscopic surgically resected cases of CD.

Methods: Data of patients who underwent endoscopic transsphenoidal surgery (ETSS) for CD were collected from the neurosurgery department at a tertiary care center in a retrospective manner from January 2015 to February 2022 and analyzed. Postoperative remission was categorized as – early morning serum cortisol <138 nmol/L within 7 days of the surgery, as per the Endocrine Society Guidelines, with significant clinical improvement in features of hypercortisolism in the operated patient and strict cutoff rate of <50 nmol/L at postop day 3 was also utilized, to look for the early identification of remission.

Results: A total of 41 patients were identified who underwent 44 ETSS during the same timeframe. Preoperative magnetic resonance imaging localized an adenoma in all 41 patients, out of which 32 were microadenoma, and nine were macroadenoma (2 with cavernous sinus invasion). Intrapetrous sinus sampling was performed in 35 (85%) patients. The rate of remission for the initial surgery was 85.4% using the standard criteria and 68.3% using strict criteria. Three patients underwent early repeat surgery for the persistent disease as the day 3 cortisol was high (306–555 nmol/L). Once the outcome of this surgery was also included, the overall rate of remission was 90.2% (37/41). None of the patients had meningitis, cerebrospinal fluid leakage, visual deterioration, or vascular injury. Permanent and transient diabetes insipidus (DI) occurred in 9.75% and 26.8% following the first ETSS, respectively. We also noted a single case of CD recurrence in 9 months during the total follow-up period of 84 months.

Conclusion: ETSS has satisfactory rates of remission for the primary treatment of CD, with rates being higher for microadenomas. A long follow-up period is needed to assess the rates of recurrence. Patients must be counseled regarding the risk of postop DI, whether transient or permanent, as a possible complication.

Keywords: Cushing's disease (CD), Diabetes insipidus, Endoscopic transsphenoidal surgery (ETSS), Microadenoma, Pituitary macroadenoma

INTRODUCTION

Cushing's disease (CD) is a rare condition with limited epidemiologic data available. Its estimated prevalence is around 40/million, and incidence ranges from 1.2 to 2.4/million/year, as per various studies.^[7,24] If left untreated, it can pose serious complications such as hypertension, osteoporosis, insulin resistance, dyslipidemia, and hypercoagulability,^[30] and this is associated with raised mortality among the patients. Endoscopic transsphenoidal surgery (ETSS) is a way to provide patients with a potential remission from CD; however, long-term follow-up and surveillance are warranted as the recurrence rates are quite high.^[24] Since its first report in the year 1997,^[15] selective removal of adrenocorticotropic hormone (ACTH)--secreting pituitary adenoma through ETSS is being considered as the first-line treatment for CD. The primary aim of this surgery is to produce remission and provide long-term disease control with the least complications. The rate of remission depends on the tumor size, cavernous sinus invasion, preoperative magnetic resonance imaging (MRI), pre-and post-operative (postop) ACTH, cortisol serum levels, and the intraoperative visualization of the tumor.^[27]

The recurrence and remission rates post-ETSS for CD vary vastly as per the criteria for defining remission,^[27] and in few other studies due to limited patient data or a short follow-up period.^[8] According to the Endocrine Society Clinical Practice Guideline 2015 – an early morning serum cortisol level of <138 nmol/L (5µg/dL) within 7 days of transsphenoidal surgery (TSS) is an indicator of remission.^[23] A more stringent postop day 3 cutoff of <50 nmol/L (1.8 µg/dL) has also been reported in the pediatric age group^[32] and is also subsequently added in the same guideline.^[23] Various studies have shown that these cutoffs correlate with higher remission and a low recurrence rate of <10% in 10 years.^[32] The primary objective of our study was to assess the outcome of ETSS for CD at a tertiary pituitary center in terms of – remission using the two well-defined criteria,^[23] recurrence rates and postop complications.

MATERIALS AND METHODS

Study design

Retrospective analysis of prospectively collected data of CD patients operated in the department of neurosurgery at a tertiary care center, through image-guided endoscopic transsphenoidal approach was conducted. Biochemical and clinical data were gathered over 7 years (84 months–January 2015 to February 2022), and the follow-up period was reviewed.

Study population

Screening for CD was done after the identification of characteristic clinical features [Table 1] along with-

Table 1: Number of patients having the specific clinical features of Cushing's Disease in our patients.

Clinical Feature	Seen in number of patients (/_/41)	Proportion %
Obesity or weight gain	39	96
Facial Plethora	34	85
Round facies	32	80
Thin skin	34	85
Decreased libido	32	80
Menstrual irregularities	23/29 females	80
HTN	39	95
Hirsutism	30	75
Depression	28	70
Hyperlipidaemia	24	60
Easy bruising	26	65
Glucose intolerance	30	73
Weakness	24	60
Osteopenia/Fractures	20	50
Buffalo Hump	20	50
Acne	12	30

- Inadequate cortisol suppression – <50 nmol/L – after an overnight dexamethasone suppression test (ONDST); OR
- Raised late-night salivary cortisol (LNSF) level; OR
- Raised 24 h urinary free cortisol (UFC) level.

According to standard guidelines,^[23] diagnosis of CD was made if there was a raised serum ACTH measurement, with confirmatory evidence of hormone response to the inferior petrosal sinus sampling (IPSS) and peripheral corticotropin-releasing hormone test. Patients with a history of undergoing TSS before the study period were not included.

After an initial suspicion of Cushing syndrome, the following evaluation protocol was followed^[23] [Figure 1]-

1. Rule out/exclude exogenous glucocorticoid exposure
2. Initial screening tests (anyone to be performed)
 - 24 h UFC -x3 the normal value (≥2 tests)
 - LNSF - >5.5 nmol/L (≥2 tests)
 - Loss of circadian rhythm of cortisol secretion
 - 1 mg ONDST
 - On day 1 at 11 pm, 1mg dexamethasone was administered, and on day 2 at 8 am, cortisol value assessed – >49.6 nmol/L (Single test)
 - Longer low-dose dexamethasone suppression test (DST) (2 mg/d for 48 h).

This is done in obese/PCOS/metabolic syndrome/pseudo-Cushing's 0.5 mg four tablets of dexamethasone are given 6 h apart on days 1 and 2. On day 3 at 8 am, if S. cortisol >1.8 mcg/dL – endogenous CD (single test).

3. If any abnormal test – Evaluation for the endogenous cause of hypercortisolism
 - 9 am plasma ACTH – sample maintained in the cold chain, transported in the cold chain, and centrifuged.

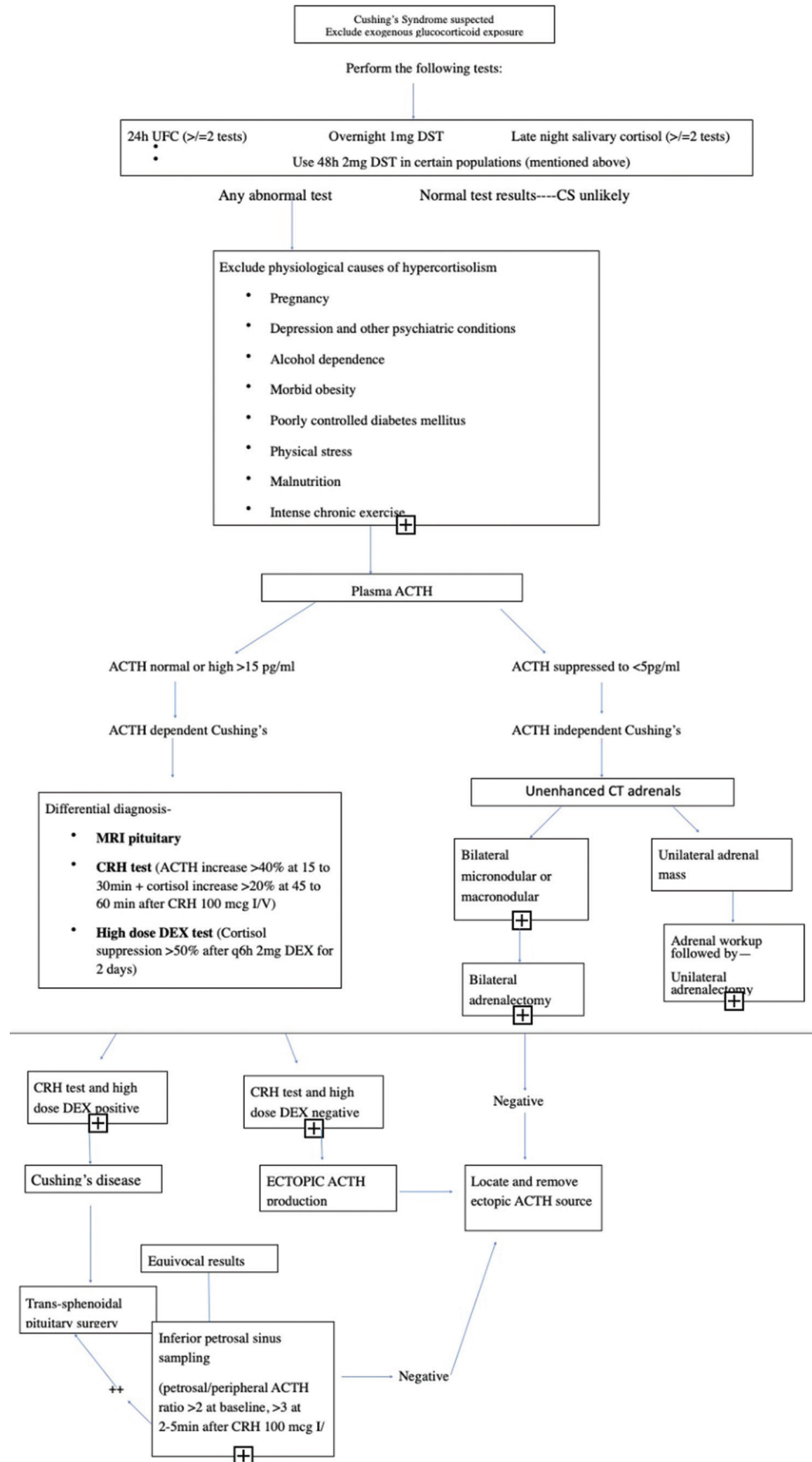


Figure 1: Flowchart showing the methodology of patients in our study. UFC: Urine free Cortisol, DST: Dexamethasone suppression test, ACTH: Adrenocorticotrophic Hormone, CRH: Corticotropin Releasing Hormone, DEX: Dexamethasone.

- ACTH >20 pg/mL – Confirmatory for ACTH dependent
- ACTH <10 pg/mL – ACTH independent
- ACTH >90 pg/mL – Ectopic ACTH syndrome

Surgical procedure

All of the ETSS procedures were carried out by three senior neurosurgeons super- specializing in endoscopic anterior skull base and pituitary surgeries. It consists of a binostrial endoscopic transsphenoidal approach. Selective adenomectomy was done on all the patients with adenomas identified on the preoperative MRI scans. Confirmation of diagnosis of ACTH-secreting adenoma or hyperplasia was done by immunohistochemical staining for pituitary hormones and histopathological examination of the postop specimens.

Postop assessment

Empirical oral hydrocortisone was given to the patients on postop day 1 and on the morning of postop day 2 before the assessment of early morning serum cortisol on postop day 3. Sampling for the same was done at 8 am on the 3rd day if the patient was clinically stable before the hydrocortisone was administered.

The Endocrine Society Clinical Practice Guideline defines postoperative biochemical remission as morning serum cortisol <138 nmol/L (5 µg/dL) within 7 postop days postoperatively^[23], which is the – standard criteria. Similarly, at our institution, we apply a biochemical cutoff of <50 nmol/L (1.8 µg/dL) at postop day 3 to allow for an early indication of biochemical remission, which is the – strict criteria.^[23]

In case the serum cortisol on postop day 3 is between 50 and 138 nmol/L, daily serial sampling is done to identify whether the cortisol is falling further or not, and an assessment of improvement or resolution of the clinical sequelae of hypercortisolemia is made (like improvement in glycemic control or blood pressure) before a repeat ETSS is taken into consideration.^[6,32]

Transient cranial diabetes insipidus (DI) was defined as the development of hypotonic polyuria in the postop period that required at least a single dose of desmopressin,^[29] that resolved before patient's discharge. A water deprivation test identified permanent DI according to the standard criteria.^[13] Thyroid-stimulating hormone (TSH) deficiency was confirmed if there was a low serum fT4 with either a low or an inappropriately normal TSH. Growth hormone deficiency was identified using either a glucagon stimulation test or an insulin tolerance test.^[14] Gonadotropin deficiency was defined in premenopausal women as amenorrhea with inappropriately low follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentration and in postmenopausal patients as inappropriately low FSH and LH concentration.

Recovery of the hypothalamic-pituitary-adrenal axis was assessed using the insulin tolerance test or the short synacthen (250 µg) test at postop 3 months and after that at every 3–6 months in cases of an initial fail test or a borderline result. After that, an annual assessment of the patients was done for recurrence of CD, and the recurrence was defined as a failure to suppress cortisol to <50 nmol/L after a 1 mg overnight DST and an elevated LNSF or a raised UFC in patients who are no longer taking hydrocortisone.

Statistics

Data are expressed as range (median) and percentage (number of patients). Fishers' Exact test was utilized for comparison of the categorical variables among the two groups. The *P*-value was considered statistically significant at less than 0.05. Statistical analysis was done using the Statistical Package for the Social Sciences Software.

RESULTS

Demographics

Forty-four endoscopic transsphenoidal procedures were performed in 41 patients. Median (range) age was 33.6 years (14–71), out of which 29 were female and 12 were male. Median (range) duration of symptoms was 39 months (6–84), among which 73% (30/41) had type 2 diabetes mellitus and 95% (39/41) had hypertension. Table 1 shows the clinical features of CD seen in our patients.

Preoperative imaging and IPSS

Preoperative MRI [Figure 2] localized an adenoma in 41 patients: 32 microadenomas and nine macroadenomas (2 with cavernous sinus invasion). IPSS was carried out

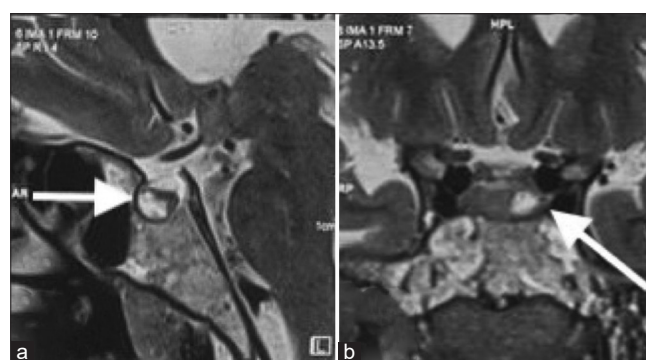


Figure 2: (a) Sagittal magnetic resonance imaging (MRI) brain showing a hypoenhancing lesion (white arrow) in the left half of the pituitary gland, measuring approximately 9 × 8 × 7.2 mm. (b) Coronal MRI brain showing heterogeneously hyperintense lesion in the pituitary gland, on T2 with multiple peripheral T2 hypointense foci, suggestive of microadenoma (white arrow).



Figure 3: Clinical image showing (a) preoperative and (b) postoperative imaging after resection of pituitary adenoma.

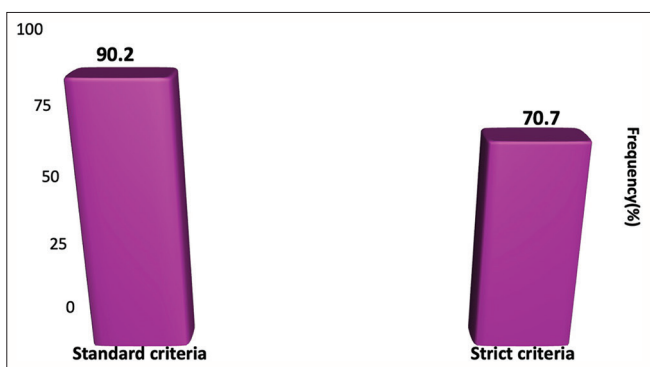


Figure 4: Postoperative rates of repeat early endoscopic transsphenoidal surgery.

in 35 (85%) patients. Figure 3 shows the preoperative and postop clinical imaging of one of our CD patients.

Postop remission

Postoperative outcomes are summarized as follows:

Using the standard criteria (8 am postop day 3 serum cortisol <138 nmol/L within 7 postop days and an improvement in the clinical features of hypercortisolism), the rate of remission in the postop period for initial surgery was 85.4% (35/41) for the whole group and 81.2% (26/32) if patients with macroadenomas were excluded from the study. Three patients had to undergo early repeat ETSS for persistent CD; postop day 3, serum cortisol levels ranged from 306 to 555 nmol/L. Including the outcome of repeat early ETSS, the overall remission rate of remission was 90.2% (37/41) [Figure 4].

Using the strict criteria of early remission (postop day 3 serum cortisol levels <50 nmol/L), the overall postop rate of remission was 68.3% (28/41) [Figure 5]. When the three patients who underwent repeat early ETSS were also included, the overall remission rate was 61% (23/38), and it was 65% (22/34) if the macroadenomas were excluded.

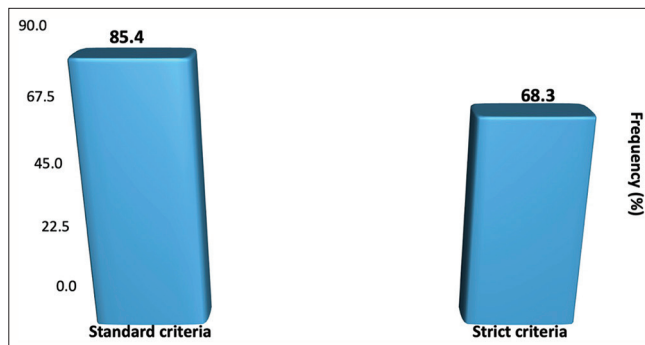


Figure 5: Postoperative rates of remission after initial endoscopic transsphenoidal surgery.

On day 3, 11 patients (26.8%) had serum cortisol between 50 and 138 nmol/L, out of which 7 received metyrapone therapy before the surgery. Six patients had daily serial measurements of 8 am serum cortisol till postop 14 days, and it was observed that it declined after day 3 in all six patients.

Persistent disease

Six patients (14.6%) had persistent hypercortisolemia after initial ETSS. Three patients had to undergo an early repeat endoscopic TSS. The rate of remission after this repeat early ETSS was 66% (2/3) using the standard criteria and 33% (1/3) using strict criteria. Out of the patients having persistent disease after the repeat surgery, radiosurgery was performed on 1 patient, while the other patient was started on medical therapy.

Postop complications

After the initial ETSS, among the 41 patients, 11 patients developed transient DI (26.8%), whereas four patients developed permanent DI (9.75%). Postoperatively, we observed 6 cases (14.6%) of new-onset TSH deficiency and 3 cases (7.3%) of gonadotropin deficiency (in premenopausal females) [Figure 6]. We did not have any case of postop cerebrospinal fluid (CSF) leak, meningitis, visual complications, or vascular injury.

Recurrence

None of our patients were lost to follow-up. The median range of duration of follow-up was 4 months, over which one patient had a recurrence of CD. Preoperative MRI showed a macroadenoma; serum cortisol on day 3 after the initial ETSS was 71 nmol/L, which fulfilled the standard criteria for remission but not the more strict criteria. The patient underwent a second ETSS 9 months later. No tumor was visible intraoperatively, so no tissue was removed. Day 3 serum cortisol concentration was 308 nmol/L, and the patient was commenced on a trial of metyrapone.

An overall schema of management of the CD cases in our series is depicted in Figure 7.

DISCUSSION

There is a varied difference among the rates of remission after an ETSS among CD patients, mainly due to the variations in the criteria used to define remission.^[10] There is the absence of a uniform consensus on criteria to exactly define “remission”

in these cases, with many institutions using a combination of clinical and biochemical criteria, which has made comparison of surgical outcomes more challenging. There is suppression of the normal corticotroph cells of the pituitary gland due to sustained hypercortisolemia in CD. After the removal of ACTH-secreting pituitary adenoma, the serum cortisol and ACTH levels should decline in the postop period. As per the Endocrine Society Clinical Practice Guideline,^[23] early morning serum cortisol level of <138 nmol/L within 7 days of the surgery is an indicator of remission, and many other surgical outcome studies have used this.^[3,10,31,34] Other research articles have quoted a much more stringent serum cortisol cutoff of less than 50 nmol/L at postop day 3 to identify early biochemical remission;^[5,10,20,33,35] Literature has suggested that this cutoff is associated with a low recurrence of around <10% at 10 years and a higher rate of remission.^[6] Our protocol is to apply the strict criteria approach; that is, if serum cortisol on postop day 3 is between 50 and 138 nmol/L, daily serial measurements are taken to determine if it falls further, and assessment is done for improvement and resolution of the clinical features of hypercortisolemia, before performing an

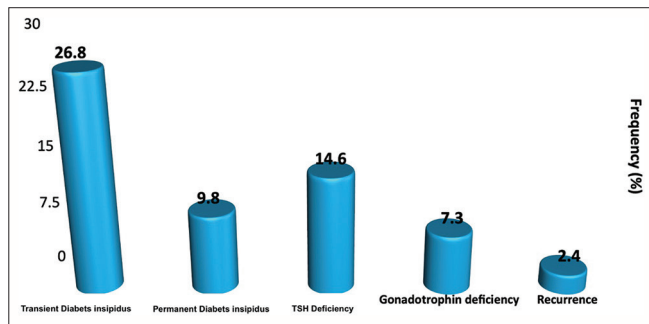


Figure 6: Frequency distribution of postoperative hypopituitarism.

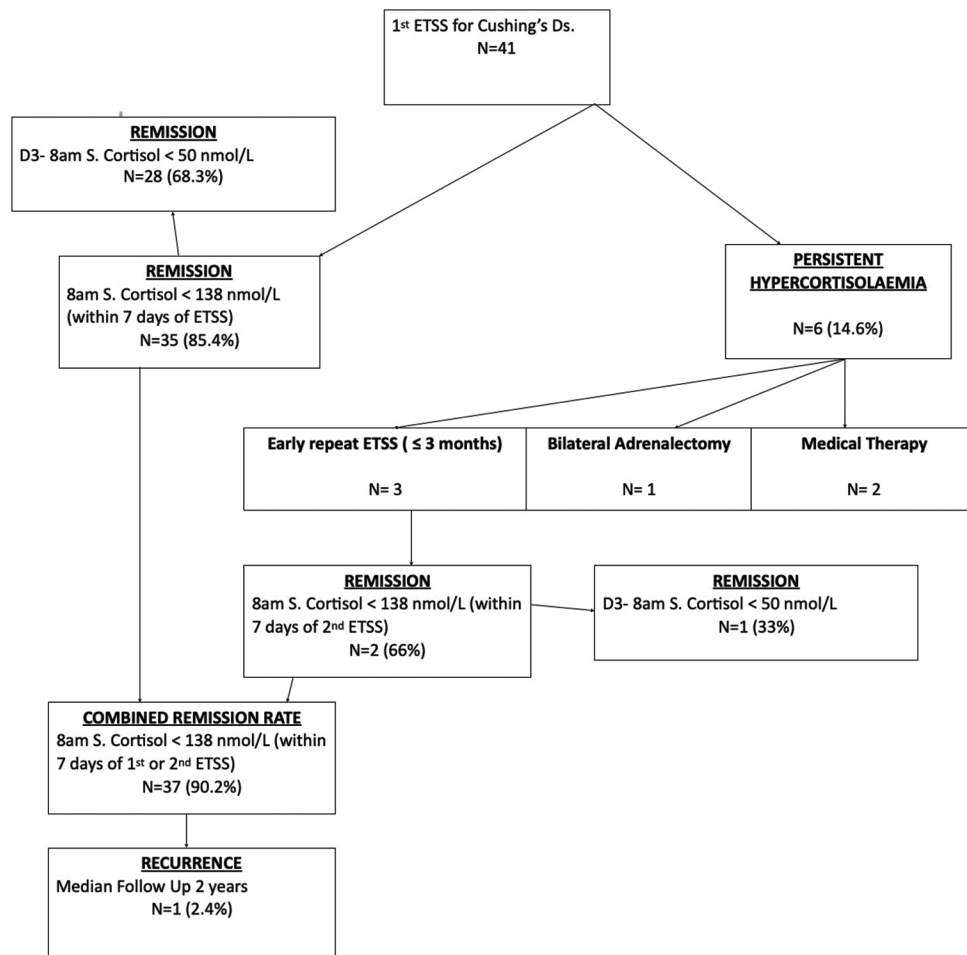


Figure 7: Schema of patients managed in our study. ETSS: Endoscopic trans sphenoidal surgery. D: Day

early repeat ETSS. It is extremely essential to make sure that the serum cortisol has reached its lowest point before considering any further interventions.

In this study, we report two different remission rates using these two criteria, which are widely accepted. Our rate of remission rate, including the patients who underwent an early second ETSS, according to the standard guidelines, is 90.2%, which is at par with the other large-scale studies.^[9,10,19,26,34] On the contrary, when we apply the strict criteria of postop day 3 cortisol <50 nmol/L, the remission was significantly lower at 68.3%. We have used these criteria at our institution to make sure that we safely identify those patients who have an early sign of remission so as to facilitate their discharge on day 3 itself. However, it has been noted that going by these rates in isolation can lead to a misleadingly low rate of remission as compared to more lenient criteria as proposed by the Endocrine Society.^[23]

Evidence also suggests that the higher postop day 3 cortisol level is associated with a higher risk of CD recurrence. A retrospective cohort study of 81 CD patients undergoing ETSS conducted by Mayberg *et al.*,^[19] reported quite high recurrence rates among patients with postop cortisol, lowest between 58 and 149 nmol/L as compared to the ones with cortisol <55 nmol/L ($P = 0.01$, 33% vs. 6%). There was a lower recurrence of CD in our study at 2.4%, and it was seen in a patient with corticotroph macroadenoma, which is known for much higher recurrence.^[12] On the assessment of this patient in the postop period, the serum cortisol was between the two criteria of remission, and it was found that according to the strict criteria, this patient had frank persistent hypercortisolemia. This patient has highlighted the challenges that we face in comparing the studies that report outcomes of ETSS in CD – the clear distinction between CD early recurrence and persistent postop hypercortisolism is not exactly clear-cut; rather, it is dictated by local protocol.

While our data are encouraging when compared to other studies on the recurrence of CD that have published rates up to 22%,^[23] a long-term follow-up is required before these rates are accurately defined. The definition of long-term CD recurrence is also vastly varied in literature. As shown by Petersenn *et al.*, who conducted a huge systematic review of 6400 studies, there were lower rates of recurrence when the studies utilized UFC with ONDST as compared to only UFC and UFC with the early morning serum cortisol as compared to UFC only.^[27] This has highlighted the need for a standardized rate of remission and recurrence criteria to ensure consistency in literature as well as in clinical practice.

The most common clinical finding seen in CD is centripetal obesity, which is nonspecific and has a poor discriminatory value.

The Endocrine Society^[32] recommends screening if:

- Central obesity with any feature of protein catabolism
- Osteoporosis/hypertension at a young age
- Children with decreasing height percentile and increasing weight
- Any incidentally detected adrenal mass – can be functional – the most likely cause is Cushing's
- Presence of obesity, hypertension, diabetes mellitus, acne, and hirsutism.

We have mentioned the clinical features of our study, as shown in Table 1.

There was a very low postop surgical complication rate in our study, and we did not have any cases of vascular injury, CSF leak, or visual compromise. Many other case series have reported an incidence of 0–7.2% of CSF leakage and 0–7.9% for meningitis.^[2,17,26,28] Meningitis in these postop cases is known to be associated with CSF leakage.^[11] Some studies have also shown that the endoscopic approach has a higher rate of carotid artery injury as compared to the microscopic approach, which can be attributed to the nature of an extended lateral approach.^[4] However, in our series of 44 cases of ETSS, we reported no cases of surgically associated carotid artery injury, which was similar to many other studies that reported a 0% morbidity and mortality due to carotid artery injury.^[2,21] Finally, postop visual disturbance is also a major concern, as it can be drastically life-changing for the patients. Factors related to visual complications are larger tumor size, pre-existing visual conditions, and the patient's age.^[18,22,25] Visual deterioration post-TSS for CD is reported in a few large case series at the rates of 0.86%^[28] and 1.9%.^[17] We did not have any cases of postop visual disturbances in our study.

Table 2 depicts the overlapping conditions and clinical features of Cushing's syndrome.

While our surgical complication rate was very low, the rate of endocrine complications was similar to the one reported in many other studies, especially in the case of DI. Permanent DI was seen in 9.8% of cases, and transient DI in 26.8% of cases. The comparatively high rate of transient DI might be due to diagnostic criteria used in our practice, as we defined transient postop DI as a single episode of hypotonic polyuria in the presence of elevated or normal plasma sodium levels, which required at least 1 dose of desmopressin. On the contrary, some studies report that any polyuria that lasts for <2 days is transient DI^[1], while many other researches document the requirement of hypernatremia for the definitive diagnosis of DI.^[16] The stricter criteria will not identify cases of transient DI; hence, it is not surprising that rates of transient DI in the 2018 meta-analysis were found to be lower at 11.3% than seen in our study.^[26] The permanent DI rates in our study merit particular attention. ETSS for CD is known to be associated with a higher risk of postop DI.^[1,22] The reason might be that the more aggressive surgical

Table 2: Overlapping conditions and clinical features of Cushing's Syndrome.

Overlapping Conditions And Clinical Features Of Cushing's Syndrome		
Discriminative Features Of Cushing's Syndrome (most do not have a high sensitivity)		
Symptoms	Signs	Overlapping Conditions
	<ol style="list-style-type: none"> 1. Facial plethora 2. Easy bruising 3. Proximal myopathy 4. In children, weight gain with decreasing growth velocity. 5. Striae (reddish purple, >1cm wide) 	
Cushing's Syndrome Features In The General Population That Are Common And/Or Less Discriminatory		
Symptoms	Signs	Overlapping Conditions
<ul style="list-style-type: none"> • Depression • Weight gain • Fatigue • Back pain • Decreased concentration • Changes in appetite • Decreased libido • Irritability • Impaired memory (especially short term) • In children, slow growth • Menstrual abnormalities 	<ul style="list-style-type: none"> • Dorsocervical fat pad (Buffalo hump) • Supraclavicular fullness • Facial fullness • Obesity • Thin skin • Acne • Peripheral oedema • Hirsutism or female balding • In children, abnormal genital virilization/short stature/delayed puberty • Poor skin healing 	<ul style="list-style-type: none"> • Hypertension • Incidental adrenal mass • Diabetes Mellitus type 2 • Vertebral osteoporosis • Hypokalaemia • Polycystic ovary syndrome • Kidney stones

approach has resulted in higher remission rates, but it was at the cost of high DI rates. Routine retesting of our patients for resolution of DI was not done once the water deprivation test at the initial postop 3 months was successful, and some cases also resolved spontaneously after that time duration.^[1,16] Regardless, the rates reported in our study are significant, and it emphasizes the necessity of counseling CD patients about the long-term risk of DI.

Strengths and limitations

We have utilized two widely accepted criteria to report the two remission rates, which is the strength of our series. All the ETSS were performed by three qualified senior pituitary surgeons, which removes the bias of surgeon experience. The disadvantage of our study is the low sample size. Furthermore, we included patients who were only recently operated on, to maximize the numbers for analysis of post-surgical complications. Along with that, we did not have full data on the longitudinal postoperative results since it was a retrospective study, and it highlights the requirement for a standardized follow-up for consistency in reporting the results.

CONCLUSION

ETSS in patients with CD offers an excellent remission rate and very low rates of morbidity. The rates of remission are much

higher when the standard criteria of early morning serum cortisol of <138 nmol/L, within postop 7 days, are compared with postop day 3 cortisol and assessed whether it is <50 nmol/L or not. A higher rate of remission was found in patients with microadenoma. It is extremely necessary to counsel patients regarding the risk of postop endocrine deficiencies, with special emphasis on permanent DI. A longer follow-up period is needed to assess the rates of recurrence accurately.

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Ethical approval

Ethical approval was not required as per our institutional guidelines.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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