Acta Neurochirurgica (2019) 161:119–127
https://doi.org/10.1007/s00701-018-3736-0

ORIGINAL ARTICLE - PITUITARIES

Long-term outcome of trans-sphenoidal surgery for Cushing's disease in Indian patients

S. Saini[1] · J. Kanwar[1] · S. Gupta[2] · S. Behari[2] · E. Bhatia[1] · Subhash Yadav[1,3]

Received: 13 July 2018 / Accepted: 9 November 2018 / Published online: 21 November 2018

Abstract

Background The results of trans-sphenoidal surgery (TSS) in Cushing's disease (CD) vary widely depending upon patient characteristics as well as surgical experience. Patients in India are often referred late to referral centers. We studied the rates of remission and endocrine deficiencies after TSS in patients with CD presenting to a referral hospital in India.

Methods Sixty consecutive patients (45 females, median age 24.5 years) who underwent TSS between 2000 and 2015 were studied. The median (range) duration of follow-up was 40 (3–138) months. Initial and long-term remission and relapse rates and pituitary hypofunction post-TSS were evaluated.

Results Eighteen (30%) patients harbored macroadenomas. Twenty-eight (47%) patients achieved remission in the immediate post-operative period (8 AM serum cortisol < 140 nmol/l), while a higher remission rate was noted at 6 months (39/54 patients, 72%). At 1 year 70% patients and at final follow-up [median duration 40 (range 3–138) months], 58% of patients were in remission. No pre- or post-surgical variables were consistently associated with remission, except for the 8-AM serum cortisol level on the fifth day after surgery. Seven (18%) patients relapsed on follow-up, including five patients who had fifth post-operative day 8 AM serum cortisol < 140 nmol/l. Twelve (25%) patients newly developed hypothyroidism and one (1.6%) patient developed amenorrhoea after TSS.

Conclusion Remission rate at 6 months was higher than immediately after TSS. A significant proportion of patients relapsed, thus necessitating life-long follow-up. New-onset hypothyroidism was frequent after TSS.

Keywords Cushing's disease · Trans-sphenoidal surgery · Remission · Relapse

Introduction

Cushing's disease (CD) is an uncommon disorder resulting from an excess production of ACTH from a pituitary corticotroph adenoma [20, 24].The disorder is associated with a high morbidity and mortality, mainly due to an increased cardiovascular risk and sepsis [24]. Various modalities of treatment, such as trans-sphenoidal surgery, bilateral adrenalectomy, radiotherapy, and medical therapy, are available for the management of CD. In most instances, TSS is the treatment of choice since it provides the highest chance of cure with the least likelihood of pituitary hypofunction [27].

The rates of remission vary widely after TSS. In the immediate post-operative period they range from 65 to 89%, while after longer follow-up they are reported between 60 and 80% [2, 4, 6, 7, 10, 14–18, 21, 36]. A smaller size of the corticotroph adenoma, its pre-operative or intra-operative localization and greater experience of the surgeon are associated with higher remission rates [13, 27]. However, it is difficult to compare results from different series due to their variable duration of follow-up and different criteria used to define remission. Unfortunately, relapse after successful TSS occurs in 4–25% patients [27]. While relapse is most common within the first year after surgery, it can occur after any duration, thus requiring life-long follow-up [2, 10].

S. Saini and J. Kanwar contributed equally to this work.

This article is part of the Topical Collection on *Pituitaries*

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00701-018-3736-0) contains supplementary material, which is available to authorized users.

✉ Subhash Yadav
subhash70@gmail.com

[1] Departments of Endocrinology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

[2] Department of Neurosurgery, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

[3] Department of Endocrinology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

There is inadequate data regarding endocrine deficiencies after TSS for CD [27]. Hypercortisolism per se can result in functional hypopituitarism (particularly hypothyroidism or hypogonadism), which may resolve after therapy [23]. TSS can also lead to new pituitary deficiencies (other than hypocortisolism), depending on the extent of surgery and the experience of the neurosurgeon [8, 9].

The management of CD in countries such as India, with limitations in health resources, presents many difficulties. Due to a lack of awareness about the disorder among primary care physicians, patients may be referred with severe manifestations [3, 31]. There is also a shortage of referral centers with facilities and experienced pituitary surgeons for management of the disease. Finally, follow-up after surgery is poor which precludes early detection and management of recurrences and pituitary deficiencies. Previous studies from India have reported remission rates in the range of 66–76% immediately after surgery, but information on remission rates and recurrence at various times after TSS is lacking [3, 30, 31]. In addition, information on hormonal deficiencies following TSS have not been reported in detail.

The aim of the current report was to study the remission rates, mortality, and pituitary endocrine deficiencies in a cohort of 60 patients who underwent TSS for CD at a referral center in north India.

Methods

Patients

Over a period of 16 years (2000 and 2015), 68 patients were diagnosed with CD in our clinic. Prior to January 2008, patient data and follow-up were obtained retrospectively from the case records, while after this date all patients were prospectively enrolled for this study. Eight patients were excluded from analysis since they underwent TSS at other centers ($n = 2$), required transcranial surgery for invasive corticotroph adenomas ($n = 2$), or were lost to follow-up prior to surgery ($n = 4$). Thus, the data of 60 patients is presented in this study (Fig. 1). The clinical and biochemical details of the patients are shown in Table 1. The median (range) age of the patients was 24.5 (13–54) years; 45 (75%) were females. Patients were symptomatic for periods ranging from 2.1 (0.3–16) years prior to TSS. The study was approved by the institutional ethics committee. Since the study

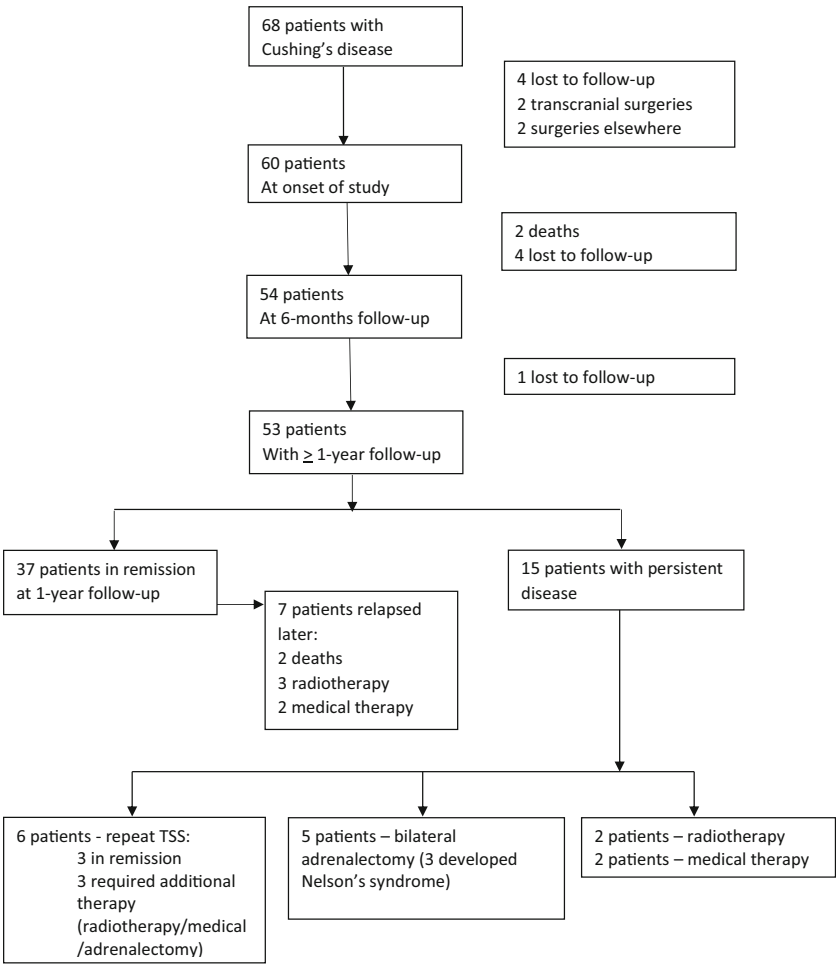

Fig. 1 Schematic outline of long-term follow-up of patients with Cushing's disease (prepared with MS Word 2013)

Table 1 Baseline clinical characteristics of patients with Cushing's disease ($n = 60$)

Characteristic	*N* (%) or median (range)
Age (years)	24.5 (13–54)
Female/male	45 (75)/15 (25)
Weight (kg)	63.5 (43–118)
Duration of symptoms before surgery (months)	26 (4–192)
Moon facies	59 (98)
Dorso-cervical hump	57 (95)
Emotional lability (including psychiatric manifestations)	16 (27)
Hyperpigmentation	25 (42)
Hirsutism	18/45 (40)
Striae	53 (88)
Easy bruisability	30 (50)
Fungal infection	18 (30)
Proximal muscle weakness	44 (73)
Hypertension (blood pressure > 130/85)	44 (73)
Diabetes/pre-diabetes	24 (40)
Osteoporosis/low bone mineral density	29/58 (50)
Menstrual irregularity	36/41 (88)
8 AM serum cortisol (nmol/l)	816 (381–1921)
Serum cortisol after LDDST (nmol/l)	599 (58–1734)
11 PM plasma ACTH (pg/ml)	68 (22–557)
Size of adenoma on MRI	
Microadenoma	34 (57)
Macroadenoma	18 (30)
No adenoma	8 (13)

Low bone mineral density defined as Z score < − 2 SD at either of lumbar spine, femoral neck, or total hip. Osteoporosis defined as T score < − 2.5 SD at either of lumbar spine, femoral neck, or total hip

LDDST low-dose dexamethasone suppression test, ACTH adrenocorticotrophic hormone, MRI magnetic resonance imaging

only required analysis of data in patient charts, the committee granted waiver of patient consent.

The diagnosis of Cushing's syndrome (CS) was based on lack of suppression of serum cortisol to < 50 nmol/l after low-dose oral dexamethasone (2 mg/day for 2 days). The 24-h urinary free cortisol was elevated (> 100 μg/day) in all 27 patients who underwent the test. All patients underwent an overnight high-dose dexamethasone suppression test (8 mg at 11 PM). Plasma ACTH was measured at 11 PM and value > 20 pg/ml was consistent with ACTH-dependent CS. All patients underwent magnetic resonance imaging (MRI) with a 3-T scanner using a dedicated pituitary imaging protocol with pre- and post-contrast images as well as dynamic imaging for microadenomas. Pituitary tumors were classified as microadenomas (< 10 mm) or macroadenomas (> 10 mm). If the adenoma was < 6 mm or no adenoma was visible, an inferior petrosal sinus sampling (IPSS) was performed ($n = 14$). A central:peripheral ACTH gradient > 2 was diagnostic of CD (stimulation with corticotrophin releasing hormone was not available). The diagnosis was confirmed in each case after TSS by histopathology and in 27 patients by ACTH staining by immunohistochemistry (IHC).

Surgery

Patients were operated upon primarily by two experienced pituitary surgeons. Of the total group of 59 patients, 47 (80%) were operated by using transsphenoidal microsurgical surgery while the remainder (20%) were removed using an endoscopic uninostril endonasal rhinoseptal or a binostril transostial transsphenoidal approach. In case of tumors non-visible in MRI, we operated on the side which was lateralized by IPSS. In case a tumor was not delineated at surgery, a hemi-hypophysectomy was performed. Cavernous sinus invasion was present in only one patient which was accessed by transspenoidal route.

Follow-up

Immediately after TSS, patients were placed on rapidly tapering doses of hydrocortisone. On fifth postoperative day, serum cortisol was measured at 8 AM after omitting hydrocortisone for 24 h. Remission was defined as serum cortisol < 140 nmol/l [24]. Patients in remission were placed on physiological

replacement doses of prednisolone (2.5–5.0 mg/day) while all other patients were followed without prescribing additional glucocorticoids. While hydrocortisone is the preferred replacement, prednisolone was used in our patients since it is inexpensive and freely available. Patients were required to follow-up at 3, 6, and 12 months and annually thereafter, or earlier if the patient developed any symptoms suggestive of relapse. Follow-up data of all 60 patients is shown in Fig. 1.

At each follow-up evaluation, patients requiring glucocorticoid replacement after surgery were advised to omit prednisolone for 48 h. If the 8 AM serum cortisol was < 140 nmol/l or if an ONDST was< 50 nmol/l, patients were considered in remission. Patients who did not require glucocorticoid replacement after surgery underwent an ONDST at each subsequent evaluation for assessment of remission. Patients not satisfying criteria for remission 6 months after surgery were classified as having persistent disease and underwent additional therapy. If the patient was remission at 6 months, subsequent abnormal ONDST was defined as relapse.

Pituitary hormone deficiencies were assessed prior to and 6 months after TSS, before the patient received any repeat pituitary surgery or radiotherapy. Serum T4 or free T4 were measured in 59 patients prior to surgery and in all patient post-surgery. Central hypothyroidism was defined as serum T4 or free T4 below reference range (< 60 nmol/l or < 11 pmol/l, respectively) with a low or normal TSH. Patients who were euthyroid on thyroxine replacement were also considered to have central hypothyroidism. Total testosterone, LH, and FSH were measured in 7 of 15 male patients before surgery and 11 patients after surgery. Central hypogonadism was diagnosed by low-serum total testosterone (< 10 nmol/l) along with low or inappropriately normal gonadotrophin values. In females, menstrual status was recorded at each visit. However, gonadotrophin levels were measured on a regular basis.

Assays

Prior to April 2009, serum cortisol, T4, LH, and FSH were measured by radioimmunoassay (Diagnostics Products Corporation, Los Angeles, USA) and subsequently by a chemiluminescence assay (Immulite 1000, Siemens, Gwynedd, UK). Total testosterone was measured by RIA (Diagnostic Products Corporation, Los Angeles or Immunotech, Prague, Czech Republic). Serum ACTH was assayed by an immuno-radiometric assay (Immunotech, Prague, Czech Republic). The functional sensitivity of the ACTH assay was 5 pg/ml.

Statistical analysis

Continuous data was expressed as median and range while categorical data was expressed as *n* (%). Categorical variables were compared using chi-squared test or Fisher's exact test, while Mann-Whitney *U* test was used for analysis of non-parametric continuous variables. A Kaplan-Meier curve was derived for assessment of relapse at various times after TSS. A p value < 0.05 was taken as statistically significant. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows (version 22.0) (Chicago, IL, USA).

Results

Baseline characteristics

The clinical characteristics of the study population are shown in Table 1. The patients were symptomatic for 26 (4–192) months prior to evaluation; 27 (45%) of them had symptoms for > 3 years. Hypertension (73%), diabetes/pre-diabetes (40%), and osteoporosis (50%) were the most frequent co-morbidities. Two patients had avascular osteonecrosis of the femoral head, while pathological hip fracture and symptomatic spine fractures were noted in four (6.7%) and six (10%) patients, respectively.

On MRI, micro- and macro-adenomas were diagnosed in 57% and 30% of patients, respectively, while in 13% no tumor was documented. IPSS lateralized an adenoma in 13/14 patients, except one case where it was located centrally. A pituitary adenoma was suspected during surgery in 59 patients. However, histopathology showed presence of pituitary adenoma in 54 patients.

Remission

Remission occurred in 47% patients in the immediate post-operative period and increased to 72% patients at 6 months (Table 2). Of the patients in remission at 6 months, 38% had fifth-day post-operative serum cortisol > 140 nmol/l. Remission rates at 1 year and at last follow-up [median duration 3.8 years (range 1–11 years)] were 70% and 58%, respectively. Of the patients who were in remission at 6 months, 87% continued to be in remission at last follow-up.

A comparison of patients in remission and without remission at different time points is shown in Supplementary Table 1. Patients in remission at 6 months and at final follow-up (≥ 1-year duration) had lower fifth-day mean post-operative cortisol, and higher proportion of patients with post-operative cortisol < 140 nmol/l, compared with those not in remission. No other parameters were consistently different. Patients in remission at last follow-up had higher median age and longer duration of symptoms prior to TSS compared with those not in remission ($p < 0.05$).

Of the 29 patients who did not remit in the immediate post-operative period, 15 were noted to be in remission at

Table 2 Remission rates after trans-sphenoidal surgery

Time after surgery	Patients in follow-up (*n*)	Patients in remission (*n*)	Remission (%)
Fifth day	60	28	47
6 months	54	39	72
1 year	53	37	70
2 years	37	23	62
5 years	19	12	63

6 months (delayed remission). A comparison of patients with immediate and delayed remission (Table 3) revealed that the latter were older and less likely to have an adenoma on MRI. However, no level cutoff of fifth-day post-operative cortisol was predictive of delayed remission. There was no difference in the subsequent frequency of relapses between the patients who remitted immediately or at 6 months.

Relapse

Seven (18%) patients who were in remission 6 months post-surgery relapsed (Fig. 2). The median time to relapse was 3.5 years (range 1–8 years) and included one patient who relapsed 8 years after surgery. Five patients who relapsed had fifth POD serum cortisol < 140 nmol/l, including three subjects with values < 50 nmol/l. There was no difference in the clinical, biochemical, hormonal, or radiological features among the patients who relapsed vs. those remaining in remission (data not shown).

Management of persistent disease/relapse

Of the 17 patients who had persistent disease after TSS, 2 patients were lost to follow-up. Repeat TSS was successful in inducing remission in 3 of 6 patients in whom it was performed, and in remaining 9 patients, trans-sphenoidal surgery was not technically feasible since the remaining tumor was not visible after repeat MRI (7 patients) or parasellar extension (1 patient) and tumor not found of histopathology (1 patient) (Fig. 1). Overall, 11 out these 15 patients were in remission at last follow-up after various forms of therapy.

Mortality

By the end of the study, five (8%) patients had died during follow up. All deaths occurred in patients with either persistent disease or relapse. Two patients died within 3 months of TSS due to infections (peritonitis, meningitis). Three patients died during later follow-up due to pneumonia, excessive intra-pituitary hemorrhage after a repeat TSS, and aggressive Nelson's syndrome.

Endocrine deficiencies

Nine (15%) patients had central hypothyroidism before surgery. Of these, 3 patients normalized their thyroid status post-operatively, all of whom were in biochemical remission. In contrast, of the 6 patients who remained hypothyroid after surgery only 1 was in remission. Twelve (25%) patients newly developed hypothyroidism after surgery. Of the 7 males with

Table 3 Comparison of patients with early remission and delayed remission (at 6 months)

Characteristics	Immediate remission (fifth post-operative day) (*n* = 24)	Delayed remission (6 months) (*n* = 15)
Age in years	22 (14–50)*	36 (15–44)
Male sex	3 (12.5%)	3 (20%)
Duration of symptoms (months)	12 (3–72)	36 (6–120)
No tumor on MRI	1 (4%)*	4 (27)
Microadenoma on MRI	16 (67)	9 (60)
No adenoma on HP	1 (4)	0
Pre-operative 8 AM serum cortisol (nmol/l)	796 (465–1379)	759 (477–1921)
11 PM plasma ACTH (pg/ml)	75 (22–250)	66 (39–95)
Fifth post-operative 8 AM cortisol (nmol/l)	46 (25–134)*	298 (150–1037)
Relapse	5 (21%)	2 (13%)

N (%) or median (range)

LDDST low-dose dexamethasone suppression test, HP histopathology

*$p < 0.05$ immediate remission vs. delayed remission, **$p < 0.05$ between delayed remission vs. no remission

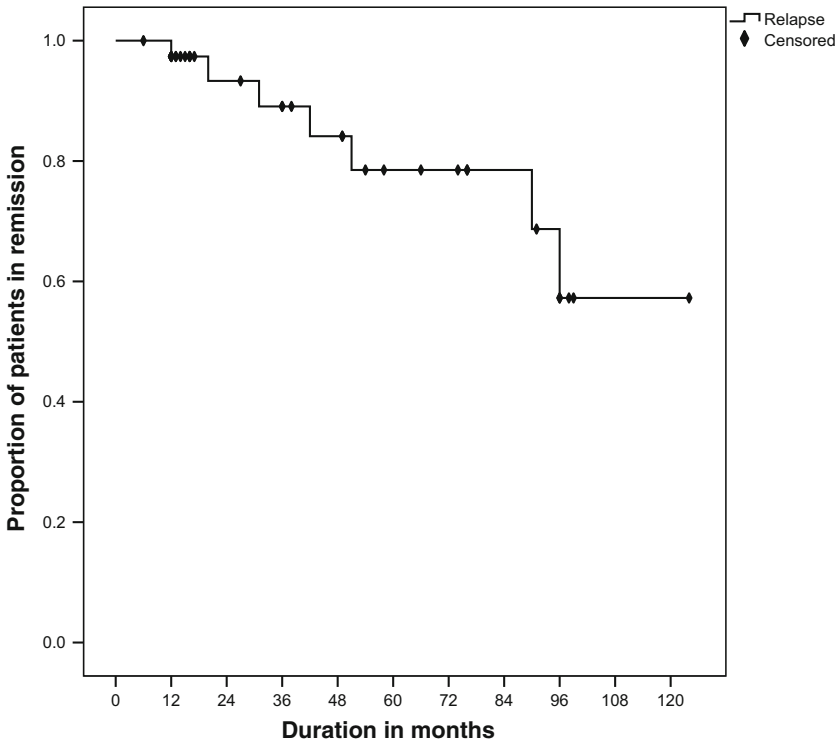

Fig. 2 Relapse after trans-sphenoidal surgery (prepared with IBM SPSS version 22)

pre-operative hypogonadism, serum testosterone normalized in 4 patients after surgery (all were in remission). Of the 28 women with oligo-amenorrhoea prior to TSS, 11 resumed regular menstrual cycles after TSS. One female patient newly developed amenorrhea post-TSS. Transient diabetes insipidus (DI) was present in 20 (33%) patients post-operatively while permanent DI was developed in 2 (3.3%) patients.

Discussion

Remission rates at final follow-up (≥ 1-year duration) were similar to that reported in recent series. However, in contrast to most studies, we noted that patients with CD had a higher remission rate at 6 months than immediately after TSS. A significant proportion of patients newly developed hypothyroidism after surgery.

While we expected an increased duration between onset of symptoms and diagnosis in our patient group, this was not found [2, 13, 19, 30, 35]. When compared with most recent reports where immediate post-operative remission ranged from 65 to 89%, remission achieved was lower (47% patients) in the current study [2, 4, 6, 7, 10, 14–18, 21, 36]. However, at 6 months post-TSS, the remission rate had increased to 72%, while remission rate at last follow-up (median duration 40 months) was 58%, compared with 60–80% in recent studies [2, 4, 10, 15, 16, 21]. The relapse frequency (18%) was also similar to other series (4–25%) [2, 4, 10, 25, 28, 36]. Of the seven patients who relapsed, five subjects had serum cortisol < 140 nmol/l immediately after TSS, while three patients had levels < 50 nmol/l, which re-emphasizes the fact that immediate post-operative remission does not guarantee a long-term relapse-free survival.

A notable feature of this study was the high frequency of delayed remission. On comparison of patients with immediate remission, those with remission at 6 months had significantly higher levels of fifth-day post-operative serum cortisol. However, a cutoff value which would predict remission at 6 months could not be delineated. Further tests such as late-night serum or salivary cortisol performed immediately after surgery may have improved prognostication [24]. The reasons for the high frequency of delayed remission are not clear. In approximately a quarter of cases who went into late remission, no adenoma was visible on MR imaging. In these, it is feasible that a small amount of tumor tissue remained immediately after surgery and atrophied after some months. As detailed in Table 4, in previous reports the frequency of late remissions after TSS have ranged from 4 to 43% [1, 12, 26, 32, 34]. Hypotheses for late remission after TSS include slow ischemia of the corticotrope adenoma after surgery or long-standing CD with some degree of adrenal autonomy due to prolonged ACTH stimulation [26, 27, 34]. In addition, immediate post-operative cortisol may be normal in those with mild or cyclic disease due to non-suppression of normal corticotropes [24].

As noted in previous studies [2, 11, 22, 29, 33], serum cortisol level on the fifth post-operative day was lower in

Table 4 Studies reporting delayed remission following trans-sphenoidal surgery in Cushing's disease

Study	Patients (*n*)	Criteria for immediate remission	Patients with immediate remission, *n* (%)	Patients with delayed remission, *n* (%)	Time to delayed remission
Edward et al. (2009) [29]	40	Serum cortisol < 138 nmol/l on day 2–5	25 (62.5%)	7 (17.5%)	2–3 months
Simmons et al. (2001) [30]	27	Multiple serum cortisol	21 (78%)	1 (4%)	8 months
Pereira et al. (2003) [31]	78	Serum cortisol < 138 nmol/l at 2 weeks	48 (62.5%)	8 (10.2%)	6 months
Valassi et al. (2010) [32]	620	24 h UFC < 80 μg/day on day 3 or ONDST < 138 nmol/l	437 (70.5%)	35 (5.6%)	38 ± 50 days
Acebes et al. (2007) [33]	44	Remission of symptoms, normal or sub-normal 24 h UFC, serum cortisol or ACTH in the first 6 months	20 (45.4%) (post-operative serum cortisol < 155 nmol/l)	19 (43%)	4–6 months
Current study	60	Serum cortisol < 140 nmol/l on day 5	28 (47%)	15 (25%)	6 months

ONDST overnight (1 mg) low-dose suppression test, UFC urine-free cortisol

subjects with remission at 6 months and at final follow-up. However, other factors implicated as having an adverse impact on the outcome of primary TSS, such as large tumor size (with suprasellar or cavernous sinus invasion), inability to demonstrate an adenoma at imaging, surgery or histopathology, and male gender, were not consistently associated with immediate or 6-month remission [10, 15, 16, 21, 24, 27]. Older patients and those with longer duration of symptoms before presentation were more likely to be in remission at last follow-up.

Nearly one third of the patients in this report presented with macroadenomas. This is in contrast to previous reports, where the frequency of macroadenomas is < 20% [5, 20, 37]. However, the adenoma size did not impact remission rates. This may be due to the fact that cavernous sinus invasion was extremely rare, and the tumors were fully excisable in all except two patients with macroadenomas, who were excluded from this study.

We noted hypothyroidism pre-operatively in 15% patients. Hypercortisolism per se can lead to suppression of the thyroid and gonadal axis [20, 23, 27]. Of these, one third resumed normal thyroid function post-TSS. However, a quarter of patients newly developed hypothyroidism after surgery. In previous reports, 3–68% of patients have been noted to have hypothyroidism post-operatively [4, 10, 27, 36]. Nine (20%) women with oligo-amenorrhoea resumed regular menstrual cycles and four (57%) males with hypogonadism normalized testosterone levels after TSS, suggesting its beneficial effects. We do not have accurate data on new-onset hypogonadism, but in previous reports this has been noted in 0.6–46% of patients [4, 10, 27, 28, 36].

In India, decreased awareness leading to late referrals, lack of adequate referral centers, and poor patient follow-up are major factors affecting the outcome of TSS. In a previous study of 65 patients from India, Shah et al. reported immediate remission rate of 77% for microadenomas and 36% for macroadenomas. However, subsequent remission rates were not reported. In a study of 81 patients, Ammini et al. reported an immediate remission rate of 67% and a relapse rate of 18.5% over a follow-up of 2.9 ≥ 2.1 years [3]. Sarkar et al. studied 64 patients who underwent endoscopic TSS and reported an immediate remission rate of 77%; on a follow-up of 20 months, four patients relapsed [30]. Data on remission and relapse rates after longer follow-up or the frequency of endocrine deficiencies have not been reported in these previous studies.

The strengths of the current study include a regular assessment and consistent definitions used to characterize remission. Detailed follow-up over a long period of time allowed accurate estimates of remission and relapses. However, our study had some limitations. Being partly a retrospective study, as well as due to adverse socio-economic issues, long-term patient follow-up was incomplete, and a uniform protocol could not be followed in some instances.

In summary, despite difficulties in early diagnosis of patients with CD, the long-term results of TSS in this study were close to that in reported from larger centers worldwide. The high frequency of late remissions suggests that it would be appropriate to wait for 6 months after initial TSS before further intervention after initial surgery. In addition, the high frequency of new-onset post-operative hypothyroidism suggests that regular testing for thyroid hormone is essential in follow-up.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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