



Duration of post-operative hypocortisolism predicts sustained remission after pituitary surgery for Cushing's disease

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Abstract

Purpose: Transsphenoidal surgery (TSS) is the primary treatment modality for Cushing's disease (CD). However, the predictors of post-operative remission and recurrence remain debatable. Thus, we studied the post-operative remission and long-term recurrence rates, as well as their respective predictive factors.

Methods: A retrospective analysis of case records of 230 CD patients who underwent primary microscopic TSS at our tertiary care referral centre between 1987 and 2015 was undertaken. Demographic features, pre- and post-operative hormonal values, MRI findings, histopathological features and follow-up data were recorded. Remission and recurrence rates as well as their respective predictive factors were studied.

Results: Overall, the post-operative remission rate was 65.6% (early remission 46%; delayed remission 19.6%), while the recurrence rate was 41% at mean follow-up of 74 ± 61.1 months (12–270 months). Significantly higher early remission rates were observed in patients with microadenoma vs macroadenoma (51.7% vs 30.6%, $P=0.005$) and those with unequivocal vs equivocal MRI for microadenoma (55.8% vs 38.5%, $P=0.007$). Patients with invasive macroadenoma had poorer (4.5% vs 45%, $P=0.001$) remission rates. Recurrence rates were higher in patients with delayed remission than those with early remission (61.5% vs 30.8%, $P=0.001$). Duration of post-operative hypocortisolemia ≥ 13 months predicted sustained remission with 100% specificity and 46.4% sensitivity. Recurrence could be detected significantly earlier (27.7 vs 69.2 months, $P<0.001$) in patients with available serial follow-up biochemistry as compared to those with infrequent follow-up after remission.

Conclusion: In our study, remission and recurrence rates were similar to that of reported literature, but proportion of delayed remission was relatively higher. Negative/equivocal MRI findings and presence of macroadenoma, especially those with cavernous sinus invasion were predictors of poor remission rates. In addition to early remission, longer duration of post-operative hypocortisolism is an important predictor of sustained remission. Regular biochemical surveillance may help in identifying recurrence early.

Key Words

- ▶ Cushing's disease
- ▶ pituitary adenoma
- ▶ transsphenoidal surgery
- ▶ remission
- ▶ post-operative hypocortisolism

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Introduction

Cushing's disease (CD) is a state of cortisol excess, caused by an ACTH-secreting pituitary adenoma. Although a rare disease with an annual incidence of 1.5 patients/million (1), it is associated with significant morbidity and mortality (2). Transsphenoidal surgery (TSS) of pituitary adenoma is the primary treatment modality, with varying remission rates (52–96.6%) reported across different centres (3). Various demographic, biochemical, radiological and histopathological features have been studied as predictors of remission following TSS. Amongst these, visualisation of adenoma on preoperative neuroradiography, tumour size, its invasiveness and histopathological confirmation of adenoma have been largely reported to be predictive of remission in various studies (4, 5, 6).

Recurrence of CD following remission after TSS is a well-recognised phenomenon and is reported to be as high as 15–66% in various long-term studies (7), emphasising the need for long-term follow-up. Understanding the predictors of sustained remission might help us to better strategise follow-up care of patients. Amongst the various factors studied, the presence of early post-operative hypocortisolism and lack of response to CRH/desmopressin stimulation tests have been reported to be positive predictors of sustained remission (8, 9, 10).

In the current study, we report long-term follow-up of CD patients after first microscopic TSS. We aim to study the post-operative remission and long-term recurrence rates, as well as their respective predictive factors.

Subjects and methods

A retrospective analysis of case records of CD patients ($n=236$) who underwent microscopic TSS as first line management at our tertiary care referral centre between 1987 and 2015 was undertaken. Institutional ethics committee approval with a waiver of informed consent was obtained for this retrospective analysis. Excluding 6 patients for whom early post-operative hormonal values were not available, data of 230 CD patients were analysed.

Baseline demographic features, pre- and post-operative hormonal values, MRI findings and histopathological features were recorded. Endogenous hypercortisolism was defined as serum cortisol $>1.8\mu\text{g/dL}$ after standard two days low-dose dexamethasone suppression test (0.5 mg dexamethasone every 6 h for 2 consecutive days) \pm sleeping midnight serum cortisol $>5\mu\text{g/dL}$ (11). ACTH dependency was confirmed by basal plasma ACTH $>10\text{pg/mL}$.

After biochemical confirmation, patients underwent dynamic contrast enhanced MRI (1.5T) pituitary. Since 2009, volume-interpolated 3D spoiled gradient-echo (VI-SGE) MR sequences have been used additionally (12). For patients with negative/equivocal MRI findings, inferior petrosal sinus sampling (IPSS) was done to confirm the central source of ACTH secretion (CRH-stimulated central: peripheral ACTH ratio >3 ; unstimulated central: peripheral ACTH ratio >2) (13). Patients with negative/equivocal MRI findings or adenomas $\leq 10\text{mm}$ were classified as microadenomas, whereas adenomas $>10\text{mm}$ were categorised as macroadenomas. For macroadenomas, the Knosp classification system was applied, and grades 3 and 4 lesions were categorised as invasive (14).

TSS was performed successively by two experienced neurosurgeons, one prior to 1999, and other from that year on. Selective transsphenoidal adenomectomy was the primary surgical approach followed by both the surgeons. Peri-operatively, patients received intravenous hydrocortisone (50 mg 6 h) on the day of surgery, which was replaced with oral prednisolone tablet (5 mg once a day in morning) on second and third post-operative day. Morning 08:00 h serum cortisol \pm plasma ACTH was documented in first post-operative week (usually fifth day, 48 h after last prednisolone dose). Patients having 08:00 h serum cortisol $<5\mu\text{g/dL}$ were considered hypocortisolemic, and were continued steroid replacement (oral prednisolone 5 mg once a day). Patients with serum cortisol $\geq 5\mu\text{g/dL}$ were given steroid replacement, only if they had symptoms attributable to hypocortisolism. All patients were advised regarding the need of stress dosage of steroids during periods of inter-current illnesses (if any). Initial post-operative follow-up visits were on a quarterly basis. On follow-up, 08:00 h serum cortisol was documented, and if it was $\geq 5\mu\text{g/dL}$, 1 mg overnight dexamethasone suppression test (ODST) was performed. Overall, patients were categorised into three groups – early remission, delayed remission and persistent disease. Early remission was defined as achieving early post-operative (usually fifth day) hypocortisolism (08:00 h serum cortisol $<5\mu\text{g/dL}$) (7). Delayed remission was defined as early post-operative 08:00 h serum cortisol $\geq 5\mu\text{g/dL}$, but achieving hypocortisolism (08:00 h serum cortisol $<5\mu\text{g/dL}$) or eucortisolism (08:00 h serum cortisol $\geq 5\mu\text{g/dL}$) and ODST serum cortisol $\leq 1.8\mu\text{g/dL}$ at initial follow-up visit (upto 6 months). Persistent disease was defined as early post-operative serum cortisol $\geq 5\mu\text{g/dL}$ with documented hypercortisolism (ODST serum cortisol



>1.8 µg/dL) at initial follow-up visits. Patients in the remission group were followed up 6–12 monthly. For the analysis of disease recurrence, patients having a minimum follow-up of 12 months post surgery were included. The hormonal evaluation at follow-up visits included 08:00h serum cortisol, ODST cortisol (done if 08:00h serum cortisol was ≥ 5 µg/dL), free thyroxine (FT₄) and thyrotropin (TSH). Another hormonal evaluation for growth, puberty and sexual function was done if clinically indicated. Patients having 08:00h serum cortisol <5 µg/dL were considered hypocortisolemic and were continued on steroid replacement (oral prednisolone 2.5–5 mg once a day). ACTH stimulation test was not performed due to non-availability of short-acting preparation of ACTH in India. Recurrence of the disease was defined as ODST serum cortisol >1.8 µg/dL in patients with prior remission.

Assays

Hormonal evaluation was radioimmunoassay based initially, and was later (after 1999) shifted to chemiluminescent assay. Cortisol was measured by a solid-phase competitive chemiluminescent enzyme immunoassay (Siemens Healthcare) with an analytical sensitivity of 0.2 µg/dL. The intra- and interassay coefficients of variability (CVs) of the cortisol assay were 6.9% and 7.3%, respectively. ACTH was measured by a solid-phase, two-site sequential chemiluminescent assay (Siemens Healthcare). The intra- and interassay CVs were 9.6% and 8.8%, respectively, and the sensitivity was 0.5 pg/mL.

Statistical analysis

Qualitative data were represented in the form of frequency and percentage. Association between qualitative variables was assessed by the chi-square test with continuity correction and Fisher's exact test when required. Quantitative data were represented using mean \pm s.d. (standard deviation). Analysis of quantitative data between the two groups was carried out using unpaired *t*-test/Mann–Whitney test, while one-way ANOVA test was used for comparing >2 groups. Analysis of recurrence on longitudinal evaluation was carried out by the Kaplan–Meier method. Receiver-operator characteristic (ROC) analysis was performed to find the optimal cut-off point for the duration of hypocortisolism in predicting recurrence in patients having remission. For all statistical tests, $P < 0.05$ was considered significant. Statistical analysis was performed using software IBM SPSS Statistics, version 23.0.

Results

Remission

In our cohort of 230 CD patients, the overall remission rate after first TSS was 65.6% (early remission rate: 46%, $n = 106$; delayed remission rate: 19.6%, $n = 45$), while 79 (34.4%) patients had persistent hypercortisolism. As shown in [Table 1](#), a comparison of clinical, biochemical, radiological and histopathological characteristics of the three sub-groups (patients with early remission, delayed remission and persistent hypercortisolism) revealed no significant differences except for the radiological characteristics. Patients with microadenomas had significantly higher (51.7% vs 30.6%, $P = 0.005$) rates of early remission, and lesser (28.6% vs 50%, $P = 0.005$) rates of persistent disease, as compared to patients with macroadenoma. However, the proportion of patients achieving delayed remission was similar (19.7% vs 19.4%, $P = 0.124$) amongst patients with microadenoma and macroadenoma. On the sub-analysis of patients with macroadenoma, patients with invasive tumours had significantly lower (4.5% vs 45%, $P < 0.001$) rates of early remission, and had higher (77.3% vs 35%, $P < 0.001$) rates of persistent disease, as compared to patients with non-invasive tumours. On the sub-analysis of patients with microadenoma, patients with unequivocal visualisation of adenoma on MRI had higher rates of early remission (55.8% vs 38.5%, $P = 0.007$), and lower rates of persistent disease (23.3% vs 46.1%, $P = 0.007$) as compared to those with negative/equivocal findings. Amongst patients with microadenoma, early remission (53.1% vs 43.5%, $P = 0.683$), delayed remission (19.3% vs 21.7%, $P = 0.683$) and disease persistence rates (27.6% vs 34.8%, $P = 0.683$) were similar in patients with histopathologically proven adenoma as compared to those with negative histopathological findings.

Recurrence

Of 151 patients achieving remission, long-term follow-up (≥ 12 months post-surgery) data were available for 117 patients (91 with microadenoma, 26 with macroadenoma), who were included in the analysis for disease recurrence. Out of these 117 patients, 78 patients had early post-operative remission, while 39 patients had delayed remission. At mean follow-up of 74 ± 61.1 months (range: 12–270 months) post-surgery, the overall recurrence rate was 41% (48/117), and mean time to recurrence was 37.2 ± 27.8 (8–96) months. The Kaplan–Meier analysis for recurrence-free survival is shown in [Fig. 1](#).



Table 1 Predictors of remission for Cushing's disease following first transsphenoidal adenectomy.

	Early remission (n=106)	Delayed remission (n=45)	Persistent disease (n=79)	P value
Female:male ratio	3.8:1 (84/22)	2:1 (30/15)	2.16 (54/25)	0.144
Age at diagnosis in years (mean±s.d. (range))	27.3±10.9 (7–60)	24.9±10.5 (10–55)	27.3±10.8 (10–53)	0.406
Duration of symptoms in years (mean±s.d. (range))	26.8±22.4 (1–120)	24.2±28 (3–144)	34.6±32.4 (3–144)	0.071
Preoperative laboratory values (mean±s.d.)				
08:00 h serum cortisol (ug/dL)	29.3±13.1	32.8±14.6	30.5±12.1	0.342
Plasma ACTH (pg/mL)	93.2±64.8	96.6±65.7	89±61.4	0.864
Sleeping midnight serum cortisol* (ug/dL)	21.2±9.1	25.7±10.3	25±14.9	0.083
LDDS cortisol (ug/dL)	9.9±11.5	22.6±15.5	21.3±11.8	0.528
Microadenoma (n=168)	87/168 (51.7%)	33/168 (19.7%)	48/168 (28.6%)	0.005**
Macroadenoma (n=62)	19/62 (30.6%)	12/62 (19.4%)	31/62 (50%)	
Macroadenomas (n=62)				
With CSI (n=22)	01/22 (4.5%)	04/22 (18.2%)	17/22 (77.3%)	<0.001**
Without CSI (n=40)	18/40 (45%)	08/40 (20%)	14/40 (35%)	
Microadenomas				
Equivocal (IPPS proven CD) (n=39)	15/39 (38.5%)	06/39 (15.4%)	18/39 (46.1%)	0.007**
Unequivocal (n=129)	72/129 (55.8%)	27/129 (20.9%)	30/129 (23.3%)	
Microadenomas				
Histopathologically				
Positive (n=145)	77/145 (53.1%)	28/145 (19.3%)	40/145 (27.6%)	0.683
Negative (n=23)	10/23 (43.5%)	05/23 (21.7%)	08/23 (34.8%)	

*Data for sleeping midnight serum cortisol were available in 146 patients; **P value significant only between early remission and persistent disease on *post hoc* analysis.

CSI, cavernous sinus invasion; IPPS, inferior petrosal sinus sampling; LDDS, low-dose dexamethasone suppression.

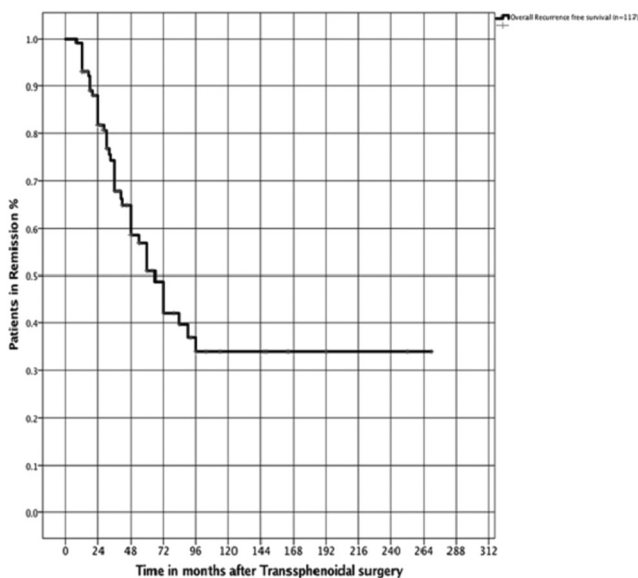
There was no significant difference in either recurrence rate (38.46% vs 50%, $P=0.367$) or mean time to recurrence (36.9 ± 24.4 vs 38.08 ± 18.2 months, $P=0.88$) when patients with microadenoma were compared to those with macroadenoma. The patients with early

remission had a significantly lower recurrence rate (30.8% vs 61.5%, $P=0.001$), with a trend towards later time to recurrence (mean time to recurrence of 41.9 ± 26.5 months vs 32.7 ± 17.7 months, $P=0.176$) as compared to those having delayed remission.

For analysing predictors of recurrence in each of the early and delayed remission groups, different demographic, biochemical, radiological and histopathological characteristics of patients with recurrence were compared to those having sustained remission (Table 2). Of these, some of the post-operative biochemical characteristics were found to be significantly different amongst these sub-groups.

Overall, there was no significant difference in early post-operative (day 5) serum cortisol levels between patients with recurrence vs those with sustained remission in both early and delayed remission groups. However, in the early remission group, a trend towards lower recurrence rate was observed in patients with early post-operative serum cortisol levels $<1.8\mu\text{g/dL}$ vs those with levels between 1.8 and $4.9\mu\text{g/dL}$ (17.02% vs 36.36%, $P=0.124$).

For calculation of duration of post-operative hypocortisolism/eucortisolism, the analysis was restricted to cohort of patients where the available longitudinal biochemical data could allow for the interpretation of

**Figure 1**

Kaplan-Meier curve showing recurrence-free survival of Cushing's disease patients who are in remission after transsphenoidal adenectomy.

Table 2 Predictors of recurrence in patients achieving remission after transsphenoidal adenomectomy.

	Early remission group (n=78)		P value
	Recurrence group (n=24)	Sustained remission group (n=54)	
Female:male ratio	3:1 (18/6)	5:1 (45/9)	0.534
Age at diagnosis in years (mean±s.d.)	25.2±9.9	27.1±11.4	0.504
LDDS cortisol (ug/dL) (mean±s.d.)	20.2±14.1	19.7±11.5	0.897*
Tumour size at baseline			
Microadenoma, (n=62)	18/62 (29%)	44/62 (71%)	0.552
Macroadenoma, (n=16)	06/16 (37.5%)	10/16 (62.5%)	
Macroadenomas (n=16)			
With CSI (n=1)	00/01	01/01 (100%)	1.00
Without CSI (n=15)	06/15 (40%)	09/15 (60%)	
Microadenomas (n=62)			
Equivocal (IPPS proven CD) (n=07)	04/07 (57.1%)	03/07 (42.9%)	0.179
Unequivocal (n=55)	14/55 (25.5%)	41/55 (74.5%)	
Microadenomas (n=62)			
Histopathology positive (n=53)	15/53 (28.3%)	38/53 (71.7%)	0.711
Histopathology negative (n=9)	03/09 (33.3%)	06/09 (66.7%)	
Post-surgery day 5 cortisol (µg/dL) (mean±s.d.)	1.9±1.3	1.5±0.9	0.222
Duration of hypocortisolism in months (mean±s.d. (range))	5.8±3.2 (2–12) (n=15)	18.5±16.9 (2–92) (n=51)	<0.001
Duration of eucortisolism in months (mean±s.d. (range))	29.2±21.7 (9–84) (n=14)	50.1±60.1 (2–250) (n=36)	0.076
Delayed remission group (n=39)			
	Recurrence group (n=24)	Sustained remission group (n=15)	P value
Female:male ratio	1.67 (15/9)	1.5 (9/6)	1.000
Age at diagnosis in years (mean±s.d.)	23.1±8.5	27.7±13.8	0.210
LDDS cortisol (ug/dL) (mean±s.d.)	22.9±14.9	21.8±16.5	0.850*
Tumour size at baseline			
Microadenoma, (n=29)	17/29 (58.6%)	12/29 (41.4%)	0.711
Macroadenoma, (n=10)	07/10 (70%)	03/10 (30%)	
Macroadenomas (n=10)			
With CSI (n=04)	03/04 (75%)	01/04 (25%)	1.00
Without CSI (n=06)	04/06 (66.7%)	02/06 (33.3%)	
Microadenomas (n=29)			
Equivocal (IPPS proven CD) (n=05)	03/05 (60%)	02/05 (40%)	1.00
Unequivocal (n=24)	14/24 (58.3%)	10/24 (41.7%)	
Microadenomas (n=29)			
Histopathology positive (n=25)	14/25 (56%)	11/25 (44%)	0.622
Histopathology negative (n=4)	03/04 (75%)	01/04 (25%)	
Post-surgery day 5 cortisol (µg/dL) (mean±s.d. (range))	16±11.5 (5.1–50)	15.4±10.6 (5.09–38)	0.873
Duration of hypocortisolism (months) (mean±s.d. (range))	6±2.6 (3–9) (n=6)	30±16.9 (12–48) (n=5)	0.044
Duration of eucortisolism (months) (mean±s.d. (range))	25.4±12.5 (5–48) (n=18)	48.6±51 (12–192) (n=12)	0.337

*Other preoperative hormonal tests (08:00h serum cortisol, sleeping midnight serum cortisol) were also not significantly different. CSI, cavernous sinus invasion; IPPS, inferior petrosal sinus sampling; LDDS, low-dose dexamethasone suppression.

approximate time points of transition in cortisol status. Mean duration of post-operative hypocortisolism was shorter amongst patients who recurred vs patients having sustained remission (early remission cohort: 5.8±3.2 months in the recurred group vs 18.5±16.9 months in the sustained remission group, $P<0.001$; delayed remission cohort: 6±2.6 months in the recurred group vs 30±16.9 months in the sustained remission group, $P=0.044$) (Table 2). Post-operative hypocortisolism of ≥ 7 months duration predicted sustained remission with 72.5% sensitivity and 76.2% specificity (ROC analysis, Fig. 2). At a cut-off of ≥ 13 months, specificity of predicting

sustained remission increased to 100% (with sensitivity of 46.4%). Duration of post-operative eucortisolism was apparently shorter (early remission: 29.2±21.7 months vs 50.1±60.1 months, $P=0.076$; delayed remission: 25.4±12.5 months vs 48.6±51 months, $P=0.337$) amongst patients who recurred vs patients with sustained remission.

Time to recurrence As depicted in Fig. 1, in overall cohort, there was a constant decline (without clustering) in the percentage of patients with recurrence-free survival till 96 months of follow-up, after which the curve

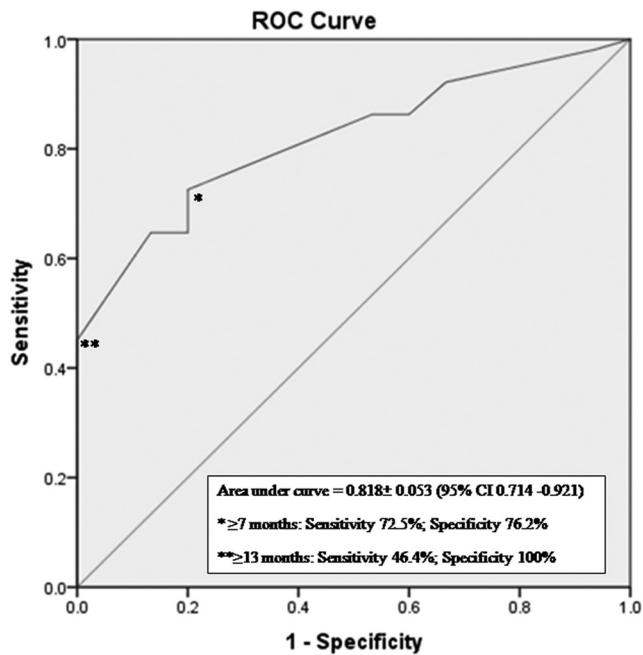


Figure 2
Receiver–operator characteristic curve showing duration of hypocortisolism as a predictor of recurrence.

plateaus. Out of 48 patients with recurrence, serial data on biochemical evaluation at regular follow-up visits (at least once in two years) were available for 33 patients, while in remaining 15 patients, follow-up was less frequent with no intervening biochemistry available to analyse precise time of recurrence. The mean time to recurrence for the former group of 33 patients was 27.7 months (median: 26 months, range: 8–60 months), with 84.38% patients recurring within first 3 years after surgery and rest (15.62%) recurring in next 2 years. No recurrences were observed after 5 years of surgery in this group. For the latter group of 15 patients with intermittent and infrequent follow-up, time to recurrence was significantly longer (mean: 69.2 months; median: 72 months; range: 48–96 months) as compared to the former group of 33 patients ($P < 0.001$).

Site of recurrence Amongst the patients with recurrence, both pre-surgical and follow-up pituitary MRI scans (at the time of disease recurrence) were available for comparison in 40 patients (macroadenoma ($n=11$), microadenoma ($n=29$, 22 with unequivocal and 7 with equivocal findings)). Out of 11 patients with macroadenomas, follow-up scans at the time of recurrence revealed adenoma in the same sellar location

(as baseline scan) in 10 patients, while it was not visualised in one patient. In patients with unequivocal visualisation of microadenoma, recurrent adenoma was found in the same sellar location (as seen in baseline scan) in 50% (11/22) of patients while in the remaining patients, it was not visualised clearly.

Discussion

Remission rates

A wide range of post-operative remission rates of CD (52–96.6%) have been reported from different centres (3). The use of different definitions of remission criteria, in terms of time of post-surgical assessment and cut-offs of serum cortisol levels in various studies, might partly account for the reported variation in remission rates. The recent clinical practice guidelines have recommended the use of morning serum cortisol $<5 \mu\text{g/dL}$ (hypocortisolism) in first week post surgery to define early remission (7). Using this criterion, in the current study, we found an overall remission rate of 65.6%, which falls within the range reported in literature. In our study, we found that 19.6% of the patients achieved delayed remission (eu- or hypocortisolism) in first 6 months post-surgery. The phenomenon of delayed remission is well recognised and reported to be 5.6–10% across different centres (15, 16, 17). Although the delayed remission rate observed in our study seems apparently higher than that reported in most other studies (5.6% in the study by Valassi and coworkers (17), 7.7% in the study by Pereira and coworkers (15)), we believe the variation in the definitions of early and delayed remissions used across studies might account for the observed differences. Valassi and coworkers (17) have grouped patients with post-operative eu- and hypocortisolism in the early remission group, while in our study, only hypocortisolemic patients constituted this group, thus making the denomination for the calculation of delayed remission rate different. Unlike our study criteria, Pereira and coworkers (15) reported delayed (at 3 months post-surgery) remission in 6/78 (7.7%) patients using stricter criteria of serum cortisol $<1.8 \mu\text{g/dL}$. This observation emphasises the need for defining uniform criteria of delayed remission to be used across centres. Proposed hypotheses for delayed remission include late necrosis of residual pituitary tumour tissue, declining adrenal autonomy or cortisol cyclicity and need to be studied in future (17).

Table 3 Summary of series reporting predictors for remission following primary microscopic TSS in CD.

Study (First author, year)	Clinical features				Radiological characteristics (MRI)				
	Remission rate % (n)	Age	Gender	Duration of disease symptoms	Pre-operative hormonal evaluation*	Microadenoma vs macroadenoma	Adenoma extension/invasion	Adenoma visualisation	Histopathology
Guilhaume, 1988 (18)	70% (60)	N	N	N	N	N [‡]	–	–	Y ^g
Mampalam, 1988 (19)	79% (216)	–	–	–	–	Y ^{‡,d}	Y ^{‡,e}	–	N
Pieters, 1989 (20)	59% (27)	N	N	N	N	–	–	–	N
Arnott, 1990 (21)	86% (28)	N	N	N	N	–	–	–	Y ^g
Bochicchio, 1995 (4)	76% (668)	N	N	–	N	N [‡]	N [‡]	Y ^{#,f}	Y ^g
Bakiri, 1996 (22)	72% (50)	N	N	–	N	–	–	N ^{#,μ}	Y ^g
Sonino, 1996 (23)	77% (103)	N	N	–	N	–	Y ^{‡,e}	–	Y ^g
Blevins, 1998 (24)	85% (96)	–	–	–	–	–	–	N [#]	–
Invitti, 1999 (25)	69% (236)	–	–	–	–	N [@]	–	N [#]	Y ^g
Chee, 2001 (26)	79% (61)	–	–	–	–	–	Y ^e	Y ^{#,μ,f}	N
Rees, 2002 (5)	77% (53)	–	–	–	–	–	–	N ^μ	N
Shimon, 2002 (27)	78% (74)	–	–	–	–	–	–	N [#]	N
Yap, 2002 (28)	69% (89)	–	–	–	–	Y ^{@,d}	Y ^e	–	N
Hammer, 2004 (29)	82% (289)	–	Y ^b	–	–	–	–	–	–
Salenave, 2004 (30)	82.7% (52)	–	–	–	–	–	–	–	–
Eposito, 2006 (31)	93% (28)	N	–	N	–	N	–	Y ^f	–
Acebes, 2007 (32)	89% (44)	N	–	N	–	N	N	N	Y ^g
Carrasco, 2008 (33)	74% (68)	N	N	–	–	N	N [‡]	–	Y ^g
Hoffman, 2008 (16)	76% (426)	N	N	–	–	–	–	–	–
Edward, 2009 (34)	80% (40)	N	–	–	N	N	–	Y ^f	–
Valassi, 2010 (17)	76% (620)	N	N	–	N	–	–	N	Y ^g
Ammimi, 2011 (35)	67% (81)	Y ^a	Y ^b	–	Y ^c	N	–	–	Y ^g
Ciric, 2012 (36)	83% (136)	–	–	–	–	–	–	N ^μ	–
Kim, 2012 (37)	70% (54)	–	–	–	–	–	–	N	N
Hassan-Smith, 2012 (38)	83% (72)	–	–	–	N	–	–	N	Y ^g
Alexandraki, 2013 (39)	68% (124)	–	Y ^b	–	–	Y ^d	–	N	Y ^g
Aranda, 2014 (40)	78% (41)	N	Y ^b	N	N	N	–	N	N
Costenaro, 2014 (6)	80% (103)	N	N	–	–	Y ^d	–	Y ^f	Y ^g
Dimopolou 2014 (41)	71% (120)	–	–	–	–	Y ^d	–	Y ^f	–
Ramm-Petersen 2015 (42)	84% (19)	–	–	–	–	N	–	N	N
Chandler, 2016 (43)	80% (276)	–	–	–	–	Y ^d	–	Y ^{#,f}	Y ^g
Shirvani, 2016 (44)	94.80% (96)	N	N	N	N	Y ^d	Y ^e	N	–
Our study, 2016	65.6% (230)	N	N	N	N	Y ^d	Y ^e	Y ^{#,f}	N

Predictor of remission: Y (yes); N (no).

*One or more of the following tests: serum cortisol, plasma ACTH, UFC, suppressibility by dexamethasone.

^aYounger age; positive predictor of remission; ^bMale gender; negative predictor of remission; ^cLower preoperative LDD5 cortisol; positive predictor of remission; ^dMicroadenoma; positive predictor of remission; ^eAdenoma extension/invasion; negative predictor of remission; ^fAdenoma visualisation; positive predictor of remission; ^gPositive histopathology; positive predictor of remission; ^hSurgical/pathological findings; ⁱNeuroimaging and/or surgical findings; ^jVisualisation of adenoma on MRI and/or CT; ^kOnly microadenomas were included.

GC, glucocorticoids.



Predictors of remission

Studying factors affecting remission is important to predict prognosis of patients undergoing TSS. Table 3 lists studies that have statistically analysed predictors for remission following primary microscopic TSS in CD (adult±paediatric) patients. Similar to that reported in most previous studies, in the current study, we found that none of the clinical or biochemical parameters had a predictive value for remission (Table 3).

Size of the adenoma (microadenoma vs macroadenoma) noted on neuroradiographic (MRI/CT) and/or surgical findings has been studied as a predictor for remission. As evident from Table 3, most of the studies reported macroadenoma to have similar or poorer outcomes as compared to microadenoma. Better surgical outcome for microadenoma observed in our study is in accordance with the recent meta-analysis (45), which reports significantly higher remission rates for patients with microadenoma than those with macroadenoma (83% vs 63%). Blevins and coworkers (24) proposed that this difference in remission rates may be due to varying tumoural biological behaviour (i.e. size and/or invasiveness). Poor remission rates for macroadenoma, especially for those with cavernous sinus invasion observed in our study group, further support this contention.

In our series, surgical results of patients with MRI-visible microadenoma were significantly better than those with IPSS-proven CD patients with negative/equivocal MRI findings. Visualisation of pituitary adenoma on pre-surgical imaging has been reported to have a better outcome in various studies (including ours), while others achieved comparable results irrespective of adenoma visualisation (Table 3). Differing methodological factors across various studies like sensitivity of imaging modalities used (CT vs MRI), confirmation of central origin with IPSS, inclusion of macroadenoma patients in sub-analysis and extent of neurosurgery performed in the absence of visible adenoma might account for the varying outcome across studies (4, 18, 25, 26). Use of sensitive MRI techniques like VI-SGE sequences is expected to enhance adenoma detection rate and may result in better outcomes (12). However in MRI-negative/equivocal cases, optimal surgical strategy (extent of exploration and resection) still needs further research.

Histopathological confirmation of an adenoma has been reported as a predictor of better remission rates in most of the studies, while others, like our study, have found no differences in the outcome. Patients achieving remission despite negative histology can possibly be

explained by in-situ necrosis and vascular damage of the adenoma following surgical exploration, loss of tissue in suction or tissue being missed on pathological sections (46).

Recurrence and its predictors

Overall recurrence rate (41%) after first TSS in our study falls within the broad range (15–66%) as reported in literature (7). As observed in our study, majority of the past studies (6, 37, 50, 52) have reported that baseline demographic, hormonal, neuroradiological and histopathological findings do not have a predictive value for recurrence. Amongst the various factors studied, post-operative cortisol dynamics seem to be a most important predictive factor for recurrence (Table 4).

Early remission vs delayed remission In our study, patients with delayed remission had higher recurrence rate than patients with early remission (61.5% vs 30.8%, $P=0.001$). This finding is similar to that of Valassi and coworkers (17) who reported 43% recurrence rate in patients with delayed remission as compared to 14% in the early remission group ($P=0.02$). It can be speculated that the residual tumour cells undergoing gradual vascular insult (over weeks) that may be responsible for the phenomenon of delayed remission are more likely to recover later (over months to years) and account for observed higher recurrence rate.

Degree of early post-operative hypocortisolism Complete removal of ACTH-secreting pituitary adenoma is expected to result in low-circulating ACTH and cortisol levels due to prolonged suppression of normal corticotrophs. Hence, achieving immediate post-surgical hypocortisolism has been recognised as the goal of successful TSS. Further parameters of post-operative hypocortisolism in terms of its degree and duration have been studied as predictors of recurrence (Table 4). In our study, we did not find degree of hypocortisolism to have a significant predictive value, but observed a trend towards lower recurrence rates in patients with early remission who have serum cortisol $<1.8\mu\text{g/dL}$ vs those with $1.8\text{--}4.9\mu\text{g/dL}$. While few of the earlier studies have reported significantly lower recurrence rates in patients with greater degree of hypocortisolism, they have used higher cut-off of $>5\mu\text{g/dL}$ to define hypocortisolism

Table 4 Summary of series reporting post-surgery cortisol dynamics as predictors of recurrence following primary microscopic TSS in CD.

Study (First author, year)	Recurrence rate % (No of patients in remission/ Total no of patients)	Degree of early post-surgery hypocortisolemia	Duration of hypocortisolemia	Early post-surgery CRH stimulation test
Tahir and Sheeler, 1992 (47)	20.6% (34/34)	–	N (need for GC)	–
Trainer, 1993 (8)	12.5% (32/48)	Y*,a	–	–
Viganti, 1994 (48)	20% (30/36)	–	–	Y ^c
Bochicchio, 1995 (4)	12.7% (510/668)	–	Y (need for GC) ^b	Y ^c
Invitti, 1999 (25)	17% (162/236)	N [#]	–	Y ^c
Imaki, 2001 (49)	13.3% (30/49)	Y*,a	–	–
Pereira, 2003 (15)	9% (56/80)	N [#]	–	–
Patil, 2008 (50)	17% (184/215)	Y**,a	–	–
Sughrue, 2011 (51)	26% (73/88)	Y*,a	–	–
Lindsay, 2011 (9)	12% (325/450)	N [#]	–	Y ^c
Ciric, 2012 (36)	9.67% (101/121)	N [#]	–	–
Alexandraki, 2013 (39)	24% (84/124)	–	Y ^b	–
Barbot, 2013 (52)	38.5% (39/57)	–	–	Y ^c
Costenaro, 2014 (6)	8% (81/101)	–	N (need for GC)	–
Dimopolou, 2014 (41)	34% (85/120)	–	N	–
Our study, 2016	41.02% (151/230)	N [#]	Y	–

Predictor of recurrence: Y (yes); N (no).

^aHigher degree of early post-operative hypocortisolemia: positive predictor for long-term remission; ^bLonger duration of hypocortisolemia: positive predictor for long-term remission; ^cLower CRH-stimulated cortisol and/or ACTH in early post-operative period: positive predictor for long-term remission;

*Cut-off of serum cortisol used to define hypocortisolemia was above 5 µg/dL; **Cut-off of serum cortisol used to define hypocortisolemia was 5 µg/dL, but also included patients with normal urinary-free cortisol; [#]Cut-off of serum cortisol used to define hypocortisolemia was ≤5 µg/dL.

(8, 49, 51). However, more recent studies using cut-off of <5 µg/dL to define hypocortisolemia (similar to cut-off in the current study) have reported no significant difference in recurrence rates in patients with serum cortisol nadir <2 µg/dL vs 2–4.9 µg/dL, which is similar to our findings (9, 15, 25, 36).

One of the limitations of our study is the absence of data on post-operative stimulation tests (CRH, desmopressin) as these tests were not routinely performed. Nevertheless, these stimulation tests in the early post-operative period have not been shown to have any additional benefit in predicting long-term remission status over that of early post-operative basal cortisol levels (7).

Duration of post-operative hypocortisolemia

Unlike degree of post-operative hypocortisolemia, its duration remains an under acknowledged predictor of long-term remission. Earliest indication of its predictive value was given in 1979 by Pont and coworkers (53), who speculated that the need for early withdrawal of steroid replacement therapy could be a clue to disease recurrence. Later, Bochicchio and coworkers (4) have reported that 97% of the patients requiring glucocorticoid replacement therapy for more than one year duration had sustained remission at mean follow-up of 5 years. In the current study, we found longer duration of post-operative hypocortisolemia

to be a positive predictor of sustained remission with a duration ≥13 months, predicting remission with 100% specificity (at sensitivity of 46.4%) over a mean follow-up of 74 months. In a similar study, Alexandraki and coworkers (39) reported that the absence of HPA axis recovery within 12 months post-surgery predicted sustained remission with specificity of 89.1% (at sensitivity of 64.7%). In contrast to these studies, Dimopolou and coworkers (41) did not find a significant difference in the mean duration of hypocortisolemia in patients with and without disease recurrence (32 months vs 48 months). Differences in definitions of recovery of adrenocortical function (normal response to ACTH stimulation test) and disease recurrence (elevated 24-h UFC/LDDS cortisol ≥5 µg/dL) used at their centre might have accounted for different results (54). Biologically, it can be speculated that shorter duration of hypocortisolemia may be a manifestation of early recovery of autonomy of residual tumour cells, while longer duration of hypocortisolemia represents later occurrence of CRH-stimulated recovery of normal corticotrophs and hence a predictor of long-term remission.

Time to recurrence In their retrospective analysis, Bochicchio and coworkers (4) have observed no apparent plateau or clustering in the distribution of recurrences in 510 CD patients over a follow-up period of 10 years.

Although we found a plateauing of recurrence on a longer follow-up period of 22.5 years, our finding of constant decrease in recurrence-free survival rates without apparent clustering in the initial 8 years was similar to that of Bochichio and coworkers (4). This emphasises the impact of duration of follow-up in studying time to recurrence. The extent of evaluation on follow-up visits (clinical vs biochemical) is another important consideration in studying time to recurrence. We observed an early identification of recurrence (at a mean time to recurrence of 27.7 months) and earlier plateauing of recurrence-free survival curve at 5 years in a sub-group of patients where serial data on biochemical evaluation (ODST) were available, as compared to that of patients with irregular and infrequent follow-up (mean time to recurrence of 69.2 months). Thus, our findings emphasise the importance of regular biochemical surveillance of patients in remission to detect recurrence before the disease becomes clinically obvious, thus allowing for timely intervention. Several biochemical tests like midnight serum/salivary cortisol, ODST and 24-h urinary-free cortisol are used to detect disease recurrence. In two longitudinal studies, midnight serum and salivary cortisol have been shown to be the earliest sign of recurrence and almost always precede elevated urine cortisol (7). However, serial data comparing sensitivity of midnight serum or salivary cortisol vs ODST to identify early disease recurrence are lacking. One of the limitations of the current study is that recurrence was defined based on ODST values alone, making its comparison with other tests impossible.

Site of recurrence An interesting observation in our study was visualisation of adenoma at the same sellar location (as baseline scan), in all patients (micro/macro adenomas) with equivocal adenoma seen on the MRI scan at the time of recurrence. Our observation is substantiated by few of the previous surgical series (55, 56, 57) where intra-operative findings at subsequent surgeries for recurrent CD have been described. In a large series of patients who underwent surgery for recurrent CD, Dickerman and coworkers (57) reported that recurrent tumour was found at the same site or contiguous to the same site as the initial surgery. Additionally at repeat surgery, adenomatous invasion of the dura mater was found in 54% and 100% of microadenomas and macroadenomas, respectively. Thus, it can be inferred that recurrent CD could result from regrowth of the residual tissue at the primary site or adjacent dura mater.

Retrospective nature of the study with its attendant data attrition forms the major limitation of our study. However, long-term follow-up of respectable number of CD patients at a single centre, thus conforming uniformity in work-up and management of entire cohort, represents the strengths of the study. Moreover, determination of remission/recurrence by biochemical evaluation, rather than self-reported clinical information, has ensured objectivity in the analysis.

Conclusion

We report long-term post-surgical follow-up of 230 CD patients managed at a single centre. Overall, remission and recurrence rates were similar to that reported in literature, but proportion of delayed remission was relatively higher. Radiological features like negative/equivocal MRI findings and presence of macroadenoma, especially those with cavernous sinus invasion, were predictors of poor remission rates. In addition to early remission, longer duration of post-operative hypocortisolism is an important predictor of sustained remission. Regular biochemical surveillance may help in identifying recurrence early.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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