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Undetectable postoperative cortisol does not always predict long-term remission in Cushing's disease: a single centre audit*

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Summary

OBJECTIVE An undetectable postoperative serum cortisol has been regarded as a definition of cure in Cushing's disease. However, we noted disease recurrence amongst patients with Cushing's disease despite undetectable postoperative cortisol levels, and this led us to audit our data. We have also previously assessed surgical outcome for acromegaly and microprolactinoma for a single surgeon. The aims of this study were two-fold: (i) to investigate the treatment and surgical outcome of patients with Cushing's disease. In particular, we wished to compare the data with outcome for other pituitary tumours in our centre; and (ii) to determine whether undetectable cortisol following surgery is predictive of long-term cure for Cushing's disease.

PATIENTS AND METHODS We performed a retrospective audit of 97 patients; mean age 39·1 (range: 14–82) years, 78/97 (80·4%) female, mean follow-up 92 months (range: 6 months to 29 years), with Cushing's disease seen in our unit between 1969 and 1998. We documented diagnostic investigation, immediate surgical outcome and disease recurrence in these patients.

RESULTS All patients had elevated urinary free cortisol (mean 1270·6 nmol/l, range: 327–3245 nmol/l). In total, 95·5% of patients did not suppress with low-dose dexamethasone suppression testing. Hypokalaemia (K < 3·2 mmol/l) was present in 15·6% of patients; 17·5% of patients did not show cortisol suppression with high-dose dexamethasone and 15·8% of patients did not show an ACTH rise of > 50% following corticotrophic releasing hormone (CRH) administration. There was no significant (> 3) gradient in ACTH or cortisol following CRH during inferior petrosal sinus sampling in 27·3% of patients who had the test. A pituitary tumour was demonstrated on imaging in 55·8% of patients; 10·3% were macroadenomas. Mortality rate following transsphenoidal surgery was 1%. Following surgery, the immediate postoperative remission rate (undetectable postoperative cortisol) was 68·5%. However, 11·5% of these patients developed disease recurrence during a mean follow-up period of 36·3 months. Considering microadenomas, Cushing's disease patients had an immediate postoperative remission rate of 63·2% which is significantly lower (P < 0·05) compared to a remission rate of 91·1% in acromegaly. Additionally, new postoperative gonadotrophin deficiency (13·9%) and TSH deficiency (25·8%) was higher in patients with Cushing's disease compared to patients with acromegaly or microprolactinoma. Immediate postoperative remission rates improved from 50% in the first decade of a surgeon's career to consistently above 60% in the second and third decades, demonstrating a trend which may be attributed to surgical experience.

CONCLUSIONS (i) Despite strict criteria for immediate postoperative remission and recurrence, undetectable postoperative cortisol is not always predictive of long-term remission. (ii) Despite an aggressive surgical approach, immediate postoperative remission rates for Cushing's disease are lower compared to other microadenomas. The development of new pituitary hormonal deficiency following surgery is also commoner than that seen amongst other microadenomas. These data have important implications for the follow-up of patients with Cushing's disease.

Cushing's disease is a rare condition with a prevalence of 39 cases per million (Etxabe & Vazquez, 1994) and occurs more commonly amongst female patients. Owing to its rarity, there have been few large series to date analysing the diagnostic work-up, treatment and outcome in Cushing's disease. Recent large clinical series have assimilated multicentre data (Bochicchio *et al.*, 1995; Invitti *et al.*, 1999) and therefore involve different investigation protocols as well as different surgeons.

*For commentary see page 19.

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Post-operative cortisol levels are used to estimate 'remission' or 'cure' of Cushing's disease. There are variable definitions of post surgical cure. Examples of these are normalization of cortisol levels to within the reference range (Mampalam *et al.*, 1988), clinical appearance of remission associated with low plasma and urinary cortisol levels (Invitti *et al.*, 1999) and cortisol suppression with the low-dose dexamethasone suppression test (Bochicchio *et al.*, 1995). However, it has been accepted in many centres that undetectable plasma cortisol (< 50 nmol/l) after surgery should be regarded as cure (Trainer *et al.*, 1993). In 1993, it was reported that amongst 20 patients with undetectable postoperative cortisol (< 50 nmol/l) at St Bartholomew's Hospital (Trainer *et al.*, 1993), there was no recurrence (median follow-up time 40 months). Simultaneously, another study described similar results of no recurrence amongst patients with undetectable postoperative plasma cortisol levels during a median follow-up period of 58 months (McCance *et al.*, 1993). An extensive further review confirmed that undetectable postoperative serum cortisol levels between 5 and 14 days after surgery was associated with good long-term outcome (McCance *et al.*, 1996).

The European Cushing's Disease Study group, which collected data between 1975 and 1990 (Bochicchio *et al.*, 1995) found that 510/668 patients demonstrated immediate postoperative remission (defined as normal suppression with low-dose dexamethasone). Out of these patients, 65 (12·7%) recurred within a mean time of 39·4 months. Amongst patients ($n = 94$) with undetectable postoperative cortisol levels (detection limits were not specified), a recurrence rate of 4·3% was seen at 24 months.

In our centre, we observed that, despite undetectable postoperative cortisol and an experienced pituitary surgeon, recurrence of Cushing's disease did occur and this led us to audit our data. We have previously assessed the outcome of surgery for acromegaly and microprolactinoma in our centre (Ahmed *et al.*, 1999; Turner *et al.*, 1999a) confirming the importance of a single experienced surgeon and hence carried out this retrospective study of patients with pituitary dependent Cushing's disease who underwent transsphenoidal adenomectomy (TSA) in Oxford by the same surgeon.

The aims of this study were two-fold: (1) to investigate the treatment and surgical outcome of patients with Cushing's disease. In particular, we wished to compare the data with outcome for other pituitary tumours in our centre; and (ii) to determine whether undetectable cortisol following surgery is predictive of long-term remission for Cushing's disease.

Patients and methods

One hundred and twelve patients who had Cushing's disease diagnosed between 1969 and 1998 were identified through our endocrine database. Patients' case notes were then extracted from medical records and studied. Exclusions were as follows: eight patients in whom surgery was performed for Nelson's syndrome, one patient with confirmed diagnosis of cyclical Cushing's, two patients who were treated medically and four with insufficient follow-up data on record. We studied 97 patients (mean age 39·1 years; 78 female, 19 male) with Cushing's disease. Fifty-seven patients had previously been included in a series by Burke *et al*. (1990) which dealt with the initial endocrine outcome. All patients had clinical features of Cushing's syndrome and 24 h urinary free cortisol (UFC) of more than 280 nmol/l (Table 1). All underwent TSA performed by a single surgeon (CBTA). Clinical features included hypertension with systolic blood pressure > 130 ($n = 67$, 69%), weight gain ($n = 66$, 68%) and hirsutism ($n = 59$, 61·5%). Follow-up duration ranged between 6 months and 29 years. Mean follow-up time was 92 months and median follow-up time was 38 months. We documented patient biochemical data, neuroradiology, surgical data, postoperative evaluation and follow-up data.

Biochemical data collected were ACTH levels, 09·00 h and midnight cortisol levels, urine free cortisol levels, serum potassium, low-dose and high-dose dexamethasone suppression tests, corticortrophin releasing hormone (CRH) stimulation test and inferior petrosal sinus sampling (IPSS). Neuroradiological data on tumour visualization was accumulated from computed tomography (CT) and magnetic resonance imaging (MRI) reports. Surgical characteristics of date, surgeon, surgical complications (including diabetes insipidus), mortality and operative findings were recorded. Biopsy results were available on 75 patients. Histological findings were divided into three groups: (i) obvious pituitary adenomas with basophil or ACTH staining; (ii) normal anterior pituitary cells with immunostaining for all pituitary hormones; and (iii) biopsies with high numbers of ACTH staining cells without evidence of adenoma.

Table 1 Summary of biochemical data obtained for diagnosis

Test	Percentage (n)
Elevated UFC	100% (74/74)
Absent low dose dexamethasone suppression	95·5% (42/44)
Hypokalaemia	15·6% (10/64)
Absent high dose dexamethasone suppression (to > 50%)	17·5% (7/40)
< 50% rise of ACTH with CRH	15·8% (3/19)
Central/peripheral gradient with IPSS with CRH L3	27·3% (3/11)

Postoperative serum cortisol was recorded in order to assess postoperative biochemical remission. The cortisol measurements were taken on the third and fourth day after surgery, and steroid cover (intramuscular hydrocortisone or oral prednisolone which was started immediately after surgery) was stopped at least 24 h prior to measurement. Immediate postoperative remission of Cushing's disease was defined as plasma levels of cortisol of < 50 nmol/l or undetectable. Replacement therapy with glucocorticoid (hydrocortisone or prednisolone) was then started.

During the follow-up period, UFC levels and early morning cortisol were measured (off steroid replacement) during intital follow-up of 3 months, 6 months and annually thereafter. If these were raised, then a low-dose dexamethasone test was performed. Disease recurrence was concluded when there was biochemical evidence in the form of elevated UFC and absence of cortisol suppression with low-dose dexamethasone.

Assessment of anterior pituitary hormone function was also performed 4–6 weeks after surgery. Thyroid function was assessed according to plasma T4 and TSH levels. In premenopausal women, gonadotrophin deficiency was assessed on the basis of absence of normal menses and inappropriately normal gonadotrophins despite low oestradiol. In post menopausal females, it was defined as inappropriately low gonadotrophin levels. In males, gonadotrophin deficiency was measured according to low testosterone levels and inappropriately low gonadotrophins. Diabetes insipidus was defined as polyuria with urine osmolality of < 350 mosm/l and plasma osmolality of > 290 mosm/l. Recovery of ACTH function was tested by the insulin tolerance test after withdrawal of steroid replacement for at least 5 days.

Reference limits for biochemical data were consistent throughout the study period except for some sample analyses between 1970 and 1974, in which case the older reference limits (09·00 h cortisol 7–25 μg/100 ml and midnight cortisol < 7 μg/100 ml) were adhered to. Methods and criteria are consistent with those given elsewhere (Howlett *et al.*, 1986; Bevan *et al.*, 1987). The ACTH assay used was a radioimmunoassay involving Vigor extraction and charcoal separation (Barts assay method). The four different cortisol assays used between 1969 and 1998 differed. A competitive binding assay using sephadex and pregnancy plasma binder for separation was used in between 1969 until 1980. An in-house radioimmunoassay was used until 1984. The assay used between 1984 and 1994 was the DPC (Diagnostic Products Corporation, Los Angeles, CA, USA). From 1994 onwards, we used the Bayer Immuno-1 assay (Euro/DPC Limited, Gwynedd, UK), which was a magnetic separation assay run on the Immuno-1 machine. Normal reference levels are ACTH 10–80 ng/l, serum cortisol 200–700 nmol/l, midnight cortisol < 50 nmol/l and urine free cortisol < 280 nmol/l. Hypokalaemia was diagnosed if serum potassium was < 3·2 mmol/l. Data on hypokalaemia were excluded if patients were on diuretics or an angiotensin-converting enzyme-inhibitor. Low-dose dexamethasone (2 mg daily given in 6-h divided doses over 2 days) and high-dose dexamethasone (8 mg daily given in 6-h divided doses over 2 days) tests were considered to have caused suppression if cortisol levels were undetectable or < 50% after 2 days, respectively (Nichols *et al.*, 1968). A response to stimulation with CRH involved sampling for ACTH and cortisol at –15, 0, 15, 30, 45, 60, 90 and 120 minutes (Chrousos *et al.*, 1984). An increment of ACTH or cortisol of > 50% over the baseline was considered a positive test. In the IPSS test, samples for ACTH and cortisol were taken basally and after administration of 100 μg of human CRH at 0, 2, 5, 10 and 15 minutes. A central/peripheral ACTH gradient of > 3 following CRH in the inferior petrosal sinus sampling test was consistent with Cushing's disease (McCance *et al.*, 1989; Landolt *et al.*, 1994).

Statistical analysis was performed using Arcus Quickstat 1·2 (Arcus Quickstat, Biomedical version 1.1, Research Solutions, Cambridge, UK). Chi-squared or the Fisher's exact test were used to compare variables depending on dataset characteristics. $P < 0{\cdot}05$ was considered statistically significant. The probability of recurrence after pituitary surgery was assessed with Kaplan–Meier analysis. The Wilcoxon and log-rank tests were used to compare estimated disease-free survival curves.

Results

Diagnosis and differential diagnosis

Although a firm diagnosis of pituitary dependent Cushing's disease was made in all 97 patients prior to surgery, not all patients underwent all diagnostic tests. For example, IPSS has been performed only in the patients in the latter years of the cohort; therefore, the denominator may differ for the test compared to other diagnostic tests performed.

All the patients who had urinary free cortisol collections (n = 74) showed elevated values (mean 1270·6 nmol/l, range: 327–3245 nmol/l). Table 1 shows a summary of the biochemical test results. Importantly, between 15% and 27% of patients failed to achieve conventionally accepted diagnostic criteria on high-dose dexamethasone, CRH and IPSS testing. During the preoperative period, metyrapone was used to suppress cortisol levels in 52 patients (53·6%). It was stopped the day before surgery.

Radiological findings

Upon imaging with CT or MRI (58 patients with CT; 23 patients with MRI; five with skull X-ray, imaging data not available in 11 patients), a pituitary tumour was visualized in 48 out of 86 patients (55·8%). Contrast was used in 12/58 (20·7%) of the CT scans and 6/23 (26·1%) of the MRI scans. Amongst these tumours, there were 10 macroadenomas. Since imaging was available for 86 patients and 10 were macroadenomas, 76 patients

Table 2 Matched pre and postoperative endocrine deficiencies (%)

Hormone deficiency	Preoperative	Postoperative
Gonadotrophin	8/36 (22·2%)	13/36 (36·1%)
Thyroid hormone deficiency	6/63 (9·1%)	22/63 (34·9%)

had microadenomas on the basis of no demonstrable macroadenoma. Extrasellar extension was seen in nine cases (six lateral, three suprasellar).

Mortality and morbidity

Perioperative mortality was defined as death occurring within 1 month from surgery. The mortality rate following TSA was 1/97 (1%; myocardial infarction). Diabetes insipidus was observed in 41/97 (42·3%) patients and was permanent in eight (8·2%). The other complications were cerebrospinal fluid rhinorrhoea (8·2%), profuse localized bleeding (6·2%), meningitis (2·1%), third nerve palsy (2·1%), deep vein thrombosis (1·0%) and myocardial infarction (1·0%).

Operative and postoperative findings

Out of the 75 available biopsy histology results, 42 (52%) demonstrated pituitary adenomas which were either basophil or ACTH staining. Normal pituitary tissue was found in 22 (29·3%) biopsies and 11 (14·6%) biopsies showed excess ACTH staining tissue without evidence of adenoma. Matched pre- and postoperative hormone deficiencies are shown in Table 2. New postoperative gonadotrophin deficiency was seen in 13·9% of patients and new thyroid hormone deficiency was seen in 25·8% of patients.

Remission and recurrence rates

Following surgery, immediate postoperative remission (undetectable postoperative cortisol) rate was 68·5% (61/89 patients; post operative remission data was not available in eight patients). Out of the 61 patients who were cured, seven (11·5%) had disease recurrence which occurred during a mean follow-up period of 36·3 months (range: 6–60 months).

Using available data on long-term remission and imaging, recurrence in the longer term, of microadenomas and macroadenomas was tabulated and compared with Kaplan–Meier analysis as shown in Fig. 1. There was no significant difference in rates of recurrence comparing micro- and macroadenomas.

A pathological specimen demonstrating the presence of pituitary adenoma was not related to immediate postoperative remission. This was seen in 28/42 (66·6%) with pituitary adenoma and 14/22 (63·6%) with normal pituitary tissue on histological testing.

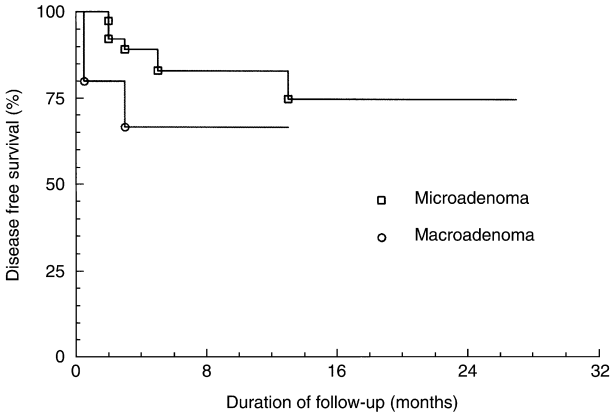

Fig. 1 The analysis of recurrence of Cushing's disease amongst patients who were in remission after trans-sphenoidal surgery. The disease free survival curves were generated according to Kaplan–Meier analysis with □ representing microadenomas and ○ representing macroadenomas. *y*-axis: disease free survival (%); *x*-axis: duration of follow-up in months.

Visualization of adenoma with CT or MRI was not related to outcome. Thirty of 48 (62·5%) of patients with tumour visualized demonstrated immediate postoperative remission whilst 31/49 (63·2%) patients whose tumours were not visualized demonstrated immediate post operative remission.

Data on the seven patients with disease recurrence after surgery is shown in Tables 3 and 4. Postoperative steroid cover with either prednisolone or hydrocortisone orally were required for all patients until recovery of ACTH function (normal plasma cortisol levels). This occurred at a mean time of 10·7 months following surgery. Not all patients had clinical features of recurrence but all had biochemical features of recurrence as defined by raised UFC and absence of cortisol suppression with low-dose dexamethasone.

Remission rates with year of surgery

We examined the remission (postoperative cure) rates of the surgeon with regards to year of surgery. The rates show a trend towards increase with time, as illustrated in Fig. 2.

Discussion

This report contains the largest single centre, single surgeon series in the literature**.** We have shown that an undetectable postoperative cortisol is not always predictive of long-term remission.

Trans-sphenoidal surgery led to an immediate postoperative remission rate of 68·5% in our centre. Other series have reported

Table 3 Age, preoperative cortisol suppression, radiology, pre- and postoperative cortisol on the seven patients with recurrence

Age	Preoperative metyrapone	Radiology	Preoperative UFC (nmol/l)	Assay method demonstrating undetectable cortisol < 50
56	No	Microadenoma	1864	DPC
29	Yes	Microadenoma	3500	Immuno-1
22	No	Microadenoma	2531	DPC
41	No	Microadenoma	1503	Immuno-1
14	Yes	Microadenoma	1245	DPC
40	Yes	Microadenoma	653	DPC
18	No	Macroadenoma	1400	Immuno-1

Table 4 Histology, time to recurrence after surgical cure, type of recurrence and treatment of the seven patients

Histology	Time to recurrence	Type of recurrence	Treatment after recurrence
ACTH staining, pituitary adenoma	12 months	Biochemical	Bilateral adrenalectomy
ACTH staining, pituitary adenoma	6 years	Biochemical	Repeat TSA
ACTH staining, pituitary adenoma	18 months	Biochemical and symptoms of weight gain, hypertension	Repeat TSA
ACTH staining, pituitary adenoma	4 years	Biochemical	Repeat TSA
ACTH staining, pituitary adenoma	3 years	Biochemical and symptoms of weight gain	Repeat TSA
ACTH staining, pituitary adenoma	5 years	Biochemical	Repeat TSA and radiotherapy
ACTH staining, no adenoma	8 months	Biochemical and symptoms of headache, weight gain	Repeat TSA and radiotherapy

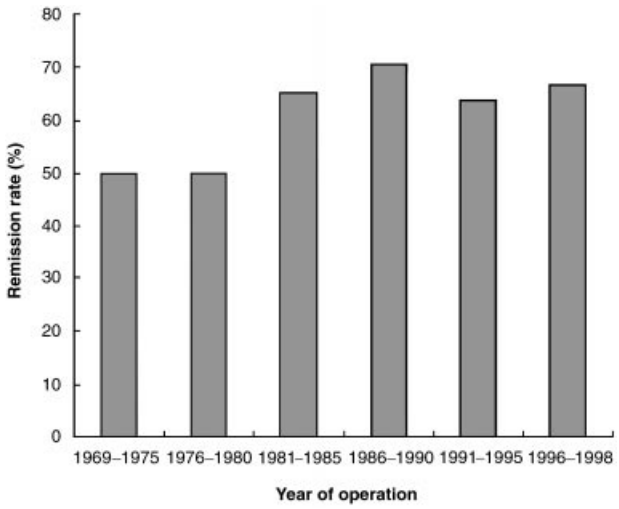

Fig. 2 This represents the remission rates (*y*-axis) according to the year of operation (*x*-axis) for the surgeon. The rates showed an improvement when the second and third decades were compared to the first decade of the surgeon's career.

rates of 42% (20/48) by Trainer *et al*. (1993); 53·3% (8/15) by McCance *et al*. (1993); and 58·6% (17/29) by van Aken *et al*. (1997).

Tests to establish the differential diagnoses showed that no single test invariably predicts the cause of Cushing's syndrome, as has been shown by others (Howlett *et al.*, 1986; Booth *et al.*, 1998; Invitti *et al.*, 1999). This is in contrast to the Bethesda data on IPSS (Oldfield *et al.*, 1991) which found 100% specificity for all patients.

There are inadequate published data on postoperative anterior pituitary function in patients with Cushing's disease. Currently, the total gonadotrophin failure rate following surgery (36·1%) for Cushing's disease in Oxford remains similar to a rate of 48% from 10 years ago (Burke *et al.*, 1990), although the rate for new gonadotrophin deficiency was not available from the previous study. A total gonadotrophin failure rate of 36·1% was higher amongst Cushing's disease patients after surgery compared to 11·1% for microprolactinoma patients (Turner *et al.*, 1999a). A new gonadotrophin failure rate postoperatively of 13·9% (36·1% postoperatively and 22·2% preoperatively) for Cushing's disease was also higher than with surgery for acromegaly where 7·9% of patients developed new gonadotrophin dysfunction (Ahmed *et al.*, 1999). Postoperative TSH deficiency of 34·9% (preoperative deficiency 9·1%) was found in this series compared to 24% of post-operative patients with nonfunctioning adenoma (Turner *et al.*, 1999b) developing TSH deficiency. Some 5% of patients with acromegaly developed new TSH deficiency after surgery (Ahmed *et al.*, 1999). Thus, there appears also to be a higher rate of new TSH deficiency seen amongst patients who have undergone surgery for Cushing's disease. The higher rates of disruption to gonadotrophin function and thyroid function following surgery for Cushing's disease compared to microprolactinomas, nonfunctioning adenomas and acromegaly is likely to be due to a more aggressive surgical approach in Cushing's disease in order to induce cure.

A pituitary adenoma was visualized on pituitary imaging (20% with contrast on CT, 25% on MRI) in approximately one-half of the patients. Similar rates have been found in other studies (Buchfelder *et al.*, 1993; Escourolle *et al.*, 1993; Invitti *et al.*, 1999). Visualization of adenoma has been associated with a better surgical outcome (Bochicchio *et al.*, 1995) but this was not seen amongst our series of patients. Since MRI with contrast is now used in radiological diagnosis of all patients, it would be interesting to see if surgical outcome improves during the next decade, along with better accuracy in visualizing tumour position.

The recurrence rate of 11·5% amongst patients with undetectable postoperative cortisol contrasts with studies which have shown that there are no recurrences amongst patients with undetectable postoperative cortisol within a similar follow-up time (McCance *et al.*, 1993; Trainer *et al.*, 1993). There have been other studies using slightly different measures to assess long-term remission. In the Rotterdam study, 14·3% (2/14) of patients with serum cortisol of < 150 nmol/l relapsed after a mean follow-up time of 80 months (van Aken *et al.*, 1997). These figures were higher than a recurrence rate of 4·3% seen amongst patients with postoperative undetectable cortisol levels in the European Cushing's Disease Study (Bochicchio *et al.*, 1995), although details on reference ranges of cortisol levels used in participating centres in the latter study were not provided.

The immediate postoperative remission rate for Cushing's disease was lower than that after treatment of acromegaly and microprolactinoma by the same pituitary surgeon. Considering microadenomas, Cushing's disease patients had an immediate postoperative remission rate of 55/87 (63·2%) which was significantly lower ($P < 0·05$) compared to a rate of 31/34 (91·1%) in acromegaly (Ahmed *et al.*, 1999). This lower rate was found despite more aggressive surgery with higher rates of postoperative hypopituitarism, which suggests that tumours in Cushing's disease may be part of a different and more aggressive disease spectrum.

It has been sugggested that undetectable cortisol levels after surgery are due to inhibition of ACTH secretion from the normal pituitary tissue around an ACTH secreting adenoma as a result of negative feedback from cortisol levels (McCance *et al.*, 1996). This hypothesis does not explain why undetectable cortisol levels were seen amongst our patients who had the potential for tumour regrowth and recurrence. A possible explanation as to why this may occur is that the effect of perioperative steroid cover (despite cessation of steroids for at least 24 h) may still be causing negative feedback. The assays used previously may not be sensitive enough to consider cortisol of < 50 nmol/l as undetectable. It has been shown that there is also variation between different cortisol assays and that this might explain the differences between the series (Clark *et al.*, 1998). Although it is possible that, for example, a cortisol of < 10 nmol/l could provide better prediction of long-term remission than cortisol < 50 nmol/l, there are no data currently available to support this hypothesis.

A trend towards improvement in immediate postoperative remission rates for Cushing's disease after 10 years was seen in this series. Such an improvement was also seen after a similar time with surgery for acromegaly (Ahmed *et al.*, 1999). One reason for this improvement is likely to be increasing surgical experience.

In comparison to bilateral adrenalectomy which has a higher mortality rate of up to 5% and also the risk of Nelson syndrome (Burch, 1985), trans-sphenoidal surgery still remains the first line treatment for Cushing's disease in many centres. Despite various reports and series, recurrence following immediate postoperative remission in Cushing's disease remains difficult to predict with biochemical tests. From this series, we have several conclusions: (i) Despite an aggressive surgical approach, cure rates for Cushing's disease are lower compared to other microadenomas. Recurrence rates are higher and development of new pituitary hormonal deficiency following surgery more frequent than that seen amongst other microadenomas. (ii) Despite strict criteria for immediate postoperative remission and recurrence, an undetectable cortisol level of < 50 nmol/l after surgery is not always predictive of total remission. We emphasize the importance of vigilance in the longer term follow-up of these patients.

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