CLINICAL STUDY

Long-term remission and recurrence rates in Cushing's disease: predictive factors in a single-centre study

Krystallenia I Alexandraki 1, Gregory A Kaltsas 1, Andrea M Isidori 1, Helen L Storr 2, Farhad Afshar 3, Ian Sabin 3, Scott A Akker 1, Shern L Chew 1, William M Drake 1, John P Monson 1, G Michael Besser 1 and Ashley B Grossman 1

Departments of 1 Endocrinology, 2 Paediatric Endocrinology and 3 Neurosurgery, St Bartholomew's Hospital, Barts and the London NHS Trust, Barts and the London School of Medicine, London, UK

(Correspondence should be addressed to A B Grossman who is now at Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, University of Oxford, Oxford OX3 7LE, UK; Email: ashley.grossman@ocdem.ox.ac.uk)

Abstract

Objective: To investigate the early and late outcomes of patients with Cushing's disease (CD) submitted to a neurosurgical procedure as first-line treatment.

Design: In this single-centre retrospective case notes study, 131 patients with CD with a minimum follow-up period of 6 years (124 operated by transsphenoidal surgery (TSS) and seven by the transcranial approach) were studied. Apparent immediate cure: post-operative 0900 h serum cortisol level ! 50 nmol/l; remission: cortisol insufficiency or restoration of 'normal' cortisol levels with resolution of clinical features; and recurrence: dexamethasone resistance and relapse of hypercortisolaemic features.

Results: In patients operated by TSS, remission of hypercortisolaemia was found in 72.8% of 103 microadenomas and 42.9% of 21 macroadenomas, with recurrence rates 22.7 and 33.3% respectively with a 15-year mean follow-up (range, 6–29 years). Of 27 patients with microadenomas operated after 1991, with positive imaging and pathology, 93% obtained remission with 12% recurrence. In multivariate analysis, the time needed to achieve recovery of hypothalamo-pituitary–adrenal axis was the only significant predictor of recurrence; all patients who recurred showed recovery within 3 years from surgery: 31.3% of patients had total hypophysectomy with no recurrence; 42% of patients with selective adenomectomy and 26.5% with hemi–hypophysectomy showed recurrence rates of 31 and 13% respectively (χ² = 6.275, P = 0.03). Strict remission criteria were not superior in terms of the probability of recurrence compared with post-operative normocortisolaemia.

Conclusions: Lifelong follow-up for patients with CD appears essential, particularly for patients who have shown rapid recovery of their axis. The strict criteria previously used for 'apparent cure' do not appear to necessarily predict a lower recurrence rate.

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Introduction

Cushing's disease (CD) is the most common cause of endogenous hypercortisolaemia but still remains a rare disease (1). Its current incidence ranges between 1.2 and 1.8 patients/million per year, but a reported trend to an increase needs to be validated by harder data (2, 3). As untreated hypercortisolaemia is associated with increased mortality and morbidity, the goal of treatment is to normalise cortisol exposure with a reversal of clinical symptoms and signs and thus limiting or abolishing its long-term sequelae (4). As most of the lesions are pituitary microadenomas, surgical removal of the tumour, which targets the source of the disease, is the current first-line therapeutic approach; this may be followed by radiotherapy and/or bilateral adrenalectomy in cases of surgical failure (5). Medical treatment may be required before surgery to treat glucocorticoid (GC) excess.

Transsphenoidal surgery (TSS) remains the procedure of choice with immediate post-operative remission rates ranging between 59 and 94% in major centres (6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21). The reason for this wide range is the variability in defining remission in each study, the inclusion or not of macroadenomas, and the number of the patients studied, rendering the interpretation of results problematic. Few studies have used undetectable or very low post-operative cortisol levels as a strict criterion of remission (10, 22, 23), while most have defined effective remission as the resolution of clinical features and the reversal of hypercortisolism (serum or urinary) along with the recovery of cortisol suppressibility after dexamethasone administration and/or...
a normal cortisol circadian rhythm or exposure to cortisol (24, 25). A number of studies argue against the use of the strictest criterion of remission (7, 12, 18, 26, 27), while other authors prefer the most restrictive criteria of remission, as it is thought that this may reduce the probability of recurrence. Despite these variations in the design of each study, the major limiting factor in published studies, even in those with more than 100 patients with CD, is the short period of follow-up. Thus, data regarding recurrence may underestimate a problem, which may increase over time. Early studies reported relatively low recurrence rates, with the more recent studies suggesting much higher recurrence rates in the long-term, often between 20 and 30% (18, 28). However, even these longer term studies have few patients followed for the longer periods.

On the other hand, it was recently shown that mortality in active CD is much elevated above that of the general population (4, 29), while patients with CD in remission appear to have an increased mortality rate (4, 30). It is therefore vital to determine risk factors associated with recurrence in order to be able to identify it early with an appropriate follow-up and therapeutic protocol, thus minimising or avoiding long-term mortality.

The aim of this study was to evaluate a large number of patients with CD, assessed following a consistent departmental protocol (31), but with long-term follow-up. Furthermore, despite the fact that a number of studies argue against the use of the strictest criterion of remission (7, 12, 19, 21, 32), we have used both strict and less strict criteria of remission to explore whether this would help predict recurrence in the long-term. We particularly concentrated on the early and late outcomes of patients with CD submitted to a TSS as first-line treatment and on the recurrence rates with a minimum follow-up of 6 years, in order to obtain a clearer perspective on recurrence rates.

**Materials and methods**

Patients with a diagnosis of CD followed in the Department of Endocrinology at St Bartholomew’s Hospital between 1969 and 2001, who underwent a TSS (selective adenomectomy or pituitary exploration) as first-line treatment for CD, were subjected to an institutional protocol, i.e. ampicillin and flucloxacillin were routinely administered for 5 days post-operatively and at 6-h intervals thereafter for 24 h. The presence of a suprasellar extension, hydrocortisone was administered for 72 h in order to limit the possibility of oedema in the region of the chiasm and hypothalamus.

**Post-operatively**, serum cortisol was measured daily at 0900 h, fasting, and at least 12 h after the last dose of hydrocortisone. According to our institutional protocol, in cases where serum cortisol remained persistently undetectable (> 50 nmol/l: 1.8 µg/dl), re-exploration of the pituitary fossa in most cases would be performed within 14 days, similar to other institutions (15, 23). Therefore, in order to simplify the presentation if a patient had more than one consecutive operation on the first admission in our department, the outcome of the later operation would determine placement in the remission or failure group with ‘persistent’ disease, as in other published studies (15).

Post-operatively, patients with fasting serum cortisol < 50 nmol/l were commenced on either non-enteric-coated prednisolone 5 mg on waking and 2.5 mg with the evening meal, as described previously (23), or hydrocortisone 20 mg daily in divided doses, and 3 months later, after persistence of adrenal insufficiency, they received hydrocortisone replacement therapy (32). Patients not remitted were considered as the failure group with persistent disease. These patients had elevated (> 300 nmol/l, 5.4 µg/dl) post-operative serum cortisol or were unsuitable for a second operation, or despite a second operation still had elevated serum cortisol along with persistence of clinical features, and they were considered for pituitary radiotherapy. This treatment was administered according to our institutional protocol, usually within 4–6 weeks post-operatively. As radiotherapy can take many years to be effective, when the mean serum cortisol level was much higher than 300 nmol/l (10.8 µg/dl), treatment with metyrapone, ketoconazole and/or mitotane was instituted on a temporary basis, as described previously (35).

During follow-up visits, in certain cases in order to explore the earliest indication of recovery and when morning cortisol was in the range of 150–300 nmol/l (5.4–10.8 µg/dl), a short synacthen test was performed (omitting the hydrocortisone doses the previous evening and the morning of the test) every 3–4 months (32) with a threshold for a ‘normal’ response to synacthen of 550 nmol/l (31). Patients on prednisolone were instructed to omit the dose from the evening before
admission and remain off prednisolone for 3 days thereafter, unless unwell. Serum cortisol was measured at 0900 h daily until prednisolone was recommenced. Furthermore, the mean of five serial serum cortisol measurements (0900, 1200, 1500, 1800 and 2100 h) was calculated for each patient. A mean daily serum cortisol of <150 nmol/l was considered as indicative of a subnormal, and a range of 150–300 nmol/l of a normal cortisol production rate, as both these targets are associated with remission of the clinical features of Cushing’s syndrome (23). Clinical judgement was used at each follow-up visit to evaluate the need to temporarily increase the dose of steroid replacement requirements during illness. When higher cortisol levels were found to confirm remission, a low-dose dexamethasone test (LDDST) was performed, and if serum cortisol at 0900 h was <50 nmol/l at 48 h, the patients were considered to be in remission.

Pituitary function, cortisol secretion and clinical features were reassessed at 6-monthly intervals for 24 months post-operatively, and at least annually thereafter or more frequently, when dictated by abnormal results. Pituitary hypothyroidism was diagnosed on the basis of low serum thyroxine and inappropriately low or normal TSH. Likewise, hypogonadism was diagnosed in the presence of low serum sex steroids and inappropriately low or normal gonadotrophins. Diabetes insipidus was considered when polyuria was present post-surgery along with inappropriate serum and urine osmolalities (31). Data for GH deficiency were carefully recorded at each visit, but routine dynamic testing was only performed in children (36, 37, 38).

For this study, the following demographic data were extracted from the case note records of each patient: gender, age at presentation, years of follow-up, type and number of neurosurgical treatments, pituitary imaging studies at presentation, histopathology results, early outcome (remission and recurrence (for definitions, see below)), rates and time point of recovery of the hypothalamo-pituitary–adrenal (HPA) axis, hormonal deficiencies and surgical complications. The duration of CD before presentation was considered as the period starting from the first CD symptoms and signs that the patients were able to recall before the time of diagnosis. A cohort of these patients was included in a previously published study (34).

The definitions used in this study are as follows:

- Post-operative ‘cure’ was defined as post-operative 0900 h serum cortisol level <50 nmol/l.
- Post-operative ‘remission’ was defined as either a cure or post-operative cortisol insufficiency with the need for GC replacement treatment or normalisation of hypercortisolism. A ‘normal 24-h cortisol production rate’ was regarded when a mean cortisol level of 150–300 nmol/l was obtained during serial serum cortisol measurements throughout the day without the need for treatment and with resolution of clinical features.
- Recurrence: shown by LDDST > 50 nmol/l and the reappearance of hypercortisolaeic features.
- Peri-operative mortality was defined as death occurring during or within 1 month after surgery.
- Adenectomy: hemi–hypophysectomy (including partial hypophysectomy) or total hypophysectomy were characterised as the final procedure performed by the surgeon, as reported in the operation notes. In the first instance, the neurosurgeon attempted to locate and remove the microadenoma, a ‘microadenectomy’. If this was not identified, then based on the results of the Bilateral Inferior Petrosal Sinus Sampling (BIPSS), when available, he performed a hemi- or total hypophysectomy depending on the age and sex of the patient, any preceding discussion with the patient, and whether it was a first or second operation. The rates of the different procedures did not change over time.
- Nelson’s syndrome was defined as increased pigmentation associated with rising levels of plasma ACTH (>1000 ng/l) with or without evidence of an enlarging pituitary tumour, as described previously (39, 40).
- Cyclic disease was defined as the presence of at least one cycle (clinical/biochemical hypercortisolaeemia followed by remission and then by a new hypercortisolaeic state) or of variability of cortisol levels characterised by a doubling or halving in the absence of therapy or without a change in therapy (34).
- Positive histology was defined as positive identification of a corticotroph tumour. The pathologists used immunostaining for ACTH on the adenomatous tissue to define an ACTH-secreting pituitary adenoma, and this defines tumour presence. The description of hyperplastic tissue and/or Crooke’s hyalinization alone did not define a positive analysis.
- ‘Positive imaging’ was defined as the presence or suspicion of an adenoma, as reported by a specialist radiologist.

Finally, in order to evaluate changes over time, an arbitrary division of cases operated before vs cases operated after 1991 were studied, allowing 10 years of data analysis; in particular, magnetic resonance imaging (MRI) was only performed routinely after this date.

In the context of data analysis, the following subgroups were studied: the cohort as a whole group included patients operated by either TSS or craniotomy, patients operated by TSS were further analysed in the following subgroups: patients with microadenomas vs macroadenomas, the patients with re-operations, patients operated before 1991 vs the patients operated from 1991 onwards, patients with positive vs patients with negative histology, patients with positive vs patients with negative imaging and patients with microadenomas operated from 1991 onwards (including further sub-categorisation of patients with
positive pathology and imaging). Cure data were only used to calculate differences regarding the recurrence of CD among patients who obtained a cure compared with those who only showed remission.

**Statistical analysis**

Statistical significance in the results was accepted at a *P* value < 0.05. Values are presented as mean values ± S.D. when normally distributed or the median value and range when not normally distributed. The normal distribution of continuous variables was assessed by applying the non-parametric Kolmogorov–Smirnov test. Quantitative data were compared using independent samples t-test or Mann–Whitney *U* test for normally or non-normally distributed variables respectively. Qualitative data were compared using a χ² analysis or by Fisher’s exact test, as appropriate. A Kaplan–Meier analysis was performed to investigate differences regarding the recurrence of CD among patients who obtained cure vs remission. Analysis was performed using SPSS (version 18.0; PASW SPSS, Inc.) for Windows XP (Microsoft Corp.). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value for the use of the recovery period to detect recurrence were calculated using the appropriate formulae.

**Results**

The mean age at diagnosis of 131 patients (102 females, 77.9%) studied was 39.2 ± 15.2 years, range: 7–95 years; 12 (9.2%) patients were < 18 years old. The patients were followed for a mean period of 15.9 ± 6 years (range, 6–37 years) after initial diagnosis and for a mean period of 15.4 ± 5.8 years (range, 6–36 years) after their operation.

The median duration of CD before diagnosis was 3 years (range, 0–30 years). Four patients who died within the 6 first follow-up years were not included in the calculations of the follow-up period: one patient died 3 months postoperatively due to an acute myocardial infarction (TSS surgery), two at 3 years (one from a cerebrovascular event (TSS surgery) and the other had a cardiac arrest during a debulking procedure of her aggressive pituitary tumour), while a fourth died at 4 years (unknown cause, although this occurred 3 weeks after she was admitted for hypoadrenalism and temporal lobe epilepsy).

With regard to the type of surgery, of the 103 microadenomas, all were operated transsphenoidally except for one operation where only a biopsy was taken. Of the macroadenomas, 21 were operated transsphenoidally and seven by craniotomy (six performed before 1991 and one since then). The remission and recurrence rates along with the imaging and histopathological findings for the total population, and for the various subgroups studied, are given in Tables 1 and 2. Overall, remission was seen in 68% with 24% recurrence in patients operated by TSS, while these figures were 73 and 23% respectively for microadenomas and 43 and 33% respectively for macroadenomas. Increased figures of remission were seen in more recently operated patients (Tables 1 and 2). Among patients operated by TSS, ‘cure’ was seen in 45% with a recurrence rate of 15%, in microadenomas the rates were 49 and 17% respectively, while in macroadenomas they were 25 and 0% respectively. When only patients with microadenomas and positive histology and imaging were considered, the ‘cure’ rate rose to 70% and recurrence rate fell to 10.5%. The differences in outcome among patients submitted to adenomectomy, hemi-hypophysectomy or total hypophysectomy are given in Table 3, with remission rates of 74, 68 and 58% respectively and recurrence rates of 31, 13 and 0% respectively. The risk factors predicting the outcome of the surgery are shown in Table 4. The factors predicting recurrence are shown in Table 4. All patients who subsequently recurred showed recovery of their axis within 3 years. Recovery within 6 months, 1 year and 2 years had PPV of recurrence of 64, 61 and 59% respectively (Table 5).

It is of interest that the probability of recurrence was less in patients remitted by the strict criteria compared with those who obtained remission using more lax criteria, although this failed to achieve statistical significance (Fig. 1 and supplementary tables, see section on supplementary data given at the end of this article).

From the rest of the data, it was revealed that six (4.8% of the whole cohort or 5.8% excluding the macroadenomas) patients had a partially empty sella, and three of them had positive imaging studies indicative of a tumour. Details on further management of patients with surgical failure or recurrence as well as the surgical complications are reported on the supplementary tables.

**Discussion**

This study was designed to investigate recurrence rates and potential contributing factors to recurrence in a large cohort of patients with CD treated in a single-centre and with prolonged follow-up in terms of a minimum follow-up of 6 years. We report that recurrence may occur even 15 years or more after an apparent cure and that the recurrence rates appear to relate to recovery of the endogenous HPA axis, as it was not seen in any patient in which HPA axis recovery occurred 3 years or more after the operation. We also confirm previous findings that the presence of a microadenoma in the histology specimen is a favourable factor for a good outcome. One important finding reinforces previous observations that recurrence is found not only in patients in whom less strict criteria were used to define a favourable surgical outcome but was also seen in apparently ‘remitted’ patients using strict criteria such as an undetectable or very
Table 1 Remission and recurrence rates, imaging and pathology findings in the total group and in the various subgroups studied.

<table>
<thead>
<tr>
<th>Subgroups studied (n, macroadenomas if applicable)</th>
<th>Remission (%)</th>
<th>Pathology (ve)</th>
<th>MRI (ve)</th>
<th>Recovery axis</th>
<th>Time of recovery (median range months)</th>
<th>Time of recurrence (years)</th>
<th>Adenomectomy/hemi-hypophysectomy/total hypophysectomy (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total group (131; 28)</td>
<td>86/131 (65.6; 24.4)</td>
<td>81/123 (65.9)</td>
<td>55/64 (85.9)</td>
<td>49/81 (60.5)</td>
<td>18 (1-240, 42)</td>
<td>63.1 ± 54.4</td>
<td>13.5; 2; 1</td>
</tr>
<tr>
<td>Operated by craniotomy (7; 7)</td>
<td>27 (28.6; 50)</td>
<td>7/7 (100)</td>
<td>1/1 (100)</td>
<td>1/2 (50)</td>
<td>12</td>
<td></td>
<td>0; 0; 0</td>
</tr>
<tr>
<td>TSS operation</td>
<td>84/124 (67.7; 23.8)</td>
<td>71/116 (60.8)</td>
<td>41/50 (82)</td>
<td>30/40 (75)</td>
<td>15 (1-243)</td>
<td>61.7 ± 54.4</td>
<td>15; 2; 1</td>
</tr>
<tr>
<td>Operated by TSS (120; 21)</td>
<td>75/103 (72.6; 27.4)</td>
<td>64/75 (85.3)</td>
<td>22/30 (73.3)</td>
<td>17/22 (77.3)</td>
<td>12 (1-240)</td>
<td>78.6 ± 54.4</td>
<td>6; 2; 1</td>
</tr>
<tr>
<td>Microadenomas (TSS: 103; 0)</td>
<td>92/114 (81.6; 18.4)</td>
<td>76/86 (87.6)</td>
<td>13/13 (100)</td>
<td>8/9 (88.9)</td>
<td>15 (1-243)</td>
<td>61.7 ± 54.4</td>
<td>15; 2; 1</td>
</tr>
<tr>
<td>Operation before 1991 (51; 4)</td>
<td>31/41 (76.8; 23.2)</td>
<td>29/36 (80.5)</td>
<td>9/9 (100)</td>
<td>8/9 (88.9)</td>
<td>15 (1-243)</td>
<td>61.7 ± 54.4</td>
<td>15; 2; 1</td>
</tr>
<tr>
<td>Operation from 1991 (73; 15)</td>
<td>57/74 (77.0; 23.0)</td>
<td>47/54 (87)</td>
<td>12/12 (100)</td>
<td>10/11 (90.9)</td>
<td>15 (1-243)</td>
<td>61.7 ± 54.4</td>
<td>15; 2; 1</td>
</tr>
<tr>
<td>Positive histology (42; 2)</td>
<td>22/24 (91.7; 8.3)</td>
<td>19/21 (90.5)</td>
<td>13/13 (100)</td>
<td>8/9 (88.9)</td>
<td>15 (1-243)</td>
<td>61.7 ± 54.4</td>
<td>15; 2; 1</td>
</tr>
<tr>
<td>Negative histology (42; 2)</td>
<td>65/95 (68.4; 21.6)</td>
<td>60/91 (65.9)</td>
<td>55/55 (100)</td>
<td>37/37 (100)</td>
<td>15 (1-243)</td>
<td>61.7 ± 54.4</td>
<td>15; 2; 1</td>
</tr>
<tr>
<td>Positive imaging (55; 21)</td>
<td>14/22 (63.6; 21.4)</td>
<td>11/22 (50)</td>
<td>0/9 (0)</td>
<td>8/9 (88.9)</td>
<td>15 (1-243)</td>
<td>61.7 ± 54.4</td>
<td>15; 2; 1</td>
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<tr>
<td>Negative imaging (22; 0)</td>
<td>10/19 (52.6; 37.4)</td>
<td>9/19 (47.4)</td>
<td>8/9 (88.9)</td>
<td>5/5 (100)</td>
<td>15 (1-243)</td>
<td>61.7 ± 54.4</td>
<td>15; 2; 1</td>
</tr>
<tr>
<td>Cyclic (TSS: 19; 2)</td>
<td>74/105 (70.5; 21.6)</td>
<td>65/97 (67)</td>
<td>50/50 (100)</td>
<td>37/37 (100)</td>
<td>15 (1-243)</td>
<td>61.7 ± 54.4</td>
<td>15; 2; 1</td>
</tr>
<tr>
<td>Negative imaging (22; 0)</td>
<td>11/22 (50; 45)</td>
<td>10/20 (50)</td>
<td>8/10 (80)</td>
<td>2/2 (100)</td>
<td>15 (1-243)</td>
<td>61.7 ± 54.4</td>
<td>15; 2; 1</td>
</tr>
<tr>
<td>Barts patients (91; 17)</td>
<td>58/91 (63.7; 10.3)</td>
<td>54/87 (61.2)</td>
<td>45/53 (84.9)</td>
<td>33/38 (86.8)</td>
<td>15 (1-243)</td>
<td>61.7 ± 54.4</td>
<td>15; 2; 1</td>
</tr>
</tbody>
</table>

NA, not applicable; ND, not done; TSS, transphenoidal surgery. P = 0.05; ± s.o. for parameters with normal distribution tested by one-sample Kolmogorov test; median value (range) for parameters without normal distribution.

*P < 0.05 vs microadenoma. **P < 0.05 vs operation before 1991. *P < 0.05 vs positive histology. Trend difference vs positive histology. *P < 0.05 vs Positive imaging. Trend difference vs cyclic CD.

The overall remission of 68% for the cohort operated by TSS falls within the lower range of those recently reported (8, 10, 12, 14, 15, 16, 18, 19, 21). Previous authors have also reported the lower remission rates we found with negative histology (15, 20, 21). However, this rate increases to 75% if we consider microadenomas alone, achieved in 1991 onwards; a further increase in remission rates with positive imaging and pathology findings is seen in our study (45). Regrettably, these are not especially surprising, as these are low post-operative morning cortisol levels. In addition, an important finding of this study is that 15% of patients were apparently cured, with a post-operative normal morning cortisol level. In addition, a substantial number of the former group of patients did not recur even with this prolonged follow-up.

It is of interest that despite the lower remission rate of patients with negative histology, the remission rate of patients with adenomas with positive imaging and pathology findings was low as opposed to previous studies (12, 20, 21). However, no difference was found in our study. A trend difference was noted in the presence of micro-adenomas with positive imaging and pathology findings, achieving a remission rate of 93% (Table 1). Regrettably, these are not especially surprising, as these are low post-operative morning cortisol levels. In addition, a substantial number of the former group of patients did not recur even with this prolonged follow-up.

An important finding of this study is that 15% of patients were apparently cured, with a post-operative normal morning cortisol level. In addition, a substantial number of the former group of patients did not recur even with this prolonged follow-up.
serum cortisol of <50 nmol/l, demonstrated recurrence on prolonged follow-up (Fig. 1). Although lower rates of recurrence have been reported in ‘cured’ compared with remitted patients, this does not seem to hold true in all series (7, 26, 27). It appears that a post-operative cortisol level <50 nmol/l might be a very stringent criterion, as many patients with remission defined as normal values of cortisol post-operatively, as well as the need for GC replacement therapy, also demonstrated long-standing remission. This threshold has been extensively discussed in previous studies (10, 22, 23). In most assays over the past years, the figure of 50 nmol/l has been taken as the limit of detection of the cortisol assay, although very recent assays have shown improved sensitivity. This limit is thus defined as ‘undetectable’ in our series; it is speculated that if there is a corticotroph tumour causing CD, then the normal surrounding corticotrophs are suppressed, and removal of the tumour should result in a complete absence of ACTH and hence an acute absence of cortisol secretion. Any figure above 50 nmol/l would imply residual tumour. However, contrary to our expectation, many patients with post-operative cortisol levels >50 nmol/l showed long-term remission. The role of the peri-operative administration of dexamethasone or hydrocortisone has been unexplored but may be a factor in masking residual disease (26). Another explanation for the detectable post-operative cortisol levels may be the mild hypercortisolism, as is the case of cyclic CD where the normal surrounding corticotrophs cannot be completely suppressed. Indeed, we noted only a 10.5% rate of apparent ‘cure’ in this group compared with 49.5% of patients without cyclicity. On the other hand, despite the small number studied with regard to this rare disease, it is of interest that we report a ‘zero’ rate of recurrence in apparently cured patients with negative histology, re-operation and macroadenomas (supplemental file). This may imply a selective utility of this criterion to predict a long remission in specific groups only. Overall, comparing the favourable outcome of patients treated by TSS following lax or strict criteria of remission, it is of note that the latter group presented lower recurrence rates than the former, although this did not achieve the statistical significant difference that may allow the former group of patients to be considered as high risk for recurrence. Furthermore, this finding does not support the hypothesis that only patients with very low post-operative cortisol levels can be considered as ‘remitted’.

Moreover, the time to recovery of the HPA axis was the most useful in predicting recurrence, although its impact is less when other parameters are taken into consideration (Table 4). If recovery of the HPA axis occurred within 2 years, recurrence was seen in more than half of the patients (Table 5). Conversely, a failure of recovery within 3 years strongly indicated that recurrence was unlikely. Previous studies have shown patients able to be weaned off replacement within 6 months always recurred (10, 53).
It is possible that some apparent failures are due to misdiagnosis and that the underlying true diagnosis was the ectopic ACTH syndrome (55). However, all patients have been under continuous follow-up, and we believe it is highly unlikely that this could account for a very small minority of patients, if any.

Our study does have some limitations. The retrospective design of this study and the fact that the total population was referred by a number of different centres are clearly not ideal; however, the cohort is large with regard to long-term follow-up, homogeneous with no other therapies such as radiotherapy before surgical treatment, as used in previous studies (12, 53), and the mean duration of follow-up is much longer than in almost all previous studies. We have calculated remission after the outcome of the second surgery as we focused on the long-term outcome of this subgroup of patients (56, 57, 58). The problems of repeat surgery problems have been previously reported in well-designed studies. However, repeat surgery was included in our specific departmental protocol despite the fact that some deviations are inevitable as some therapies may be delayed for social or medical reasons. Nevertheless, awaiting a delayed response over 4–6 weeks has been considered inappropriate, as most surgeons feel that re-operation should be performed within 2 weeks, and the possibility of a delayed response, while theoretically of interest, occurs in only a small minority of patients (20). Despite the fact that the repeat surgery resulted in total hypophysectomy in nine patients, hemi–hypophysectomy in five and adenomectomy in four, only 50% remitted; however, of these only one (with adenomectomy) recurred, while negative pathology was still present even after the second operation, (data not shown) as previously noted (6, 56, 57, 59). Furthermore, our data regarding the patients submitted to a unique operation are also included. Regarding the extension of surgery and the impact of this extension depending on year of TSS performance, in Table 1, it can be seen that no difference was seen in the type of operation between both subgroups treated before and from 1991 onward. Certainly, as a major referral centre, we expect that our results are biased

Table 4 Factors associated with a positive surgical outcome and with recurrence in univariate and multivariate logistic regression analysis in the population operated by transsphenoidal surgery.

<table>
<thead>
<tr>
<th>Factors associated with a positive surgical outcome</th>
<th>Univariate logistic regression analysis</th>
<th>Multivariate logistic regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Macroadenoma presence</td>
<td>0.28 (0.106–0.7379)</td>
<td>0.01</td>
</tr>
<tr>
<td>Gender</td>
<td>2.692 (1.132–6.406)</td>
<td>0.025</td>
</tr>
<tr>
<td>Positive histology</td>
<td>3.048 (1.353–6.869)</td>
<td>0.007</td>
</tr>
<tr>
<td>Extension of surgery</td>
<td>0.214 (0.053–0.855)</td>
<td>0.029</td>
</tr>
<tr>
<td>Time of recovery HPA axis</td>
<td>0.926 (0.872–0.982)</td>
<td>0.011</td>
</tr>
<tr>
<td>Positive histology</td>
<td>4.25 (0.893–20.233)</td>
<td>0.069</td>
</tr>
</tbody>
</table>

aYes, 1 and no, 0.
bFemale, 1 and male, 0.
c1, Adenomectomy; 2, hemi–hypophysectomy and 3, total hypophysectomy.
in terms of referral of the more complex patients lacking clear tumour imaging resulting in a more aggressive operation. It is important to take into consideration the complexity of factors that determine the post-operative serum cortisol levels and thus the limitations of this single measure of success in these cases. The completeness of tumour removal as shown pathologically, the assessment of prior medical therapy with the possibility of partial restoration of HPA axis suppression and the degree of secondary or tertiary adrenal hyperplasia (which may be associated with measurable serum cortisol despite complete tumour removal) are factors that have to be evaluated when an assessment of ‘remission’ is attempted (32). Finally, assay methods of cortisol used during all the years of this study should be different in particular compared with currently used assays but the information from such a long-term follow-up outweighs this possible limitation.

**Conclusions**

In this study, we confirm that the risk of relapse in patients with CD persists for more than 10 years after surgery, up to 29 years, particularly in those who obtained rapid recovery of their HPA axis post-operatively. Thus, any attempt to assess recurrence rates after surgical success in CD needs to consider an extended duration of follow-up. Previously used strict criteria to define ‘apparent cure’ do not appear to predict a lower recurrence rate compared with achievement of eucortisolaemia. Physicians should be aware that late recurrence can occur, even in patients defined as in remission using the strictest criteria, lifelong follow-up for these patients is warranted.

**Supplementary data**

This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-12-0921.

**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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