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Aken, M.O. van

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Chapter 9

Long-term Predictive Value of Postsurgical Cortisol Concentrations for Cure and Risk of Recurrence in Cushing's Disease

Alberto M. Pereira¹, Maarten O. van Aken¹, Hans van Dulken², Pieter J. Schutte², Nienke R. Biermasz¹, Jan W.A. Smit¹, Ferdinand Roelfsema¹ and Johannes A. Romijn¹

Department of Endocrinology & Metabolism¹ and Department of Neurosurgery², Leiden University Medical Center, Leiden, The Netherlands

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ABSTRACT

We assessed the value of postoperative plasma cortisol concentrations to predict cure and recurrence of Cushing's disease (CD) after transsphenoidal surgery (TS). Seventy-eight out of 80 consecutive patients treated by TS for CD were evaluated. TS cured 72% of the patients. Two weeks after surgery, patients with plasma cortisol levels below 138 nmol/L (n=50, 3 macroadenomas) and 8 (27%) out of 30 patients (9 macroadenomas) with cortisol > 138 nmol/L were cured. Six (5 with a macroadenoma) of these eight patients had cortisol values below 50 nmol/L, 3 months after surgery. Therefore, the optimal cut-off value of cortisol predicting remission was 138 nmol/L, measured 3 months after surgery (positive and negative predictive values 87 and 90 %, respectively). Five patients (9 %) had recurrent CD during a median follow-up of 7 years. Recurrence occurred in 4 of 24 (17%) patients with a follow-up of > 10 years. Therefore, cortisol levels above 138 nmol/L, obtained two weeks after TS, should be repeated, since they do not predict persistent CD in 27% of those patients. Postoperative cortisol levels do not positively predict recurrence of disease during long- term follow up of initially cured patients.

INTRODUCTION

Transsphenoidal microsurgery (TS) is the treatment of choice in patients with Cushing's disease (1). Although TS allows cure of the disease, the reported success rates vary from 50 to almost 90% (2-6). The skill and experience of the neurosurgeon is a very important factor determining this outcome of TS (7). Additional factors determining the high variability in success rate are differences in criteria used to define remission and differences in duration of follow up, which may result in a low rate of late relapses during short-term follow up. In recent years, several centres for pituitary diseases published their results of TS performed by a single surgeon (8-11) or by different neurosurgeons (12) (Table 1). Because they used more or less similar criteria for remission, the variability in long-term success rates decreased substantially, resulting in remission rates ranging from 60 - 75%. However, low post-surgical cortisol levels even when defined according to the most stringent criteria, like postoperative serum cortisol levels below 50 nmol/L or adequate suppression on low-dose dexamethasone testing, failed to predict long-term recurrence in 11 to 15% of patients (9, 11). Conversely, a remarkable phenomenon has been observed in two patients who were cured by TS, but in whom unsuppressed postoperative cortisol levels in subsequent weeks decreased to 200 nmol/L in one, and even to undetectable levels in the other patient (13). At the Leiden University Medical Center, TS for Cushing's disease is performed by a single neurosurgeon (HvD) since 1978. We audited our data retrospectively and report the outcome of TS in 80 consecutive patients with Cushing's disease, performed between 1978-2002. We focussed on the predictive value of post-operative cortisol levels for cure as well as recurrence. A subgroup of 24 patients, cured by the initial operation and with postoperative follow-up of more than 10 years was analyzed separately. In addition, we investigated the predictive value of other parameters like tumor size.

PATIENTS AND METHODS

Patients and operations: (figure 1)

We evaluated 81 consecutive patients who underwent TS for Cushing's disease between 1978 and 2002, 72 patients as primary treatment and 9 secondary to failure of earlier instituted therapy (unilateral adrenalectomy followed by pituitary irradiation). Eight of 81 patients were operated by TS twice and one patient three times, but in our analysis we focussed on the first operation, unless stated otherwise. One patient died three days after the operation due to cardiorespiratory failure, leaving 80 patients for the first postoperative evaluation. The immediate postoperative follow-up could not be extended because of insufficient data in one patient and because of acute cardiac death after three months in another. Postoperative cortisol values in these patients were 70 and below 50 nmol/L,

Table 1: Single center, single surgeon series: the effect of definition of postoperative cure on longterm remission and recurrence rates

	Number of patients	Follow up (months) median (range)	Postop cortisol measurement	Criteria for cure	Postoperative cure	Long-term remission	recurrence during prolonged follow up
Sonino et al (1996) (Padova)	103	72 (24 – 192)	5-15 days	24 h UFC < 248 nmol normal low dose dex test	77%	58%	24%
Yap et al (2002) (Oxford)	89	38 (6 - 348)	3-4 days 3 and 6 months	cortisol 9.00 am: < 50 nmol/L	68.5%	61 %	11.5%
Chee, et al (2001) (Newcastle)	61	88	2,6 weeks 1 year	cortisol 9.00 am and midnight: within reference range	79%, median 9 am cortisol: 162.5 nmol/L (at 2w) 221 nmol/L (at 6w)	67 %	12.5%
Rees, et al (2002) (Cardiff)	54	72 (6 - 252)	< 1week	cortisol 9.00 am: < 50 nmol/L if not: further definite therapy	77%	74%	5%
Estrada, et al (2001)* (Madrid)	58	mean 68 (6 - 198)	8-12 days postop, every 3 to 6 months	cortisol 9.00 am: < 60.7 +/- 38.6 nmol/L, if also *normal circadian rhythm + normal response to ITT	71% 57%*	72%	not reported
present series (Leiden)	80	86 (12 - 288)	2,6,12 weeks, 6 months annually thereafter	cortisol 9.00 am: < 50 nmol/L <138 nmol/L	48% (2w) 55% (12w) 69% (<138 nmol/L)	65 %	9% (7 yrs) 17% (14.5 yrs)

* part of a larger series of 109 patients of whom 34 had persistent hypercortisolism. Of the remaining 75, 58 patients were selected for an extensive postoperative evaluation, ref 14

respectively. We therefore present the outcome of 78 patients, which could be evaluated with a follow-up of 12 months to 24 years. Informed consent was obtained from all these patients. The mean age of the patients was 37 years (range 12-81 years) and 80% were female patients. Thirty-two patients with a follow-up duration of more than 10 years after surgery were analyzed separately. The mean age of these patients was 38 years (range 19-68 years) and 81% were female.

Evaluation

The diagnosis of Cushing's disease was made on clinical grounds together with biochemical confirmation of Cushing's disease, based on the following tests: increased 24 h urinary free cortisol excretion (24 h UFC, criterion > 220 nmol), failure of serum cortisol to suppress following low-dose dexamethasone (one evening dose of 1 mg or 2 mg/day for 48 h), suppression of serum cortisol during a 7 h intravenous dexamethasone suppression test as described by Biemond et al (14), and an exaggerated or normal response of serum cortisol and ACTH on intravenous CRH stimulation (15). Pituitary imaging by CT or MRI with intravenous contrast was performed in all patients. In those patients in whom the radiological findings with respect to the visualisation of a pituitary adenoma were inconclusive, bilateral, simultaneous sampling of the inferior petrosal sinuses (IPSS) was performed (23 patients, 28% of cases).

Treatment

Presurgical treatment with cortisol lowering agents, metyrapone or ketoconazole, was given to 40 patients.

At the day of surgery dexamethasone was started (1 mg every six hours). From the first postoperative day dexamethasone was gradually decreased from 1 mg every twelve hours to 0.5 mg per day on the fifth postoperative day. A hydrocortisone substitution dose (30 mg, in recent years 20 mg per day divided in two doses) was given from the sixth postoperative day until the day prior to endocrinological evaluation. The interval between the last dose of dexamethasone and the first measurement of fasting plasma cortisol was at least 120 hours.

Follow-up

The first postoperative assessment of cortisol and ACTH secretion was performed at 0900 h. in the second postoperative week, 24 hours after the last dose of hydrocortisone. Dynamic stimulation tests were performed with an i.v. bolus of insulin (0.1 IU/kg body weight) or with 10 IU lysin-vasopressin i.m., and since 1983 with an i.v. bolus of CRH (100 µg hCRH). Serum cortisol concentrations (and since 1986 also plasma ACTH) were measured in all tests at baseline, and every fifteen minutes thereafter for 90 minutes.

Patients with basal serum cortisol concentrations < 138 nmol/L and insufficient reaction after stimulation with CRH, ITT or lysin/vasopressin were considered hydrocortisone dependent. These patients were re-evaluated after 6 months by

measurement of fasting morning serum cortisol concentrations after hydrocortisone withdrawal of 24 h. Patients with serum cortisol concentrations > 138 nmol/L and a peak cortisol of > 550 nmol/L after stimulation were considered to be hydrocortisone independent. Patients with basal serum cortisol concentrations > 138 nmol/L were re-evaluated with fasting morning cortisol measurements every two to four weeks within the first three months, 6 months after surgery, and annually thereafter. From the six months after the operation onwards, the biochemical evaluation for all the hydrocortisone independent patients included an annual evaluation with a low dose dexamethasone suppression test as well as two 24 h UFC measurements.

Criteria for cure and relapse

Clinical cure was defined six months after surgery by dependency on hydrocortisone substitution according to the above mentioned criteria, or by hydrocortisone independency without any biochemical signs of hypercortisolism and regression of the clinical signs.

Biochemical cure was defined as normal suppression to 1 mg oral dexamethasone (cortisol < 100 nmol/L the following morning) and normal 24 h UFC excretion on two consecutive samples. Persistent Cushing's disease was defined as failure to fulfil clinical and biochemical criteria for remission after the first operation and before a second intervention.

Relapse was defined as the recurrence of hypercortisolism, reflected in insufficient suppression of plasma cortisol to 1 mg oral dexamethasone (cortisol > 100 nmol/L the following morning) on more than one occasion and/or abnormal 24 h UFC excretion on two consecutive samples, and re-occurrence of clinical signs.

Assays

Cortisol was measured with three different immuno assays over time. Between 1978 and 1986 cortisol was measured by in house RIA with an interassay coefficient of variation of 10% and with a detection limit of 50 nmol/L). Between 1986 and 1994 a fluorescence energy-transfer immunoassay Syva-Advance (Syva Company, Palo Alto, CA) was used, with an interassay variation coefficient of 3.6-6.1% and a detection limit of 50 nmol/L. From 1994 cortisol was measured by fluorescence-

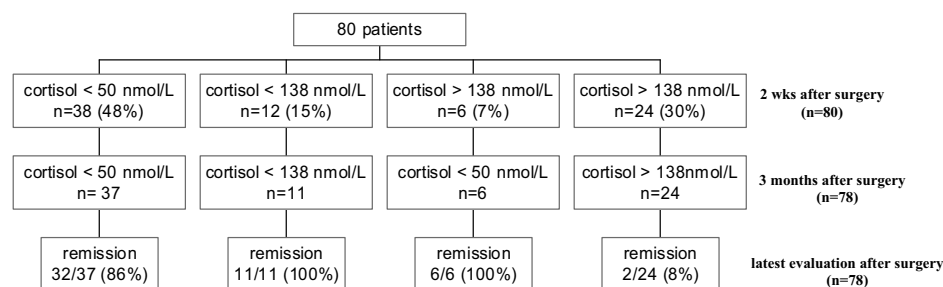


Figure 1: Biochemical and clinical outcome of Transsphenoidal Surgery (TS)

polarisation assay on a TDx (Abbott, Abbott Park, Ill). The interassay variation coefficient is 5-6% above 500 nmol/l and amounts to 12% under 200 nmol/L. The detection limit is 20 nmol/L. The methods correlated well with each other, and therefore no correction factors were introduced for follow-up of patients.

ACTH was measured since 1986 (n= 60 patients), using an immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA) with a detection limit of 3 ng/L. The intra- and interassay average variations ranged from 2.8–7.5% across the sample range observed.

Statistics

Differences between groups were analyzed using the two tailed Student's t test for unpaired samples, using SPSS for Windows software version 10.0. Receiver operating characteristic (ROC) curves were constructed to describe the relationship between sensitivity and specificity at various cut off levels, using all postoperative cortisol values measured 2 and 12 weeks after surgery, respectively. The cut off value between 50 to 200 nmol/L was increased, in steps of 2 nmol/L, to determine the optimal combination of sensitivity and specificity. Uni- and multivariate logistic regression analyses were performed to determine possible independent predictors of remission like adenoma size, preoperative cortisol concentration, pre-treatment with cortisol lowering agents, and postsurgical ACTH concentration. $P < 0.05$ was considered significant.

RESULTS

Cure of Cushing's disease

TS cured Cushing's disease in 56 of the initial 78 patients (72 %), at the evaluation at 6 months postoperatively.

Serum cortisol concentrations (figures 1 and 2)

Two weeks postoperatively (n=78), 37/78 (47%) of the patients had fasting plasma cortisol concentrations below 50 nmol/L (two macroadenomas), and 11 patients (14 %) had plasma cortisol concentrations between 50 and 138 nmol/L (one macroadenoma). All these patients appeared later to be cured of Cushing's disease. In the two weeks postoperatively, a plasma cortisol level < 50 nmol/L identified 66 % of the cured patients (37 out of 56 patients), and a plasma cortisol concentration < 138 nmol/L identified 86 % of the cured patients. The remainder of the patients (n = 30, 38%) had plasma cortisol concentrations > 138 nmol/L (nine macroadenomas), of whom 8 appeared to be cured of Cushing's disease during long-term follow-up. Thus, with regard to the effect of adenoma size on postoperative cortisol concentrations, 5/8 (63%) cured macroadenomas had postoperative cortisol values at two weeks above 138 nmol/L (mean 301 ± 95 nmol/L) vs. only 2/48 (4%) of cured microadenomas (mean 61 ± 9 nmol/L)($P < 0.05$).

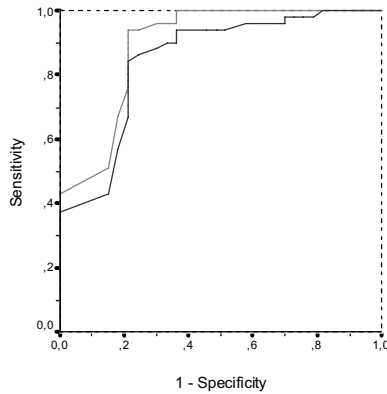


Figure 2: Receiver-operating-characteristic curves of postsurgical cortisol concentrations at 2 weeks (in blue) and 3 months (in red) after surgery. Area under the receiver-operating-characteristic curves: at two weeks: 0.846 (95% confidence interval 0.76-0.93) at 3 months: 0.892 (95% confidence interval 0.82-0.97). Optimal cut-off value: 138 nmol/L, 3 months after surgery; sensitivity 94%, specificity 79%, positive predictive value, 87% negative predictive value 90%.

Plasma ACTH concentrations

Two weeks postoperatively ACTH values ranged from < 3 to 226 ng/L (mean $\pm$ SEM: 29.1 ± 5.4 ng/L). The ACTH values of the patients who were in remission were significantly lower than those of the failures (16 ± 3 vs 61 ± 15 ng/L, $P < 0.001$).

Three months after the operation, 6 of the 30 patients with initial cortisol concentrations above 138 nmol/L had cortisol concentrations < 50 nmol/L. In these 6 patients initial fasting cortisol levels were 407 ± 95 nmol/L (mean $\pm$ SEM), but post absorptive cortisol levels decreased, reaching a nadir below 50 nmol/L, six to twelve weeks after surgery. Remarkably, five of these 6 patients had macroadenomas, whereas one patient had an adenoma of 9 mm. (see Table 2). The remaining 24 patients (31 % of all assessable patients) had persistent cortisol concentrations > 138 nmol/L. Four of these patients had macroadenomas. During prolonged follow-up, two of these 24 patients did not develop any clinical or biochemical sign of Cushing's disease during a follow-up of 2 and 12 years, respectively. The other 22 patients had both clinical and biochemical signs of persisting Cushing's disease. The diagnosis of Cushing's disease in these 22 patients was established by positive ACTH immunostaining in 17 patients, by positive IPSS in one patient, and by documented remission of disease after pituitary irradiation in the remaining four patients.

Thus, a serum cortisol < 50 nmol/L determined three months after surgery, identified 77 % of the cured patients (43 out of 56 cured patients). Serum cortisol levels < 138 nmol/L determined three months after surgery, identified 96 % of the cured patients (54 out of 56 cured patients). Postoperative cure rate, defined by the disappearance of clinical and biochemical signs of Cushing's disease at 6 months after surgery, irrespective of postoperative cortisol levels, was 72 % (56 out of 78 assessable patients). In contrast to the results obtained 2 weeks after surgery, there was no difference in cortisol values between cured macro- and microadenomas 3 months after surgery. This is explained by the remarkable pattern of postoperative cortisol concentrations in six of the patients, of whom 5 had macroadenomas.

Sensitivity, specificity, positive predictive values and negative predictive values

Table 2: Characteristics of patients with postoperative cortisol levels > 138 nmol/L after 2 weeks, but cortisol levels < 50 nmol/L after 3 months: (n=6)

Patient	Tumor size (Hardy-Wilson)	Previous therapy	Preop. cortisol (nmol/L)	Postop cortisol (nmol/L) (2 wks)	Postop cortisol (nadir)	Postop CRH test: cortisol (nmol/L) (basal-max level)	Postop CRH test: ACTH (ng/L) (basal-max level)	Outcome	Follow-up (yrs)
1	IV-B-E	None	710	440	<50 (6wks)	220 - 460	23 - 84	remission	2
2	IV-B	None	1170	760	<50 (6 wks)	370 - 820	18- 272	remission	8
3	II -0 (12 mm)	Ketoconazole	670	200	<50 (12 wks)	200 - 500	25 - 43	remission	7
4	III-A	Ketoconazole	590	570	<50 (6 wks)	570 - 920	4 - 14	remission	2.5
5	II-A	Ketoconazole	1000	320	<50 (6 wks)	320 - 870	10 - 36	remission	1
6	I (9 mm)	None	1040	150	<50 (8 wks)	150 - 200	26 - 100	remission	4

Prediction of cure and recurrence in Cushing's disease

for cure of cortisol concentrations of 50 nmol/L and 138 nmol/L at 2 weeks and 3 months after surgery, are given in Table 3. The ROC curves and the area under the ROC curves (AUC) are shown in Figure 2. The AUC for cut off values at two weeks was 0.846 (95% confidence interval 0.76-0.93) and 0.892 (95% confidence interval 0.82-0.97) for cut off values at 3 months. The optimal cut-off value to detect and predict remission was 138 nmol/L, 3 months after surgery, with a sensitivity of 94% and a specificity of 79%. The positive predictive value was 87% and the negative predictive value 90%.

Table 3: Sensitivity, specificity, and predictive values of postoperative cortisol concentrations to predict cure

Cortisol (nmol/L)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
50 (2 wks)	67	79	74	60
138 (2 wks)	84	79	86	77
50 (12 wks)	76	79	85	68
138 (12 wks)	94	79	87	90

Recurrence of Cushing's disease in initially cured patients during prolonged follow-up (n = 56)

The recurrence rate of disease in all initially cured patients was 9 % (5 out of 56 patients) during a median period of follow-up of 7 years. Therefore, the long-term cure rate of Cushing's disease was 65% (51/78) for the whole group studied.

Postoperative plasma cortisol levels did not predict positively long-term recurrence of the disease in initially cured patients. Five of 37 patients (14 %) with initial postoperative cortisol values below 50 nmol/L, who were cured, relapsed after a median of 7.2 years (range 2-20 years). The clinical details of these five patients are described in Table 4. Eleven of the 12 patients with initial postoperative serum cortisol concentrations between 50 and 138 nmol/L, could be evaluated for more than two years after the operation. None of these 11 patients developed a recurrence of the disease. In addition, all six patients with initial postoperative cortisol concentrations above 138 nmol/L, but who reached plasma cortisol levels below 50 nmol/L 6-12 weeks after surgery, remained in remission during prolonged follow-up (1 to 8 years). Finally, the two clinically cured patients, with persistent plasma cortisol levels above 138 nmol/L did not develop recurrence of the disease.

Recurrence rate of Cushing's disease in patients with a follow up of more than 10 years

Twenty four of the initially cured patients had a postoperative follow up of more than 10 years (median 14.5 yr, range 10-24 yr). Four of these patients developed recurrence of disease (16.7 %). Only one patient developed recurrence of disease more than 10 years after the initial operation (patient 5, Table 4).

Table 4: Characteristics of cases with late relapses (n=5)

Patient	Hardy-Wilson classification	Previous therapy	Postop cortisol (nmol/L)	Duration of remission	Second intervention	Outcome
1	I	ketoconazole	< 50	6 years	radiotherapy	remission
2 *	I	ketoconazole	<50	3 years	transsphenoidal operation	relapse after 3 years
	I	ketoconazole	<50	3 years	transsphenoidal operation	relapse after 3.5 years in remission after radiotherapy
3	I	none	<50	2 years	transsphenoidal operation	remission
4	II-0	none	<50	4 years	transsphenoidal operation	failure; in remission after bilateral adrenalectomy
5	I	none	<50	20 years	transsphenoidal operation	remission

* patient # 2 relapsed twice

Predictors of outcome

Preoperative variables (adenoma size, preoperative cortisol concentration, and pre-treatment with cortisol lowering agents) did not significantly influence long-term remission rates in multivariate logistic regression analysis. Postoperative ACTH values did significantly influence long-term remission rates. Univariate logistic regression analysis revealed that ACTH was a significant predictor of remission ($P = 0.03$), but not of relapse.

Outcome in patients with unsuccessful TS

Of the 22 patients with initial failure of surgery, 8 patients (2 macroadenomas) had a second operation and one patient (microadenoma) was operated three times. The median time between the two operations was 3 years. Six of these 10 operations were classified as failures. Thus, long-term cure rates after repeated surgery was 40% in these patients versus 65% after first surgery in the total group. Fifteen patients underwent subsequent radiotherapy (one patient after the third operation), of whom 13 (87 %) are in long-term remission.

DISCUSSION

In our institution, transsphenoidal surgery cured 72 % of the patients with Cushing's disease. Plasma cortisol levels in the immediate postoperative period are used to predict cured or persistent Cushing's disease. In accordance with previous publications (4,8,9,12), we found that a low postoperative plasma cortisol level (i.e. below 138 nmol/L), irrespective whether determined 2 weeks or 3 months postoperatively, is a good predictor of cure of the disease. However, the present study also indicates that plasma cortisol levels above 138 nmol/L, obtained two weeks after TS, can not be used indiscriminately to predict persistent Cushing's disease. The data in our patients demonstrate that the accuracy of a serum cortisol value in postoperative patients to determine disease status is limited. The optimal test would result in a ROC curve with an AUC of 1, whereas our most optimal ROC curve showed an AUC of not more than 0.892. We propose that repeat immediate surgery for persistent postoperative Cushing's disease, as advocated by some, would have been inappropriate in 27 % of these patients, because they were cured despite detectable postoperative cortisol levels. In other words, if these patients would have had immediate repeat surgery, their cure would have been incorrectly attributed to the second operation. Finally, the current study proves that postoperative cortisol levels do not positively predict recurrence of disease during long-term follow-up of initially cured patients, in accordance with previous observations (*e.g.* 8).

Several publications indicate that immediate postoperative serum cortisol levels below 50 nmol/L are associated with long-term clinical cure (4,16). However, in our series no differences in cure rates were found between patients with cortisol levels below 50 nmol/L and levels between 50 and 138 nmol/L. Moreover, all patients with serum cortisol concentrations between 50 and 138 nmol/L remained in long-term remission. We found the optimal postoperative cortisol cut-off value for prediction of cure of Cushing's disease by TS to be 138 nmol/L, measured 6-12 weeks postoperatively.

Six patients were cured despite initial postoperative cortisol levels above 138 nmol/L and showed a remarkable pattern of postoperative cortisol levels (see Table 2 and Figure 1). After initial fasting plasma cortisol levels above 138 nmol/L measured two weeks postoperatively, post absorptive serum cortisol levels decreased, reaching a nadir 6 to 12 weeks after the operation. Interestingly, five of these six patients had macroadenomas, while the sixth patient had a relatively large adenoma diameter of 9 mm. All these patients are still in remission to date during prolonged follow-up. We could not detect any differences with other cured patients in parameters that could predict this sequence of events like pre-treatment with cortisol lowering agents or reaction to postoperative CRH testing. Nevertheless, recent studies indicate differences in biological behaviour between micro- and macroadenomas in Cushing's disease (17). Although there are no differences in the response of micro- and macroadenomas to CRH, significant differences are present

in the ACTH and cortisol responses to hexarelin, a growth hormone secretagogue (18). When investigating the proliferation and apoptotic indices in ACTH secreting adenomas, a significant difference was found in cell growth fraction, being higher in macroadenomas (19). However, it is unclear to us how these differences between micro- and macroadenomas explain the above mentioned pattern of postoperative cortisol levels in some of these patients with macroadenomas. Another possibility is that (semi)autonomous adrenal nodules were present, which might explain the initial ability to maintain higher cortisol level. Since no ultrasound or CT- or MRI scan of the adrenals was performed, we can not exclude this possibility. However, postoperative ACTH values in these six patients (see Table 2) were comparable to those of the whole group of patients that were in remission (14 ± 4 ng/L, range 4–26, *vs* 16 ± 3 ng/L, range <3–82, $P=NS$, respectively), which makes the above mentioned possibility less likely. Given these data, we suggest that in patients with macroadenomas and non-suppressed early cortisol concentrations, the measurement of postsurgical plasma ACTH has an additional value in the prediction of cure.

Recurrence of Cushing's disease developed in 9 % of the initially cured patients during long term follow up of 2-20 years. Remarkably, the recurrences occurred exclusively in the patients with the lowest postoperative plasma cortisol values, according to the most stringent criteria proposed by others (4,16). The rate of recurrence of Cushing's disease was in accordance with other observations using postoperative cortisol cut-off values of 50 nmol/L: 14% (5/37) in our series *vs* 11.5% (7/61)(8). However, in our study there were no recurrences in initially cured patients, who had intermediate or even non-suppressed cortisol levels in the first two weeks after the operation. Therefore, cortisol levels obtained during the first few weeks after the operation can not be used to predict recurrence of Cushing's disease during prolonged follow up.

It can be argued that the administration of dexamethasone during the first few days after surgery might have resulted in falsely low levels of plasma cortisol obtained in the second week after operation, even though the interval between the last dexamethasone administration and the cortisol measurement was at least 120 hours. This could explain the recurrence that occurred only in the 5 patients with the lowest postoperative cortisol levels. However, plasma cortisol levels were also evaluated at additional time points (2, 6, 12 and 26 weeks after surgery as well as annually thereafter) in all patients. The five patients, who had long-term recurrence of Cushing's disease had undetectable plasma cortisol levels at all these time points, and three of these patients were still hydrocortisone-dependent one year after surgery. The two other patients, who became hydrocortisone- independent, were free of disease, as documented by normal 24h UFC excretion as well as a normal suppression to low dose oral dexamethasone. Therefore, it is highly unlikely that the peri-operative dexamethasone schedule resulted in false negative serum cortisol concentrations in the patients who exhibited recurrence of disease after many years.

In theory, the preoperative use of steroid biosynthesis inhibitors could also have influenced the cortisol values obtained in the early postoperative period. However,

analysis of the data according to absence or presence of pre-treatment with ketoconazole and metyrapone did not reveal statistically significant differences between the two groups. Therefore, we think that it is unlikely that our interpretation with respect to the early postoperative cortisol concentrations is influenced by preoperative treatment with steroid biosynthesis inhibitors.

Interestingly, pituitary exploration in patients with inconclusive preoperative radiological investigation of the pituitary identified an adenoma in 87 % of cases. This relatively high rate of identification of pituitary adenomas during pituitary exploration is in accordance with published data of other centres (*e.g.* 7). Moreover, long-term remission rates in these patients did not differ from those with an identified pituitary adenoma on radiological imaging. Apparently, extensive pituitary exploration in experienced hands does not influence negatively cure rate.

Previously, we documented a cure rate of 61 % in patients with acromegaly treated by TS by the same pituitary surgeon (20), compared to the surgical cure rate of 72 % of Cushing's disease in the present series. Moreover, TS cured Cushing's disease in 8 of the 12 macroadenomas. Therefore, the cure rate of macroadenomas causing Cushing's disease was not different from that of microadenomas, a finding that is consistent with our reported series on acromegalic patients operated by the same neurosurgeon (20). We also compared the long-term recurrence rates of acromegaly in initially cured patients during a follow up of more than 10 years. The incidence of recurrent disease in acromegaly during prolonged follow up was 19 % (20), which compares well with the value of 17 % in patients with recurrent Cushing's disease during a follow-up of more than 10 years. This is surprising, since it is believed that the long-term recurrence rate of Cushing's disease is lower than for other hormonally active pituitary adenomas (21).

In conclusion, a postoperative plasma cortisol level below 138 nmol/L is a strong predictor of cure of Cushing's disease by TS. However, postoperative plasma cortisol levels above 138 nmol/L, obtained two weeks after TS, should be repeated, unless there are other strong indicators of persistence of Cushing's disease. These unsuppressed postoperative cortisol levels did not predict persistent Cushing's disease in 27 % of those patients, especially in macroadenomas. Furthermore, postsurgical cortisol levels do not predict positively recurrence of disease during long-term follow-up of initially cured patients, since recurrence of disease occurred in our series only in patients with the lowest postoperative plasma cortisol values. Considering the risk of recurrent disease, all patients with Cushing's disease cured by surgery require long term follow up.

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