Factors Influencing the Immediate and Late Outcome of Cushing's Disease Treated by Transsphenoidal Surgery: A Retrospective Study by the European Cushing's Disease Survey Group

DOMENICO BOCHICCHIO, MARCO LOSA, MICHAEL BUCHFELDER, AND THE EUROPEAN CUSHING'S DISEASE SURVEY STUDY GROUP*

Institute of Endocrine Sciences, Ospedale Maggiore IRCCS (D.B.), and Department of Neurosurgery, Ospedale San Raffaele IRCCS (M.L.), University of Milan, Milan, Italy; and Department of Neurosurgery, University of Erlangen-Nürnberg (M.B.), Erlangen, Germany

ABSTRACT

Hypercortisolism attributable to hypersecretion of ACTH by a pituitary adenoma is an uncommon and progressively lethal disease. Because of its rarity, it has been difficult to collect a large series of patients in order to identify the prognostic factors influencing the outcome after transsphenoidal surgery. We conducted a multicenter, retrospective analysis of the early and late results of surgical treatment of Cushing's disease.

Files of patients with Cushing's disease who underwent transsphenoidal surgery between 1975 and 1990 were collected from 25 institutions throughout Europe. Data from 668 of 716 patients were suitable for statistical analyses. Surgical mortality was 1.9%, and major morbidity occurred in 97 patients (14.5%). Clinical and biochemical remission of Cushing's disease after surgery occurred in 510 cases (76.3%). Identification of the tumor by neuroradiological imaging or at operation with histopathological corroboration was associ-

ated with remission of hypercortisolism. Recurrence of the disease occurred in 65 (12.7%) of 510 patients in remission after surgery at a mean time of 39.3 months (range 6–104 months). The distribution of the recurrences did not show any apparent plateau or cluster throughout the follow-up period. Low postoperative steroid levels, absence of cortisol response to CRH, and the need for long-term glucocorticoid substitution therapy were all associated with a high probability of long-term remission.

Our study demonstrates that transsphenoidal surgery is a safe and effective treatment for patients with Cushing's disease. However, after successful surgery there is a steady increase in the percentage of recurrences, which continues with time. Patients who after operation had hypoadrenocorticism and needed long-term glucocorticoid substitution therapy had the lowest risk of relapse. (*J Clin Endocrinol Metab* **80:** 3114–3120, 1995)

H YPERCORTISOLISM attributable to overproduction of ACTH by a pituitary adenoma (Cushing's disease) is rare. Its incidence in the general population is estimated to be between 0.7 and 2.4 cases/million inhabitants per year (1, 2). In most patients, hypercortisolism leads to severe complications and is associated with premature mortality if left untreated. At this time, microsurgical removal of the pituitary adenoma is the treatment of choice for Cushing's dis-

ease (3). Other therapeutic options, such as bilateral adrenalectomy (4, 5), medical therapy with adrenostatic drugs (6), radiotherapy (7), and radiosurgery (8), have been proposed either as alternatives to pituitary surgery or as adjunctive therapy in cases of incomplete remission of the disease after operation. In the last decade, several institutions have reported the results of transsphenoidal surgery in patients with Cushing's disease. Although most authors describe a remission rate of 70–90%, the only other available retrospective multicenter survey reported considerably less favorable results in centers in the United States (9). Moreover, an increasing rate of late recurrence of the disease to as high as 20% at 5–6 yr has been reported, especially in those series with the longest follow-up (10–13). The rarity of Cushing's disease has precluded the collection of a large series of patients undergoing transsphenoidal operation in the same institution, thus making it difficult to assess the preoperative and postoperative factors influencing the immediate and late outcome of the disease. To address this problem, we carried out a retrospective, multicenter study in European countries in order to gather enough patients who had undergone surgery for Cushing's disease, thus allowing us to perform a meaningful analysis of the possible prognostic factors linked to either failure or recurrence.

Materials and Methods

Study design

Endocrine and neurosurgical centers throughout Europe were asked to participate in a retrospective study on the surgical treatment of Cushing's disease; a study protocol was elaborated, discussed, and amended by all participants, and a questionnaire was prepared accordingly (a copy is available on request).

All consecutive patients at each center were included in the study when the following criteria were met: 1) planned transsphenoidal surgery for suspected Cushing's disease. Criteria for the diagnosis of Cushing's disease were not explicitly given because of the great variability of the diagnostic tests used in the different countries during the period of the study. However, from a survey conducted among the participating centers, patients were diagnosed to have Cushing's disease on the basis of at least the clinical picture and the lack of steroid suppression during low-dose dexamethasone administration. Patients for whom an operation had been scheduled but not completed because of technical failure or patients who were later found to harbor an ectopic ACTH-secreting tumor were also included on an intention-to-treat basis; 2) operation performed between January 1, 1975, and December 31, 1990. The former limit was chosen because microsurgical removal of pituitary tumors was not common before 1975; and 3) no prior pituitary surgery.

The questionnaire had five sections. The first contained the general demographic data of the patient and the presumed year of onset of the disease. The second section contained endocrinological data (baseline cortisol, ACTH, and urinary steroid levels; ACTH and steroid responses to TRH/GnRH and to corticotropin-releasing hormone (CRH) administration; and results of bilateral inferior petrosal sinus sampling) and neuroradiological characteristics [plain skull radiography, computed tomography (CT) scan, and magnetic resonance imaging (MRI)]. The third section concerned surgical characteristics (date of surgery, type of surgery, and diameter, location, invasiveness, and histological confirmation of a pituitary lesion), early endocrinological postoperative evaluation, and the need for and the duration of postoperative glucocorticoid substitution therapy. The fourth section referred to the last available follow-up information (date of last visit; baseline cortisol, ACTH, and urinary steroid levels; present status of the patient and in the case of death, date and cause). If the patient had a clinical and biochemical recurrence of Cushing's disease after successful operation, participants were asked to complete the fifth section of the questionnaire concerning the endocrinological and neuroradiological characteristics of the patient at relapse.

Hormonal data were described qualitatively as high, normal, or low according to the reference limits applied in each center. Similarly, responses to stimulation tests were described as normal, high, or no response, as the large time span of the study and the different methods used throughout Europe for the measurement of hormone levels prevented the possibility of any meaningful quantitative analysis. However, to keep the results as homogeneous as possible, general criteria for determining normal and pathological responses were given. Thus, an increment of ACTH levels of at least 50% over baseline or an increase of cortisol concentrations of at least 160 nmol/L after the administration of TRH/GnRH or both were required to define a paradoxical response to this test. Participants were requested to specify the criteria they used for classifying the response to the CRH test (ovine or human). ACTH and cortisol increments lower than 50% over baseline after CRH administration were regarded as indicating no response. There was more variability in the definition of the upper normal limit because this is usually derived from data in normal controls tested in each center. Therefore, the classification of the response given by each investigator was usually accepted. The results of bilateral inferior petrosal sinus sampling included the study of both basal and CRH-stimulated ACTH secretion in most cases. Because at the time the study was planned no patient with the ectopic ACTH-syndrome was known to show a baseline ACTH ratio greater than 1.4 between the petrosal sinus levels and the peripheral venous concentrations, this value was regarded as indicative of pituitary-dependent hypercortisolism (14, 15). The same value has been used to indicate the presence of a left or right gradient at the pituitary level (15).

A detailed explanation of all definitions given in the questionnaire was included. All of the questionnaires received were individually checked for inconsistencies before statistical analysis.

Statistical analysis

The major goal of the study was to detect the main prognostic factors linked to either failure of treatment or recurrence of Cushing's disease after transsphenoidal surgery. For this reason, analysis of the data was divided in two parts. In the first, the response of patients was categorized as either treatment failure, *i.e.* patients who needed additional therapy for persisting clinical and biochemical hypercortisolism, or as treatment success, *i.e.* patients who did not need any additional treatment as they showed clinical remission of the disease and return of a normal suppression of steroid levels during low-dose administration of dexamethasone. If recurrence of the disease occurred within 6 months after surgery, patients were considered as treatment failure.

In the second part, we focused on the recurrence of Cushing's disease. In this analysis we included only patients who were classified as treatment success after surgery (see above). They were then subdivided into patients who had a relapse and those who did not have evidence of relapsing Cushing's disease until the last follow-up visit.

Quantitative variables are expressed as mean ± SEM. Qualitative data were analyzed by the χ^2 statistic without Yates' correction. Quantitative variables were analyzed by the Mann-Whitney test to avoid assumption about the gaussian distribution.

The occurrence of relapse is related to the length of follow-up; therefore, the cumulative probability of no relapse during the follow-up was estimated by means of survival analysis [product-limit method according to Kaplan and Meier (16)]. The differences in the disease-free experience among the classes of the investigated variables were tested by Breslow generalized Wilcoxon test (17).

To obtain reliable estimates, the disease-free curve was stopped at 120 months, which is when the number of patients remaining at risk was approximately less then 5% of the starting sample. As some information was not gathered at the time of original diagnosis or treatment, missing data were dealt with by carrying out complete case analyses in which patients were excluded from particular analyses if their files did not contain data on the required variables.

Results

Patient characteristics

The total number of questionnaires received was 716. After careful scrutiny of the data, 668 forms were retained for final analysis. The reasons for exclusion of the remaining 48 questionnaires were the following: patients actually had Nelson's disease (n = 10); patients had been operated on after the date for inclusion in the study (n = 12); and important data were missing (n = 26). A clear preponderance of female patients was observed (female/male ratio: 3.32). Mean age at surgery was 38.2 ± 0.55 yr (range 8–84 yr, median 38 yr). The estimated interval between onset of the disease and diagnosis of Cushing's disease was 53.3 ± 1.82 months (range 5–355 months, median 40), and the mean interval between diagnosis and surgery was 10.2 ± 1.05 months (range 1–342 months, median 3.4 months). Surgery was performed before 1981 in 95 patients (14.2%), between 1981 and 1985 in 277 patients (41.5%), and after 1985 in 296 patients (44.3%).

Mortality and morbidity

Perioperative mortality was defined either as any death occurring within 1 month from surgery or as death resulting from a complication of operation. The perioperative mortality rate was 1.9% (13 patients). Death occurred between 5 and 134 days after operation. Of the patients who died, 3 were operated on before 1981 (3.2%), 6 were operated on between 1981 and 1985 (2.2%), and 4 were operated on after 1985 (1.4%). Major complications of surgery were reported in 97 patients (14.5%) and were distributed unevenly among cured and not cured patients. The most frequent adverse events were cerebrospinal fluid rhinorrhea (4.6%), diabetes insipidus for at least 6 months (3.0%), meningitis (2.8%), vascular injury or profuse bleeding (1.3%), and pulmonary embolism (0.6%). Twenty-two patients experienced 2 or more complications. The most frequent association was meningitis after postoperative cerebrospinal fluid rhinorrhea (7 patients).

Early postoperative results

After operation, 158 patients (23.7%) were considered as treatment failure and 510 (76.3%) were judged to be in remission. The percentage of failure varied among the different centers from 0% to 47.6% (median 18.2%). When considering only centers with at least 20 evaluable patients, the failure rate ranged from 7.4%–47.6% (median 14.6%). No significant association was found between the general demographic characteristics of the patients and the occurrence of failure. There was a nonsignificant trend toward a declining percentage of surgical failures in more recent years (28.4%, 25.6%, and 20.3% for the periods 1975–1980, 1981–1985, and 1986–1990, respectively). Previous therapy with drugs, radiotherapy, and partial adrenalectomy, alone or in combination, reported in 176 patients (26.5%), did not correlate with the outcome.

Baseline ACTH, cortisol, and urinary steroid levels were not associated with the outcome of surgery. Preoperative dynamic testing of ACTH and cortisol secretion with CRH and TRH/GnRH was reported in 208 and 100 patients, respectively. Patients with normal or excessive ACTH and cortisol response to CRH showed a failure rate (22.9%) that was significantly lower than in the group with no response (44.0%; $P < 0.05$). The presence of a paradoxical increase of cortisol levels after TRH/GnRH administration, reported in 27 patients (27%), had a near-significant negative prognostic value (percentage of failure in this group 37% vs. 20.5% in the group without such response; $P < 0.10$).

Bilateral sampling of inferior petrosal sinus was performed in 98 patients. The overall failure rate in this group (23.5%) was similar to that of patients who did not undergo the procedure (23.7%). Seventeen patients did not show a positive central-peripheral gradient but they were subjected to surgery nonetheless; 6 of them did not achieve remission of the disease. In the 3 patients lacking histological confirmation of a pituitary adenoma, an ectopic ACTH-syndrome was strongly suspected. However, at the last follow-up (4, 35, and 40 months after surgery), no source of ectopic ACTH secretion was detected. In the patients with a gradient, the percentage of failure was significantly higher in patients who did not have a left or right gradient (50%) than in those who did have a left or right gradient (13.3% and 17.9%, respectively; $P < 0.05$).

Visualization of the adenoma by CT, reported in 281 (47.7%) of 589 patients, was strongly correlated with a good outcome (failure rate of 14.9% as compared to 28.4% and 29.7% of patients with normal or equivocal findings, respectively; $P < 0.001$). Analysis of MRI, although performed in only 115 patients, confirmed a similar trend (failure rate of 12.9% in patients in whom the adenoma was identified vs. 26.4% in patients with no evidence of the tumor; $P < 0.10$).

Selective adenomectomy, selective adenomectomy with wide margins, and hemihypophysectomy had similar failure rates of 20.0%, 23.8%, and 19.7%, respectively. Total hypophysectomy still carried a failure rate of 32.5%. Failure of surgery was common (69.6%) when the surgeon did not identify any lesion at surgery.

Macroadenomas (reported in 20.7% of the patients), extrasellar extension of the tumor (14.5%), and tumor invasiveness (6.7%) as well as the location of the adenoma did not influence the outcome of surgery. Lack of histological documentation of an ACTH-secreting adenoma was more frequent in patients not in remission (47.1% vs. 16.6%; $P < 0.001$).

Evidence for an underlying misdiagnosed ectopic ACTH syndrome in the group not in remission after surgery was sought by reviewing the cause of death of the patients. Five of 26 patients died of cancer (metastatic tumor of unknown origin, uterine carcinoma, ovarian cancer, breast cancer, and metastatic carcinoid) 2, 10, 27, 42, and 57 months after operation, respectively. In 2 additional patients, a clinical suspicion of ectopic syndrome was reported. Thus, misdiagnosis of ectopic ACTH-syndrome seems to be a possible explanation for the therapeutic failure in a small subgroup of patients.

Recurrences

The analysis of the recurrences included the 510 patients who were considered in remission after operation. One hun-

dred three patients (20.2%) were either lost to follow-up (15.1%) or died (5.1%) while they were still disease-free, after a mean follow-up of 24 ± 0.1 months (median = 13 months).

Sixty-five patients (12.7%) had clinical and biochemical recurrence of the disease during follow-up. Recurrence occurred after a mean time of 39.3 months (median 33 months) within a range of 6–104 months. The overall disease-free curve is shown in Fig. 1. There was a constant decline in the percentage of patients without relapse, approaching 83% at 60 months.

Demographic variables did not correlate with the risk of recurrence. Only younger age at surgery, *i.e.* less than 38 yr (the median population age), conferred a higher risk of relapse, but the difference was of borderline significance ($P = 0.055$). The results of preoperative hormonal studies did not correlate with the occurrence of relapse. Only the paradoxical cortisol response to TRH/GnRH showed a weak but nonsignificant ($P < 0.10$) association with relapse of disease (36.8% of patients with such a response *vs.* 17.9% of those without the abnormal response). Patients with preoperative visualization of the pituitary tumor by MRI or CT showed earlier recurrence after surgery ($P < 0.03$ and $P = 0.053$, respectively) (Fig. 1, *upper right*). Perioperative variables such as type of surgery, tumor size, location and invasiveness,

extrasellar growth of the adenoma, and histologic confirmation were not significantly different between the two groups of patients.

Early postoperative assessment of steroid secretion was highly predictive of long-term outcome. Recurrences increased from 4.3% in patients with postoperative, undetectable circulating cortisol levels to 26.3% in patients with high-normal levels ($P < 0.0001$) (Fig. 1, *lower left*). The same pattern occurred for postoperative urinary steroid measurement ($P < 0.0001$), even though the number of patients investigated was lower ($n = 266$). Early postoperative CRH test was performed in only 82 patients. Persistence of a normal or exaggerated cortisol response predicted a higher likelihood of recurrence (17.5% and 42.9%, respectively, *vs.* 0% of patients with no cortisol response; $P < 0.01$). Need for and duration of glucocorticoid substitution therapy were strongly and inversely correlated with the occurrence of relapse ($P < 0.0001$) (Fig. 1, *lower right*). When replacement therapy was needed for more than 1 yr, the probability of recurrence of the disease at 5 yr was low (3% *vs.* 24% for glucocorticoid therapy less than 1 year and 47% in patients not requiring any substitution therapy).

Discussion

Our survey study allowed us to asses the results of transsphenoidal pituitary surgery in 668 patients throughout Europe who were operated on for Cushing's disease from 1975 to 1990. In common with all multicenter and retrospective studies, our survey has inherent bias. Because of the great variability of methods used in the different countries and throughout the study period, we could not perform any quantitative analysis of hormonal data. However, the large number of patients and the long follow-up allow some conclusions to be drawn about immediate and late outcome. Our study confirms that transsphenoidal microsurgery is a safe procedure in patients with Cushing's disease, with a perioperative mortality rate of 1.9%, comparable with that of other large series from single institutions (11, 18, 19).

The definition of successful operation rested mainly on clinical grounds, *i.e.* remission of signs and symptoms of hypercortisolism and no additional requirement for therapy to control hypercortisolism for at least 6 months. The latter criterion was chosen to lessen the probability of postoperative misclassification such as cyclical Cushing's disease (20). By these criteria, 510 patients (76.3%) were in remission of disease after operation, a percentage of success similar to that reported in other surgical series from single institutions (11, 13, 18, 19, 21–34; Table 1), even though the great variability in the definition of cure makes direct comparison of these results difficult.

Burch (9), in a multicenter survey carried out in the United States in 1983, found a great variability in the remission rates, which ranged from 10–100%. In our multicenter study, the results were more homogeneous among the participating centers (from 52.4%–100%) and showed a trend toward higher remission rates in recent years, probably reflecting the increasing experience with the diagnosis and therapy of Cushing's disease.
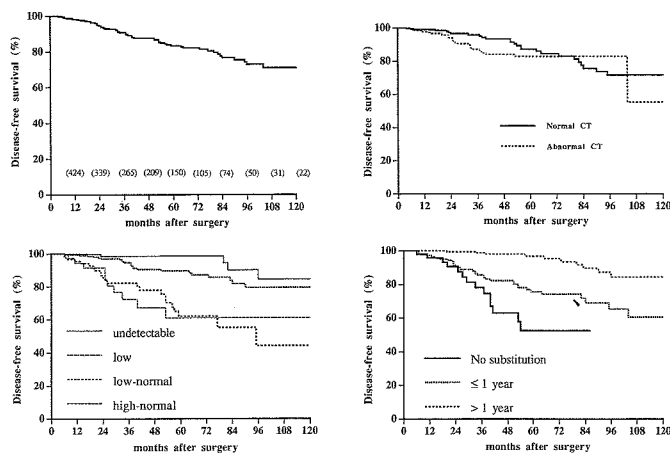

FIG. 1. Analysis of the recurrence of Cushing's disease in the patients who were in remission after transsphenoidal operation. In the *upper left*, the disease-free survival in the whole group is shown (numbers in brackets represent patients at risk at the end of each year). In the *upper right*, the disease-free survival according to the presence of a normal (n = 220) or abnormal (n = 239) pituitary CT scan among the 459 who were examined before surgery is reported. Patients with an abnormal preoperative CT scan had a higher risk of recurrence, but the difference was of borderline significance ($P = 0.053$). In the *lower left*, the disease-free survival according to the early postoperative morning cortisol level is shown for the 482 patients for whom the result was available. Patients with undetectable (n = 94) and low (n = 250) cortisol levels had fewer recurrences during follow-up than did patients with low-normal (n = 97) and high-normal (n = 41) cortisol levels. The overall difference among the four groups was highly significant ($P < 0.0001$). In the *lower right*, the disease-free survival according to the length of glucocorticoid substitution therapy is reported for all of the 510 patients who had successful operations. Patients who did not need any substitution therapy (n = 82) and those who required glucocorticoid replacement for less than 1 yr (n = 248) showed a higher risk of recurrence than did patients treated for more than 1 yr (n = 180). The overall difference among the three groups was highly significant ($P < 0.0001$).

TABLE 1. Results of transsphenoidal surgery for Cushing's disease

Author	Year	Success rate	Recurrences	Mean follow-up (Months)
Salassa et al. (21)	1978	16/18 (88.9%)	0/16 (0%)	18
Hardy (22)	1982	63/75 (84.0%)	0/63 (0%)	21
Thomas and Richards (23)	1983	13/16 (81.2%)	Not stated	Not stated
Semple et al. (24)	1984	17/19 (89.4%)	1/17 (5.9%)	40
Burch (25)	1985	9/14 (64.3%)	1/9 (11.1%)	Not stated
Tagliaferri et al. (26)	1986	19/23 (75.6%)	2/19 (10.5%)	39
Chandler et al. (27)	1987	24/34 (70.5%)	Not stated	Not stated
Nakane et al. (28)	1987	86/100 (86.0%)[a]	8/86 (9.3%)[b]	38
Guilhaume et al. (11)	1988	42/61 (68.9%)[a]	6/42 (14.3%)	24
Mampalam et al. (18)	1988	171/216 (79.2%)[c]	9/171 (5.3%)	46
Arnott et al. (29)	1990	24/28 (85.7%)	3/24 (12.5%)[d,e]	22
Burke et al. (30)	1990	44/54 (81.5%)	2/44 (4.5%)	56
Post and Habas (31)	1990	29/37 (78.4%)	1/29 (3.4%)	Not stated
Tindall et al. (19)	1990	46/53 (86.8%)	1/46 (2.1%)	57
Robert and Hardy (32)	1991	60/78 (76.9%)[f]	5/60 (8.3%)[g]	77
Tahir and Sheeler (13)	1992	34/45 (75.6%)	7/34 (20.6%)	69
Trainer et al. (33)[h]	1993	39/48 (81.2%)	3/39 (7.7%)[d]	Not stated
Ram et al. (34)[i]	1994	205/222 (92.3%)	Not stated	Not stated
Present series	1995	510/668 (76.3%)	65/510 (12.7%)	46

Single series published by participants in this survey are not included.

[a] Negative predictive factor of immediate outcome: no adenoma found at operation.

[b] Negative predictive factor for recurrence: short duration of replacement therapy.

[c] Negative predictive factor of immediate outcome: extrasellar adenoma.

[d] Negative predictive factor for recurrence: higher postoperative steroid levels.

[e] Negative predictive factor for recurrence: no adenoma found at operation.

[f] Negative predictive factor of immediate outcome: invasive adenoma.

[g] Negative predictive factor for recurrence: younger age.

[h] Ten patients were subjected to repeated pituitary exploration within 10 days of surgery because of measurable cortisol levels.

[i] Seventeen patients underwent repeat pituitary surgery 7–46 days after first operation because of persistent hypercortisolism.

Early outcome of surgery was associated with few preoperative characteristics. Among hormonal variables, only the lack of response to CRH had a predictive negative value. A similar result was reported by Pieters and co-workers (12) who showed that preoperatively the mean increment of cortisol levels after the administration of CRH was higher in the group of successfully operated patients. As the absence of cortisol and ACTH response to CRH does not suggest a pituitary origin of hypercortisolism (35), the higher failure rate in such patients might reflect misdiagnosis of an ectopic ACTH-syndrome. On the other hand, 14 of the 25 patients with a negative response to CRH had a remission after pituitary surgery, suggesting that at least 50% of these patients had pituitary tumors not responsive to CRH.

As already suggested by Pieters and co-workers (12), patients with the paradoxical cortisol responsiveness to TRH/GnRH had a trend toward a higher percentage of surgical failure, but unfortunately the number of patients who underwent the test (100 subjects) was probably too small to allow adequate statistical analysis.

Since the early 1980s, bilateral inferior petrosal sinus sampling has been introduced in order to identify with certainty the origin of ACTH hypersecretion (36) and to improve the surgical results by selecting the side of hemihypophysectomy in those patients with a negative pituitary exploration (37). The latter expectation, however, has not been corroborated by the same author (36) and by other groups (14, 15), probably because the diagnostic accuracy in localizing the intrapituitary side of the adenoma did not reach the desired 100%. Our results, although showing no significant differ-

ence in the success rate among patients who did and did not undergo the procedure, do not allow definitive conclusions to be drawn about the impact of inferior petrosal sinus sampling on surgical results because of the limited number of patients available for analysis (98 of 668).

Preoperative visualization of the pituitary lesion by either CT scan or MRI was associated with a better outcome, probably because identification and removal of the pathological tissue at operation was easier. On the other hand, this advantage was counterbalanced by a higher rate of tumor recurrence (see below). These findings suggest that additional refinements of neuroradiological tools, leading to a more precise intrapituitary localization of small tumors in Cushing's disease, should bring an important amelioration of the early surgical results in the future.

Operative variables did not influence the outcome of surgery, with the exception of a negative pituitary exploration and a negative histopathology. In the past, total hypophysectomy has been advocated as the procedure of choice in patients with Cushing's disease (23) because it was presumed that the improvement of postoperative results would counterbalance the sacrifice of anterior pituitary function. Our survey clearly shows that compared with hemi- or total hypophysectomy, a more conservative surgical approach does not reduce the success rate. At variance with data in GH- and PRL-secreting tumors (38, 39), other variables such as tumor size, invasiveness, and extrasellar extension did not significantly affect the results, probably because only a minority of ACTH-secreting tumors possessed such features.

Thus, it may be necessary to analyze many more cases in order to detect a significant difference for these variables.

Until recently, the recurrence of Cushing's disease after successful operation was regarded as a rare event. Indeed, many surgical series, especially the oldest ones, reported few late relapses (Table 1). On the contrary, in recent years it has become clear that recurrence of the disease is more frequent than was previously thought (Table 1). In our study, 65 (12.7%) of 510 patients in remission after surgery relapsed during a mean follow-up period of 57 months. Interestingly, the occurrence of relapses did not show any time-related plateau but did show a progressive upward trend, as first suggested by Guilhaume and co-workers (11). This fact stresses the need for continued and careful monitoring of patients.

To date, and because of the few cases studied in each single surgical series, no clear preoperative characteristic has emerged as a strong predictive factor for the occurrence of relapse. Only younger age at surgery was suggested as carrying a higher risk of recurrence of disease (32). Our results showing a higher risk of relapse in younger patients lend support to this suggestion. However, Magiakou and co-workers (40) recently reported a low recurrence rate (6.3%) in a group of children with Cushing's disease who were operated on at the NIH.

Paradoxical responsiveness to TRH/GnRH had a weak but nonsignificant correlation with recurrence of disease. However, a larger sample of patients is needed before definitive conclusions about the predictive value of the test can be drawn. Visualization of the adenoma by neuroradiological studies was correlated with a higher risk of relapse. To explicate the divergence between the immediate and late results, it is likely that adenomas visible at pituitary imaging are usually large enough to be easily detected by the surgeon, which explains the better immediate postoperative results. On the other hand, the larger the tumor, the higher the probability that some adenomatous cells may remain and eventually cause regrowth of the tumor.

Early postoperative results were strongly associated with late outcome. Increasing rates of recurrence were associated in ascending order with the postoperative levels of serum and urinary steroids, as previously suggested by Pieters and co-workers (12). Similarly, the persistence of a cortisol response after CRH administration was correlated with a higher risk of relapse. The same finding was reported previously (12, 41, 42). After operation, normal secretion of ACTH and cortisol, either at baseline or in response to CRH, might suggest that residual adenomatous tissue is still present, as normal corticotrophs should remain completely suppressed by the preoperative chronic hypercortisolism (33). On the basis of this assumption, Trainer et al. (33) recommended early reoperation or radiotherapy in patients with detectable steroid levels after surgery. However, because in our series only 33 of 135 patients with normal postoperative circulating cortisol levels had a relapse, we emphasize that normal steroid levels after surgery are not necessarily followed by recurrence of the disease, making the aggressive policy of early reoperation and radiotherapy highly questionable, inasmuch as they often result in panhypopituitarism and permanent diabetes insipidus (33).

It is well known that after surgery most patients show transient secondary adrenal insufficiency requiring replacement therapy with glucocorticoids for variable periods of time (43). Our study clearly shows that the longer the need for glucocorticoid substitution, the higher the probability that the patient will remain free of disease in the long term (Fig. 1, *lower right*). When substitution therapy was needed for longer than 1 yr, the percentage of disease-free patients at 5 yr was 97%, whereas it declined to 76% and 53%, respectively, when such therapy was required for less than 1 yr or not at all.

In conclusion, transsphenoidal surgery is a safe and effective treatment modality in patients with Cushing's disease, as confirmed in our multicenter study by the early success rate of about 76%. Moreover, our results show that recurrence of Cushing's disease is not a discrete phenomenon, inasmuch as it occurs progressively over the years without any apparent tendency to plateau. Hypocortisolism after surgery is the most important factor predicting a good long-term outcome: the longer the need for glucocorticoid replacement, the lower the probability of relapse. However, although a careful follow-up is mandatory, early reoperation is not recommended in patients with normal steroid levels postoperatively in view of the high percentage of those who do not relapse.

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