

THE LONG-TERM OUTCOME OF PITUITARY IRRADIATION AFTER UNSUCCESSFUL TRANSSPHEOIDAL SURGERY IN CUSHING'S DISEASE

JAVIER ESTRADA, M.D., MAURO BORONAT, M.D., MERCEDES MIELGO, M.D., ROSA MAGALLÓN, M.D., ISABEL MILLÁN, M.S., SANTIAGO DíEZ, M.D., TOMÁS LUCAS, M.D., AND BALBINO BARCELÓ, M.D.

ABSTRACT

Background Irradiation of the pituitary is widely considered the most appropriate treatment for patients with Cushing's disease in whom transsphenoidal microsurgery has been unsuccessful. However, there is little information about the long-term efficacy of this treatment.

Methods We used external pituitary radiation to treat 30 adult patients with persistent or recurrent Cushing's disease after unsuccessful transsphenoidal surgery. The mean (\pm SD) dose of radiation was 50 ± 1 Gy. Pituitary and adrenal function was assessed every six months after radiation therapy. Remission was defined as the regression of symptoms and signs of Cushing's syndrome, normal urinary cortisol excretion, and a low plasma cortisol concentration in the morning after the administration of 1 mg of dexamethasone at midnight.

Results Twenty-five patients (83 percent) had remissions during a median follow-up of 42 months (range, 18 to 114). The remissions began 6 to 60 months after radiation therapy, but in most cases (22 patients) remission occurred during the first 2 years. None of the 25 patients had a relapse of Cushing's disease after remission was achieved. There was no relation between the response to radiotherapy and sex, age, urinary cortisol excretion before radiotherapy, the interval between surgery and radiotherapy, whether a pituitary adenoma was found by pathological examination, or tumor size. Seventeen patients had a deficiency of growth hormone after radiation therapy, 10 had a deficiency of gonadotropins, 4 had a deficiency of thyrotropin, and 1 had a deficiency of corticotropin.

Conclusions Pituitary irradiation is an effective and well-tolerated treatment for patients with Cushing's disease in whom transsphenoidal surgery is unsuccessful. (N Engl J Med 1997;336:172-7.)

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CUSHING'S disease results from excessive stimulation of the adrenal glands caused by the oversecretion of corticotropin by an adenoma, or, occasionally, hyperplasia of the corticotroph cells of the pituitary.^{1,2} It is the most frequent cause of spontaneous Cushing's syndrome in adults, accounting for about 70 percent of cases.³

Selective resection of the corticotropin-secreting tumor by the transsphenoidal approach is the standard treatment for the disease. Approximately 70 to

80 percent of patients are cured, although the success of the procedure depends on the skill and experience of the surgeon and the criteria used to define a cure.^{1,4-7} Patients who have persistent or recurrent disease after pituitary microsurgery are usually treated by external pituitary radiation; other options are drug therapy with adrenal-enzyme inhibitors, bilateral total adrenalectomy, other forms of radiation therapy, or repeated transsphenoidal surgery.^{8,9}

The efficacy of radiotherapy for these patients is not well documented, however. Aside from 14 patients who were included in our previous report,¹⁰ we could find published results for only 9 patients treated by postoperative radiation therapy. Among these nine patients, five (56 percent) had remissions during a median follow-up of 3 years after radiotherapy (range, 1.2 to 11.1 years).¹¹ In other reports, the treatment was judged effective, but documentation of normal hormone values after radiation was lacking.^{12,13} In contrast, primary radiotherapy for patients with Cushing's disease, which has been studied more extensively, is effective in only 50 to 60 percent of adults with the disease.^{11,14-17} We report here our experience with the use of pituitary irradiation after unsuccessful pituitary surgery in 30 patients; this report contains further follow-up data on patients included in our earlier report.¹⁰

METHODS

Patients

Between January 1980 and June 1993, 82 patients with Cushing's disease underwent transsphenoidal surgery and were subsequently followed at our institution. Thirty of these patients had persistent or recurrent disease after surgery and underwent pituitary irradiation. The diagnosis of Cushing's syndrome was made on the basis of clinical features, the absence of a circadian rhythm in plasma cortisol concentrations, increased urinary cortisol excretion, unresponsiveness of plasma cortisol concentrations to insulin-induced hypoglycemia, and characteristic plasma cortisol responses to the administration of dexamethasone.^{18,19} The diagnosis of pituitary-dependent disease was usually established by findings of inappropriately high plasma corticotropin concentrations, reduction of plasma cortisol concentrations in an overnight high-dose (8-mg) dexamethasone suppression test²⁰ (the traditional two-day high-dose dexamethasone test was used¹⁸ before 1987), and imaging of the sella turcica (with computed tomog-

From the Departments of Endocrinology (J.E., M.B., M.M., S.D., T.L., B.B.), Radiation Oncology (R.M.), and Biostatistics (I.M.), Clínica Puerta de Hierro, Universidad Autónoma, Madrid, Spain. Address reprint requests to Dr. Estrada at the Servicio de Endocrinología, Clínica Puerta de Hierro, San Martín de Porres, 4, 28035 Madrid, Spain.

raphy or magnetic resonance). The radiologic findings were interpreted as normal in 19 patients; a microadenoma was identified in 6 patients, and a macroadenoma (more than 10 mm in diameter) in the remaining 5. In eight patients in whom the laboratory and radiologic studies were inconclusive, the diagnosis was based on the results of bilateral, simultaneous inferior-petrosal-sinus sampling, as described earlier.²¹

At the time of transsphenoidal exploration, tissue thought to be a microadenoma was identified and resected in 13 patients; pathological studies confirmed the presence of an adenoma in 5 of these patients, whereas the excised pituitary tissue was apparently normal in 5 patients and was too small for adequate evaluation in the rest. In five other patients, a macroadenoma was partially removed and confirmed pathologically. Finally, in 12 patients in whom a discrete tumor was not seen at surgery, a central wedge of pituitary tissue was removed; pathological studies demonstrated an adenoma in 3 of these patients. The five adenomas studied were positive on selective immunostaining for corticotropin.

All patients underwent endocrinologic evaluation 8 to 12 days after surgery. Twenty-eight patients (Patients 1 through 28) had persistent disease when reevaluated after surgery. Patients 1 through 20 had increased urinary cortisol excretion ($>120 \mu\text{g}$ [$>331 \text{ nmol}$] per day) and did not have suppression of plasma cortisol values in the morning after the administration of 1 mg of dexamethasone at midnight. The mean value for postoperative urinary cortisol excretion in this group was $314 \mu\text{g}$ (865 nmol) per day (range, 140 to $1092 \mu\text{g}$ [386 to 3013 nmol] per day). Seventeen of the 20 patients underwent pituitary irradiation within 6 months after surgery; the remaining 3 patients (Patients 1, 2, and 20) initially refused secondary treatment but were ultimately treated by irradiation 60, 12, and 36 months later, when Cushing's syndrome became clinically more severe.

Patients 21 through 28 had normal urinary cortisol excretion (20 to $120 \mu\text{g}$ [55 to 331 nmol] per day) and adequate suppressibility of plasma cortisol concentrations with dexamethasone in the postoperative period; none of them had adrenal insufficiency or needed glucocorticoid replacement when they were discharged from the hospital. The mean postoperative urinary cortisol excretion among these eight patients was $57 \mu\text{g}$ (156 nmol) per day, (range, 33 to $110 \mu\text{g}$ [91 to 303 nmol] per day). All eight patients were followed and underwent pituitary irradiation when their urinary cortisol values and responsiveness to dexamethasone became abnormal between 12 and 60 months after surgery.

Patients 29 and 30 had postoperative hypocortisolism (plasma cortisol values, $<5 \mu\text{g}$ per deciliter [$<138 \text{ nmol}$ per liter] and urinary cortisol excretion, $<10 \mu\text{g}$ [$<28 \text{ nmol}$] per day) and needed glucocorticoid-replacement therapy for 14 and 12 months, respectively, after which their adrenal function was normal, including suppressibility of plasma cortisol values with dexamethasone, responsiveness of plasma cortisol to induced hypoglycemia, and circadian rhythm in cortisol secretion. These two patients had clinical and biochemical relapses of Cushing's syndrome 9.5 and 10.5 years after surgery, respectively. Endocrinologic reassessment confirmed the presence of pituitary-dependent Cushing's syndrome, and both underwent irradiation at that time. The characteristics of the patients at the time of radiation therapy are summarized in Table 1.

Radiation Therapy

The patients were treated with radiation from an 18-MV linear accelerator, at a total dose of 48 to 54 Gy. Radiotherapy was administered in fractions of 1.8 to 2 Gy per day, five days per week. Two opposed lateral fields were used.

After irradiation, ketoconazole was given to control hypercortisolism until radiotherapy could correct the excess of cortisol. With doses between 400 and 800 mg per day, all patients had normal urinary cortisol excretion, but basal plasma cortisol concentrations at 8 a.m. were above $10 \mu\text{g}$ per deciliter (276 nmol per liter).

Endocrinologic Evaluation

Long-term follow-up studies consisted of the measurement of basal plasma corticotropin concentrations, measurement of plasma cortisol concentrations at 8 a.m. after the administration of 1 mg of dexamethasone at midnight, and a low-dose dexamethasone suppression test (0.5 mg every six hours for eight doses). The latter test was used only during the first few years among patients with longer follow-up. All patients were evaluated postoperatively, before irradiation, and every six months thereafter. Ketoconazole was always discontinued one month before any hormonal evaluation was performed and was discontinued permanently after remission was documented.

We defined remission after radiotherapy as the combination of regression of the clinical manifestations of Cushing's syndrome, persistently normal urinary excretion of cortisol, and morning plasma cortisol concentrations below $5 \mu\text{g}$ per deciliter after the administration of 1 mg of dexamethasone at midnight.

The plasma cortisol response to insulin-induced hypoglycemia and the existence of a circadian rhythm in cortisol secretion were assessed to evaluate the integrity of the hypothalamic-pituitary-adrenal axis. The response to hypoglycemia was considered to be normal if the plasma cortisol concentration was above $18 \mu\text{g}$ per deciliter (497 nmol per liter) at any time during the test.²² Plasma cortisol values at 11 p.m. that were less than 60 percent of the values at 8 a.m. were considered indicative of a normal circadian rhythm of cortisol secretion.

Anterior pituitary function was simultaneously evaluated with measurements of serum thyrotropin, prolactin, luteinizing hormone, and follicle-stimulating hormone before and after the combined intravenous injection of gonadotropin-releasing hormone and thyrotropin-releasing hormone. Basal plasma free thyroxine, total or free testosterone (in men), and estradiol (in women) were also measured. Central hypothyroidism was diagnosed when low plasma thyroxine concentrations were associated with low or normal plasma concentrations of thyrotropin. Hypogonadotropic hypogonadism was considered present when low plasma concentrations of sex steroids were associated with low or normal gonadotropin concentrations in men or postmenopausal women or with amenorrhea in premenopausal women. Growth hormone reserve was assessed after the patients entered remission; deficiency was diagnosed if plasma growth values were below $5 \mu\text{g}$ per liter after the inducement of hypoglycemia.

Hormone Assays

Plasma corticotropin was measured by radioimmunoassay before 1989 (with kits obtained from Immuno Nuclear Corporation, Stillwater, Minn.) and thereafter by immunoradiometric assay (Nichols Institute, San Juan Capistrano, Calif.). Plasma cortisol was measured by radioimmunoassay until 1992 (ICN Biomed-

TABLE 1. CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF 30 PATIENTS WITH PERSISTENT OR RECURRENT CUSHING'S DISEASE AT THE TIME OF SURGERY AND RADIOTHERAPY.

CHARACTERISTIC	MEAN (RANGE)
Age (yr)	40 (18-61)
Urinary cortisol excretion ($\mu\text{g}/\text{day}$)*	
Before surgery	560 (193-1550)
Before radiotherapy	403 (140-1092)
Time between surgery and irradiation (mo)	23 (1-114)
Radiation dose (Gy)	50 (48-54)
Follow-up after radiotherapy (mo)	55 (18-114)

*The normal range is 20 to $120 \mu\text{g}$ per day. To convert values to nanomoles per day, multiply by 2.759.

cals, Costa Mesa, Calif., and Immunotech International, Marseille, France) and thereafter by time-resolved fluorescence immunoassay (Delfia Sistem, Pharmacia, Wallac Oy, Turku, Finland). Cortisol was measured in unextracted urine at low pH by radioimmunoassay (Diagnostic System Laboratories, Los Angeles, and ICN Biomedicals). Serum thyrotropin was measured by immunoradiometric assay (Kodak Amerlite TSH-30 Ultrasensitive assay, Amersham International, Buckinghamshire, United Kingdom). Plasma estradiol and testosterone and serum luteinizing hormone, follicle-stimulating hormone, and prolactin were measured with fluoroimmunoassays (Delfia Sistem, Pharmacia).

Statistical Analysis

The probability of the persistence of Cushing’s disease after radiotherapy was calculated by the Kaplan–Meier method. Remission-free time was defined as the interval from the date of completion of radiotherapy to the date of onset of clinical and biochemical remission.

Various clinical and treatment-related factors were evaluated by univariate analysis to assess their effect on the probability of the persistence of Cushing’s disease. These factors were sex, age, urinary cortisol excretion before radiotherapy, time elapsed between surgery and radiotherapy, whether there was pathological confirmation of a pituitary adenoma, and the presence or absence of a pituitary macroadenoma. Six months was chosen as a cutoff value

for use in grouping patients according to the length of time between surgery and radiotherapy. Medians were used to group patients according to other continuous variables. Differences between curves were evaluated by the Mantel–Cox test. Urinary cortisol values during follow-up were compared with unbalanced repeated-measures analysis of variance. All tests were two-tailed.

Values are given as means with ranges, unless otherwise indicated. BMDP statistical software was used for data analysis.²³

RESULTS

Rate of Remission

All patients had immediate and progressive clinical improvement after the initiation of ketoconazole treatment. In all patients who later had remissions, centripetal obesity, cutaneous atrophy, hirsutism, myopathy, and menstrual changes had regressed at the time the drug was permanently discontinued.

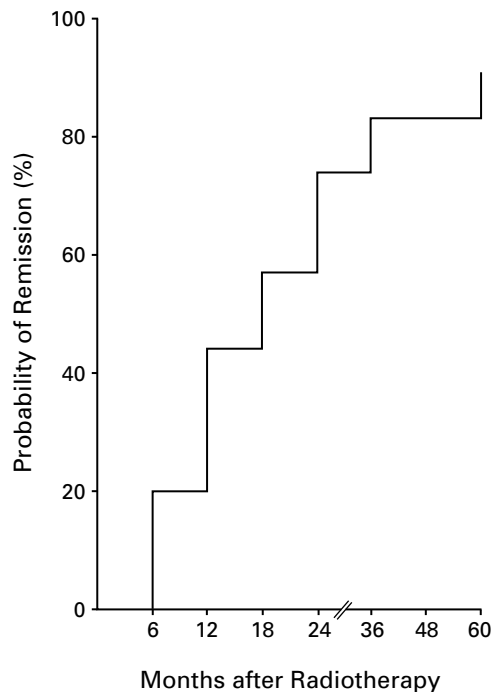
After the completion of radiotherapy, during a median follow-up period of 42 months (range, 18 to 114), 25 of the 30 patients met the three criteria for remission, for an overall rate of remission of 83 percent. The length of time from radiotherapy to the onset of remission averaged 18 months (range, 6 to 60); in the majority of cases it occurred during the first 2 years: 6 patients (20 percent) were in remission at 6 months, 13 patients (43 percent) at 12 months, and 18 patients (60 percent) at 18 months. Eighteen of the 26 patients who were followed for the entire 24-month follow-up period entered remission. (Four patients were followed for 18 months.) Among the 12 patients followed for 60 months, 11 (92 percent) were in remission. According to the product-limit method, the actuarial probability of remission of Cushing’s disease was 44 percent at 12 months and 83 percent at 36 months after radiotherapy (Fig. 1). Once remission occurred, none of the 25 patients had relapses of hypercortisolism during a median follow-up of 30 months.

Decline of Cortisol Secretion

Urinary cortisol excretion fell rapidly, from a mean (\pm SD) value of $403 \pm 270 \mu\text{g}$ ($1112 \pm 745 \text{ nmol}$) per day before radiotherapy to $154 \pm 110 \mu\text{g}$ ($425 \pm 304 \text{ nmol}$) per day after six months ($P < 0.001$). The mean value at 12 months was $112 \pm 73 \mu\text{g}$ ($310 \pm 200 \text{ nmol}$) per day ($P = 0.03$). Thereafter, urinary cortisol excretion fluctuated within the normal range (Fig. 2). The results of the 1-mg dexamethasone suppression test are shown in Figure 3.

Factors Influencing Outcome

The five patients in whom Cushing’s disease persisted after radiotherapy were followed for a median of 36 months (range, 24 to 66); their poor response to irradiation is therefore not explained by insufficient follow-up. None of the variables selected as potential predictors of responsiveness to radiotherapy had an influence on the likelihood of remission (Table 2).



	6	12	18	24	36	60
No. of patients followed up	30	30	30	26	19	14
No. of patients entering remission during 6-mo interval	6	7	5	4	2	0
Total no. of patients in remission at follow-up	6	13	18	18	15	11

Figure 1. Probability of Remission of Cushing’s Disease in 30 Patients Treated with Pituitary Irradiation after Unsuccessful Transsphenoidal Surgery.

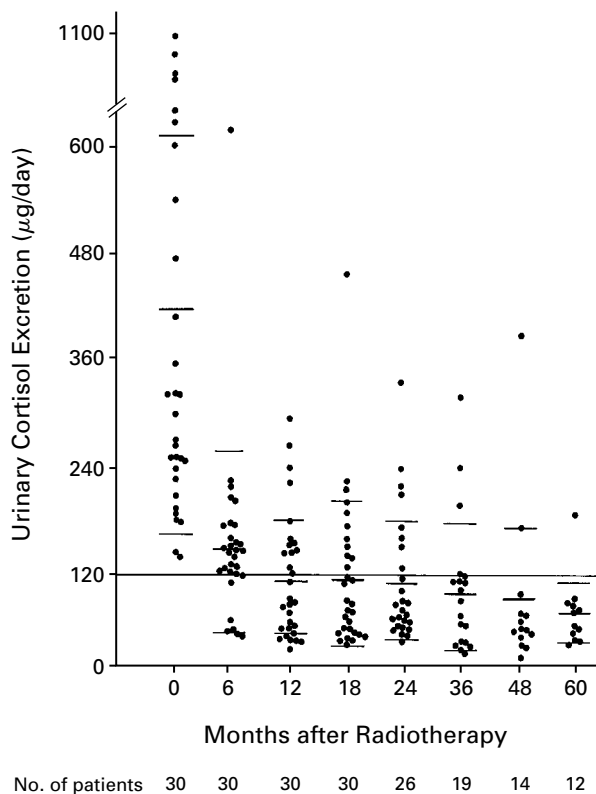


Figure 2. Urinary Cortisol Excretion in 30 Patients with Cushing's Disease Treated with Radiotherapy after Unsuccessful Transsphenoidal Surgery.

The short horizontal lines indicate the mean and standard deviation at each follow-up visit. The horizontal line at 120 μg per day signifies the upper limit of the normal range. To convert values to nanomoles per day, multiply by 2.759.

Hypothalamic-Pituitary-Adrenal Function

Before radiotherapy, all 30 patients had a lack of the normal circadian rhythm of cortisol secretion and no increase in the response of plasma cortisol to induced hypoglycemia. All five patients with persistent disease continued to have these abnormalities. Among the 25 patients who had remissions, both these factors remained abnormal in 16 (64 percent); 4 patients (16 percent) recovered responsiveness to hypoglycemia, and in the remaining 5 (20 percent) both measures became normal. Recovery of hypothalamic-pituitary-adrenal function followed a sequential progression. The onset of remission was the first event in all patients, followed by the return of normal responsiveness of plasma cortisol after the induction of hypoglycemia (mean, 19 months [range, 6 to 60] after remission) and then restoration of the circadian rhythm of cortisol secretion (mean, 32 months [range, 6 to 84] after remission). No patient recovered the circadian rhythm of cortisol secretion without previous or simultaneous normalization of the response to hypoglycemia.

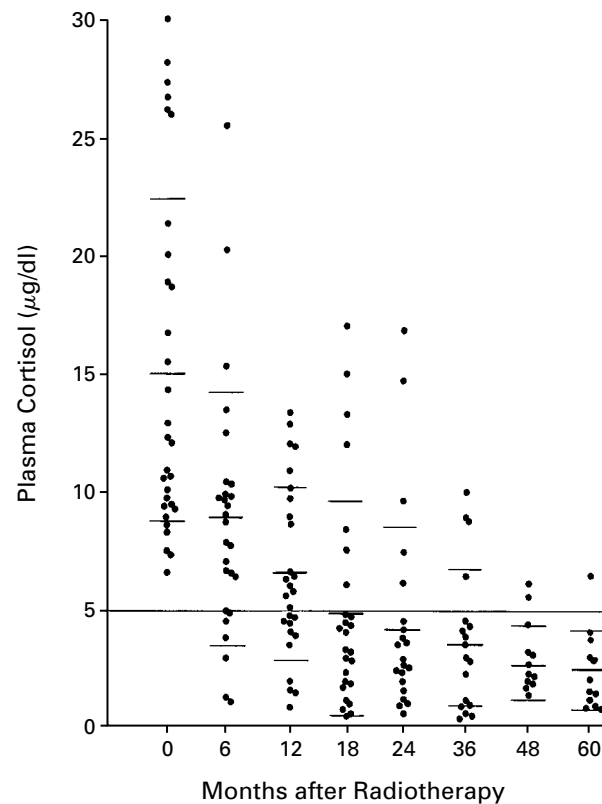


Figure 3. Plasma Cortisol Concentrations at 8 a.m. after the Administration of 1 mg of Dexamethasone at Midnight in 30 Patients with Cushing's Disease Treated with Radiotherapy after Unsuccessful Transsphenoidal Surgery.

The short horizontal lines indicate the mean and standard deviation at each follow-up visit. The horizontal line at 5 μg per deciliter signifies the upper limit of the normal range. To convert values to nanomoles per liter, multiply by 27.59.

Adverse Effects

Growth hormone deficiency occurred in 17 (57 percent) of the patients, in 7 of whom it was isolated. Six patients had growth hormone and gonadotropin deficiency, three patients had deficiencies of growth hormone, gonadotropin, and thyrotropin, and one patient had complete hypopituitarism. Hyperprolactinemia did not develop in any patient. No patient had visual impairment, a second tumor, or brain necrosis.

DISCUSSION

If the excision of a pituitary adenoma by transsphenoidal surgery is complete in patients with Cushing's disease, corticotropin secretion will decline abruptly to very low levels, because of the suppression of the nontumorous corticotroph cells. The result is immediate adrenocortical insufficiency, which may persist for many months after surgery.²⁴⁻²⁷ The

TABLE 2. DISTRIBUTION OF POSSIBLE FACTORS AFFECTING RESPONSIVENESS TO RADIOTHERAPY IN PATIENTS WITH PERSISTENT OR RECURRENT CUSHING'S DISEASE AFTER TRANSSPHEOIDAL SURGERY.

FACTOR	PATIENTS WITH REMISSION (N=25)	PATIENTS WITHOUT REMISSION (N=5)
Age — yr		
Mean	39	46
Range	18–61	30–59
Sex — no. (%)		
Female	18 (82)	4 (18)
Male	7 (88)	1 (12)
Urinary cortisol excretion before radiotherapy — $\mu\text{g}/\text{day}^*$		
Mean	382	510
Range	144–992	140–1092
Interval between surgery and irradiation — mo		
Mean	27	4
Range	1–126	1–6
Results of pathological evaluation — no. (%)		
Adenoma present	11 (85)	2 (15)
No adenoma present	14 (82)	3 (18)
Macroadenoma present — no. (%)	4 (80)	1 (20)

*The normal range is 20 to 120 μg per day. To convert values to nanomoles per day, multiply by 2.759.

subsequent recovery of corticotropin secretion will result not only in quantitative restoration of adrenal function (normal plasma and urinary cortisol values that are normally suppressible with dexamethasone), but also in the gradual acquisition of the normal physiologic characteristics of the hypothalamic–pituitary–adrenal axis (response to stress and circadian rhythm).²⁷ Patients with normal postoperative plasma cortisol values and normal suppressibility after the administration of dexamethasone, but in whom the results of tests of hypothalamic–pituitary–adrenal function do not become normal, must be considered to have residual disease, despite whatever improvement has been induced by partial removal of the tumor. Hypercortisolism develops in most such patients during postoperative follow-up.

Although other treatments are available, radiotherapy is frequently recommended after noncurative pituitary surgery,^{8,9} even though primary treatment with radiotherapy is not consistently effective^{11,14–17} (it may be more effective in children).²⁸ The addition of mitotane improves the outcome of patients treated with primary radiotherapy,²⁹ probably as a result of the drug's adrenocorticolitic action. Control of Cushing's disease with secondary radiotherapy has been poorly documented, as noted earlier. Using a standard irradiation technique in 30 patients, we documented remission rates of 60 percent at 18 months and 91 percent at 5 years. These figures are noticeably better than those in reports on the use of

radiotherapy as primary treatment, possibly because of the debulking of pituitary tumor tissue. Most patients entered remission within the first two years after radiotherapy, but additional patients had remissions later. Our results support the view that radiotherapy should not be considered to have failed until at least five years after it has been administered. We identified no factors, such as age, sex, or the severity of Cushing's disease, that were associated with responsiveness to radiotherapy.

As noted previously by Lamberts et al.²⁷ and demonstrated in Patients 20 through 28 of our series, patients with normal plasma and urinary cortisol values but no need for glucocorticoid replacement after surgery tend to have recurrence of hypercortisolism. What should be the timing of irradiation in these patients? Some authors recommend early therapy,²⁶ before cortisol excess recurs. However, it is not certain that every patient with normal postoperative plasma and urinary cortisol values will ultimately relapse. In addition, we found that the rate of remission was not lower in patients in whom radiotherapy was delayed for more than six months. On the basis of these data, we do not think radiotherapy should be given after unsuccessful surgery until hypercortisolism (high urinary cortisol excretion) has recurred.

Despite the efficacy of radiotherapy in controlling hypercortisolism in these patients, only five had both a normal circadian rhythm of cortisol secretion and normal responsiveness to hypoglycemia, and these changes occurred relatively late after treatment. These findings support the view that dysregulation of the hypothalamic–pituitary–adrenal axis is a residual functional abnormality, tending to disappear along with the gradual loss of adenomatous cells. Thus, corticotropin secretion by the tumor is finally eliminated and adrenal function is governed only by normal corticotroph cells, in connection with the hypothalamus.

Relapses of Cushing's disease have been described in patients who had remission after radiotherapy, mainly when the radiation doses were low (20 Gy).¹⁶ As yet, none of our patients have had relapses, but longer follow-up is needed.

Hypopituitarism is the most common side effect of pituitary irradiation,^{12,13,15} and it is more frequent when the radiotherapy is preceded by surgery.¹² Nevertheless, the frequency of impaired pituitary function in our patients was similar to that after radiotherapy alone. We conclude that the pituitary irradiation is effective therapy for Cushing's disease in patients in whom transsphenoidal surgery has been unsuccessful.

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