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Outcomes of Therapy for Cushing's Disease due to Adrenocorticotropin-Secreting Pituitary Macroadenomas*

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ABSTRACT

We reviewed our experience with 21 patients who had Cushing's disease due to ACTH-secreting macroadenomas to clarify the natural history of this disease. All patients had typical clinical and biochemical features of ACTH-dependent hypercortisolism. Their mean maximal tumor diameter was 1.6 ± 0.1 cm, and the range was 1.0–2.7 cm. Six patients had cavernous sinus invasion, three had invasion of the floor of their sella, and nine had suprasellar extension. The observed remission rate was significantly lower in macroadenoma patients than in microadenoma patients (67% *vs.* 91%; $\chi^2 = 5.7$; $P < 0.02$). Cavernous sinus invasion (odds ratio, 35; 95% confidence interval, 2.6–475; $P < 0.008$) and presence of a maximum tumor diameter 2.0 cm or more (odds ratio, 12.9; 95% confidence interval, 1.4–124; $P < 0.02$) emerged as the only predictors of residual disease after surgery. The observed recurrence rate was significantly higher in macroadenoma patients than in microadenoma patients (36% *vs.* 12%; $\chi^2 = 4.2$; $P < 0.05$). Macroadenoma patients tended to suffer from recurrences earlier than did microadenoma patients (16 *vs.* 49 months). Stepwise multiple logistic regression did not identify any predictors of disease recurrence in macroadenoma patients. Eight macroadenoma patients underwent a total of nine repeat surgical procedures, but none of these resulted in clinical remissions. Only four of seven (57%) patients followed for a sufficient period of time achieved normal urinary free cortisol levels after conventional radiotherapy. Three (75%) of these four patients had re-recurrent hypercortisolism after brief periods of eucortisolism. Pharmacological agents and adrenalectomy were effective in the management of hypercortisolism in patients with residual and recurrent disease. Our results indicate that ACTH-secreting macroadenomas are more refractory to conventional treatments than are ACTH-secreting microadenomas. (*J Clin Endocrinol Metab* **83:** 63–67, 1998)

TRANSSPHENOIDAL adenomectomy is the preferred treatment for adult subjects with *de novo* Cushing's disease (CD). Sustained remissions can be expected in 74–95% of affected patients (1–13). Other therapeutic modalities (*i.e.* hypophysectomy, irradiation, or adrenalectomy) are usually employed with limited success in patients with residual and recurrent disease and when patients are not candidates for surgical therapy (3, 4).

We have encountered several patients with CD due to ACTH-secreting pituitary macroadenomas who have been relatively more refractory to therapy than patients harboring ACTH-secreting microadenomas. Although numerous papers have been published describing the results of therapy for CD, they provide only limited information on the long term outcomes of therapy in macroadenoma patients. We, therefore, reviewed our experience with 24 patients harboring ACTH-secreting pituitary macroadenomas to answer several questions. 1) Are there true differences in the remission and recurrence rates following transsphenoidal surgery between macroadenoma and microadenoma patients? 2) Are there any preoperative predictors of either residual or recurrent disease in macroadenoma patients? 3) Can any long term benefit be derived from sequential primary and adjuvant therapy in macroadenoma patients?

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* Parts of this manuscript were previously published in long abstract form (17).

Subjects and Methods

Patient identification

A computerized database search identified 124 patients who had undergone transsphenoidal surgery at Emory University Hospital for treatment of presumed CD between 1972 and 1995 (Table 1). To our knowledge, no transfrontal procedures were performed on patients with CD during this era. We did not attempt to identify patients who had undergone primary treatment with other therapeutic modalities (*e.g.* radiotherapy or adrenalectomy) during the same period.

Pertinent information was abstracted from each patient's medical records and recorded on data collection forms. Telephone and written communications with patients and their physicians extended the follow-up periods when necessary.

Two patients with macroadenomas and 13 patients with microadenomas were excluded from the analysis because follow-up was not sufficient to decide their immediate postoperative status. Five patients, one with a macroadenoma and four with microadenomas, were excluded because their follow-up periods were less than 6 months; each of these patients, however, had clinical and biochemical evidence of remission at the time of their last assessment. Two patients subsequently diagnosed with ACTH-secreting bronchial carcinoid tumors were also excluded from the analysis.

Patient characteristics

The mean ages at the time of diagnosis were similar in macroadenoma patients and microadenoma patients (37 *vs.* 39 yr). The female to male ratio was 10:1 in macroadenoma patients and 4.5:1 in microadenoma patients. All patients had typical clinical features of CD, elevated 24-h

TABLE 1. Final diagnoses of 122 patients who underwent transsphenoidal surgery for Cushing's disease at Emory University Hospital, 1972–1995

	n	%
Microadenoma	92	75.4
Macroadenoma	24	19.7
Nelson's syndrome	2	1.6
Corticotroph hyperplasia	4	3.3

urinary free cortisol (UFC) levels, and either normal or elevated plasma ACTH concentrations. Dynamic studies (*i.e.* dexamethasone suppression, metyrapone, CRH stimulation tests, *etc.*) were performed according to standard testing protocols at the discretion of the treating physicians.

In the group of macroadenoma patients, the mean maximal tumor diameter was 1.6 ± 0.1 cm and ranged from 1.0–2.7 cm. Six patients had cavernous sinus invasion, and 3 had tumors invading the floor of their sella. Nine (41%) patients had suprasellar extension, but only 1 of these had documented visual field deficits. Hematoxylin- and eosin-stained slides of formalin-fixed paraffin-embedded tumor fragments from all patients were examined with the aid of a microscope by staff neuropathologists. Pituitary adenoma was confirmed in all 21 patients. Immunohistochemical preparations using polyclonal antibodies directed against ACTH were studied in 19 patients. All of these patients had ACTH-immunopositive tumors.

Statistical analysis

True Epistat 5.3 (Epistat Services, Richardson, TX), a medical statistics software package, was employed to organize data and perform statistical analyses.

Evaluable patients were classified as having either macroadenoma (maximum tumor diameter, ≥10 mm) or microadenoma. Afterward, they were grouped according to whether they had entered remission after transsphenoidal surgery or had residual postoperative hypercortisolism. Remission was defined as the presence of either frankly low postoperative serum cortisol levels (<5 μg/dL) or low UFC (<15 μg/24 h) requiring steroid hormone replacement for any period, and 6 months after transsphenoidal surgery, either normal cortisol suppressibility after the administration of dexamethasone or low plasma and urinary cortisol levels. Patients who had entered remission were then grouped according to whether they had remained disease free or had recurrent hypercortisolism during the follow-up period. Recurrence was defined as the development of Cushingoid features and biochemical evidence of pathological hypercortisolism (UFC >120 μg/24 h and abnormal dynamic endocrine tests) regardless of whether a pituitary tumor was demonstrated radiographically.

Differences between various groups were analyzed using the Mann-Whitney U test, two-tailed Student's *t* test, Fisher's exact test, or the two-sample χ^2 test when appropriate depending on the distributions and characteristics of the datasets compared. Stepwise multiple logistic regression employing various models was used to identify covariates predictive of either residual or recurrent disease. The probability of disease-free survival was estimated using the product-limit method of survival analysis according to Kaplan and Meier. Survival analysis was not extended beyond 96 months due to the small proportion of study patients remaining at risk for recurrence beyond that time. Cox proportional hazards analysis was employed in an attempt to identify covariates predictive of the disease-free survival time. The Wilcoxon test was employed to compare the estimated disease-free survival curves. Quantitative results are presented as the mean ± SEM.

Results

Initial transsphenoidal surgery

Remission was achieved in 14 of 21 (67%) macroadenoma patients after their initial transsphenoidal surgical procedure. Thus, 7 of 21 (33%) patients were considered primary treatment failures because of postoperative absolute or relative hypercortisolism. By way of comparison, remission was achieved in 68 of 75 (91%) microadenoma patients. The observed difference in remission rates is significant (67% *vs.* 91%; $\chi^2 = 5.7$; $P < 0.02$).

In macroadenoma patients, cavernous sinus invasion [odds ratio, 35; 95% confidence interval (CI), 2.6–475; $P < 0.008$) and presence of a maximum tumor diameter 2.0 cm or more (odds ratio, 12.9; 95% CI, 1.4–124; $P < 0.02$) emerged as the only predictors of residual disease after initial transsphenoidal surgery. Basal UFC, basal plasma ACTH concentration, age at diagnosis, duration of symptoms, and results of dexamethasone suppression testing were not significant predictors of residual hypercortisolism.

There were no postoperative deaths. No patient suffered from postoperative visual field deficits, cranial nerve injury, other neurological injury, hyponatremia, or meningitis within the first 30 days after surgery (Table 2).

Recurrent hypercortisolism

Five of 14 (36%) macroadenoma patients had clinical and biochemical evidence of recurrent hypercortisolism. By way of comparison, 8 of 68 (12%) microadenoma patients developed recurrent disease. The observed differences in recurrence rates between the 2 groups was significant (36% *vs.* 12%; $\chi^2 = 4.2$; $P < 0.05$).

Stepwise multiple logistic regression did not identify any predictors of disease recurrence in macroadenoma patients. Covariates tested in various models included age at the time of initial diagnosis, tumor size, presence of cavernous sinus invasion, results of baseline and postoperative urinary and plasma cortisol levels, and duration of postoperative adrenal insufficiency.

The probabilities of disease-free survival (persistent remission) over time after initial transsphenoidal surgery are depicted in Fig. 1. The differences between the estimated disease-free survival curves for macroadenoma and microadenoma patients were significant ($\chi^2 = 4.5$; $P < 0.04$). The mean time to recurrence in macroadenoma patients was 16 months and ranged from 10–57 months. The mean duration of follow-up for macroadenoma patients who remained in remission was 62 months and ranged from 12–164 months. The mean time to recurrence in microadenoma patients was 49 months and ranged from 8–142 months. The mean duration of follow-up for microadenoma patients who remained in remission was 49 months and ranged from 8–218 months. Cox proportional hazards analysis failed to identify

TABLE 2. Complications following initial transsphenoidal surgery in 22 patients with ACTH-secreting pituitary macroadenomas

	%
Diabetes insipidus	
Temporary	45
Permanent	9
Transient cerebrospinal fluid rhinorrhea	27
Permanent hypogonadism	14
Permanent hypothyroidism	14
Cardiovascular	14
Sinusitis	14
Abdominal wound infection	5
Epistaxis	5

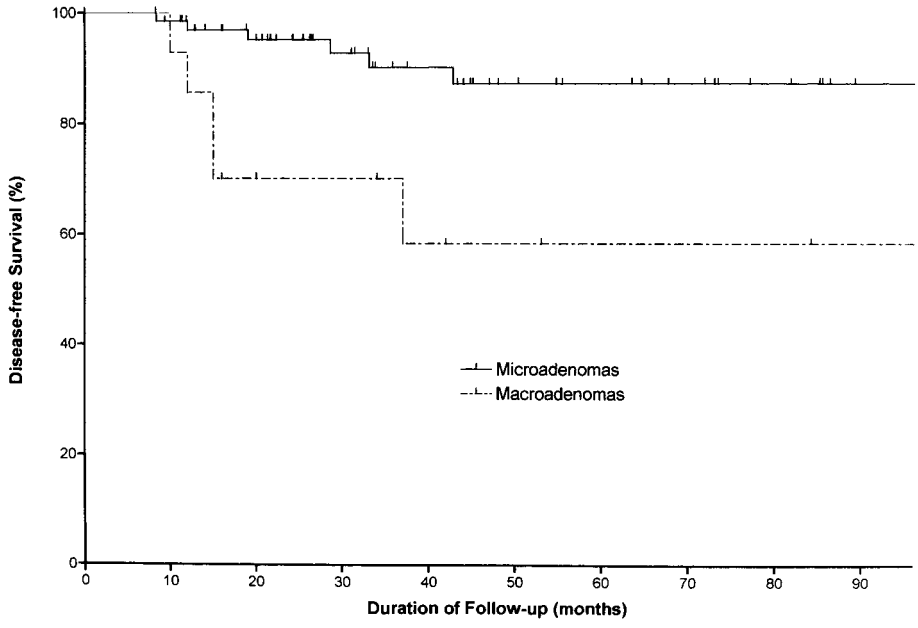

FIG. 1. Kaplan-Meier estimated disease-free survival curves for microadenoma (A) and macroadenoma (B) patients who entered remission after initial transsphenoidal surgery. The mean time to recurrence was 16 months for macroadenoma patients and 49 months for microadenoma patients.

any predictor of the disease-free survival time in macroadenoma patients.

Repeat transsphenoidal surgery

Four of seven macroadenoma patients with residual disease and radiographically evident tumors had repeat transsphenoidal surgery; one patient had a third similar procedure. Four of five patients with recurrent disease and obvious tumors had a second procedure. None of these nine repeat procedures on macroadenoma patients resulted in remission, whereas four of nine (44%) microadenoma patients entered remission after repeat transsphenoidal surgery (Fig. 2).

Adjuvant radiotherapy (XRT)

Five patients with residual disease and three patients with recurrent disease were treated with conventional XRT (4500–5020 cGy). One patient was lost to follow-up approximately 3 months after the completion of radiotherapy. Of the remaining seven patients, only four (57%) patients achieved normal UFC levels after XRT. The mean time of follow-up in the nonresponders was 42 months and ranged from 28–64 months. The mean time to normalization of UFC in the responders was 15 months and ranged from 2–27 months. Three (75%) of these four patients had re-recurrent hypercortisolism after brief periods of eucortisolism (7, 16, and 24 months, respectively). One patient is still in remission after only 9 months of follow-up. Three patients were treated with a second course of XRT (two stereotactic and one interstitial). They did not have subsequent improvement in their UFC excretion rates.

Adjuvant medical therapy

Nine of the 22 macroadenoma patients received adjuvant medical therapy during the follow-up period. Pharmacological agents were tapered or discontinued when necessary at the discretion of the treating physicians (*i.e.* to assess the patient's response to XRT).

Six patients were treated with ketoconazole. The duration of treatment ranged from 6 weeks to 29 months. Two patients developed self-limited hepatitis. Five of six patients achieved and maintained normal UFC for the duration of drug therapy. One patient has been treated with aminoglutethimide for 8 months and has a normal UFC. Two patients were treated with bromocriptine. One stopped the medication after only a short trial period because of sedation. The other patient maintained a normal UFC for 4 months, then developed recurrent hypercortisolism. Five patients were treated with a combination of cyproheptadine and bromocriptine. One patient has maintained a normal UFC for 33 months. Two patients enjoyed normalization of UFC for only 4 and 20 months, respectively. One patient had a partial response for 5 yr until a second surgical procedure was performed to debulk his tumor. Afterward, his residual hypercortisolism was abolished by continued combination therapy. Two patients were treated with metyrapone. One of these has achieved and maintained a normal UFC. The other patient was treated with metyrapone and ketoconazole, but remained hypercortisolemic.

Tumor progression resulted in breakthrough hypercortisolism in some of these patients, necessitating adjustment of drug doses. One patient's tumor progressed to invade the cavernous sinuses, compress the optic chiasm, and cause a frontal lobe syndrome during a period of prolonged medical therapy after two courses of XRT and two debulking surgical procedures.

Adjuvant adrenalectomy

Three patients required bilateral adrenalectomy because of intractable hypercortisolism. Two developed complications thought to be related to progressive tumor enlargement after adrenalectomy. One of these patients developed a cerebro-

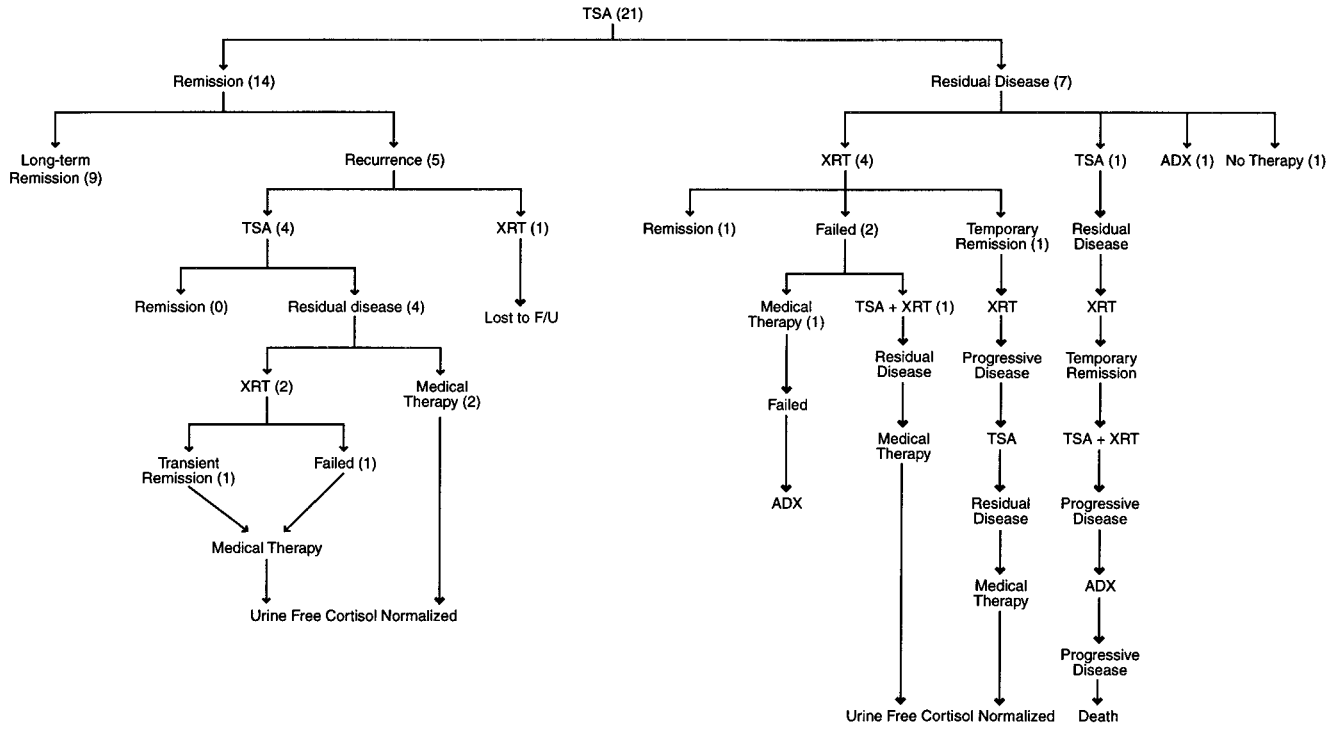

FIG. 2. Flow diagram summarizing the outcomes of therapy in 21 patients with ACTH-secreting pituitary macroadenomas. TSA, Transsphenoidal adenomectomy; ADX, adrenalectomy.

spinal fluid leak complicated by *Hemophilus influenzae* meningitis. She is now doing well after transethmoidal repair of the cerebrospinal fluid leak. The other patient died of coma and cardiorespiratory arrest attributed to brain stem compression by tumor that had also invaded the bones of the base of the skull. Both of these patients had been treated with XRT before adrenalectomy.

Discussion

Remission was achieved in only 67% of *de novo* macroadenoma patients with CD after transsphenoidal surgery at Emory University between 1972 and 1995. By way of comparison, 91% of *de novo* microadenoma patients with CD entered remission after surgery during the same time period. These observed differences in remission rates may be due to differences in biologic behavior (*i.e.* size and invasiveness) between the two tumor subtypes. In support of this contention, cavernous sinus invasion and the presence of a tumor 2.0 cm or more in diameter were characteristics associated with an increased likelihood of residual disease after surgery in our macroadenoma patients.

Mampalam *et al.* reported similar success rates in a review of the outcomes of transsphenoidal surgery in 216 patients with CD (3). They achieved remissions in 53% of macroadenoma patients and 88% of microadenoma patients. Nakane *et al.* also showed a higher initial surgical success rate in microadenoma patients than in macroadenoma patients (96% *vs.* 76%) (4). To our knowledge, neither these investigators nor others have systematically attempted to determine, as we have done, whether tumor size in macroadenoma patients is a reliable predictor of the results of surgery.

Nakane *et al.* reported that four patients with macroadenomas and cavernous sinus invasion remained hypercortisolemic after surgery; another similar patient suffered from recurrent disease (4). They did not, however, indicate whether other initially successfully treated macroadenoma patients had any evidence of cavernous sinus invasion. Thus, their observations do not permit one to make reliable estimates of the value of cavernous sinus invasion as a predictor of failure of transphenoidal surgery. In contrast, Bochicchio *et al.* recently reported the results of transsphenoidal surgery from a retrospective multicenter study of 668 patients with Cushing's disease conducted by the European Cushing's Disease Survey Study Group (13). They showed that tumor size, invasiveness, and extrasellar growth did not influence the outcomes of surgery. Their report does not, however, indicate whether they studied macroadenoma patients (20.7%; ~138 patients) independently of the microadenoma patients to determine whether any preoperative variables might be predictive of residual disease, recurrence, *etc*. We anticipate that such an analysis would confirm our findings and contribute further to our understanding of the clinical behavior of ACTH-secreting pituitary macroadenomas.

Recurrent hypercortisolism was more common in our macroadenoma patients than in our microadenoma patients (36% *vs.* 12%). Overall, disease recurrences were evident much earlier in macroadenoma patients than in microadenoma patients (mean time to recurrence, 16 *vs.* 49 months). Recurrences were characterized by periods of postoperative adrenal insufficiency followed by transient periods of normal adrenal function during which the urinary corticosteroid excretion rates increased over time, and then by the development of frank hypercortisolism. These observations suggest that recurrences are probably due to progressive growth

of unresected or residual adenomatous tissues rather than to the development of second neoplasms. It appears that in these patients, near-total tumor resection reduces residual tumoral ACTH secretion to levels below those necessary to maintain normal adrenal function. The expected postoperative adrenal insufficiency ultimately resolves as tumoral ACTH secretion progressively increases and cortisol production rates are restored to normal. Recurrent CD is then diagnosed once tumoral ACTH secretion increases to a degree capable of resulting in clinical and biochemical features of adrenal hyperfunction. We were unable to identify any pre- or postoperative predictors of recurrent disease or of a shortened disease-free survival time in macroadenoma patients. In contrast, Bochicchio *et al.* have shown that the likelihood of recurrence is greater in patients with postoperative cortisol levels in the higher part of the normal range than in patients with undetectable postoperative cortisol levels (13). They also showed that the duration of postoperative glucocorticoid replacement therapy is inversely correlated with the risk of recurrent hypercortisolism (13).

Repeat transsphenoidal surgery did not induce remissions in any of our macroadenoma patients with either recurrent or residual disease. Repeat surgery did, however, play an important role in the management of tumor-related mass effects and resulted in beneficial reductions in urinary corticosteroid excretion rates followed by improvement in clinical indicators of disease activity in some patients. In contrast, four of nine (44%) patients with microadenomas entered remission after repeat transsphenoidal surgery. Thus, repeat transsphenoidal surgery seems justified in some patients suffering from residual and recurrent CD regardless of the size of the tumors.

Conventional XRT was not effective in achieving long term remissions in macroadenoma patients with either residual or recurrent disease but did, however, result in a beneficial transient lowering of corticosteroid excretion rates in some patients. The effects of adjuvant XRT were assessed in apparent nonresponders while they were still taking adrenal steroid biosynthesis inhibitors. Thus, the efficacy of XRT in this study, as judged by posttreatment urinary corticosteroid excretion rates, cannot be expressed as a function of the pretreatment values (*i.e.* percentage of the basal or pretreatment value). Published remission rates in patients with tumors of varying sizes and CD range from 23–83% (14–16). We are unaware of other reports documenting similar poor responses to XRT in a large group of macroadenoma patients with CD.

Our limited experience with adrenalectomy in macroadenoma patients suggests that they may be at increased risk for devastating complications related to progressive growth of residual tumor after correction of their hypercortisolism. Similar tumor progressions were seen in at least two of our patients treated with pharmacological agents. Most of these patients had been treated with adjuvant XRT before measures to lower their cortisol levels. We can only speculate that their tumors may have progressed more rapidly had they not been previously irradiated. Several investigators have shown a decreased incidence of Nelson's syndrome after adrenalectomy in CD patients previously treated with XRT (2, 16). Thus, it seems prudent to treat patients harboring ACTH-secreting macroadenomas with XRT before adrenalectomy or therapy with inhibitors of cortisol biosynthesis.

In summary, patients with CD due to ACTH-secreting macroadenomas are more refractory to conventional treatments than are patients with ACTH-secreting microadenomas. They are less likely to enter remission after initial transsphenoidal surgery and are more likely to suffer from recurrent disease than are microadenoma patients. Repeat surgery and adjuvant conventional XRT are useful in the management of problems related to tumor mass and may result in improvement in the clinical and biochemical indexes of disease activity in macroadenoma patients. These modalities, however, are not likely to result in either complete eradication of tumor or persistent clinical and biochemical remission. Relief of hypercortisolism by adrenalectomy or pharmacological agents results in dramatic resolution of the clinical features of affected patients, but may be followed by devastating complications related to progressive growth of residual tumor despite pretreatment with conventional XRT.

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