Long-term results in transsphenoidal removal of nonfunctioning pituitary adenomas

MICHAEL J. EBERSOLD, M.D., LYNN M. QUAST, R.N., EDWARD R. LAWS, JR., M.D., BERNDT SCHEITHAUEI~ M.D., AND RAYMOND V. RANDALL, M.D.

Department of Neurologic Surgery, Mayo Clinic, Rochester, Minnesota

Little has been written about the long-term results of transsphenoidal treatment for clinically nonfunctioning pituitary adenomas. The records of 100 patients who had undergone a transsphenoidal procedure for excision of such tumors were reviewed. ImmunocytoLOGY for pituitary hormones was performed in all cases. The group consisted predominantly of null-cell adenomas, although a small number of prolactinomas and gonadotropic tumors were found. The mean diameter of the tumors at the time of detection was slightly more than 2 cm. In most cases, the presenting symptoms were due to the mass effect of the tumor (that is, visual symptoms in 72 patients, hypopituitarism in 61, headache in 36, and cranial nerve disturbance other than visual loss in 10). Radiation therapy was recommended for patients in whom subtotal removal of the adenoma was expected. Six patients developed symptomatic tumor recurrence, and 10 patients demonstrated radiographic recurrence during the 48 to 100 months (mean 73.4 months) of follow-up observation. Only three of 10 deaths during the follow-up period were due to pituitary disease or treatment.

KEY WORDS • transsphenoidal surgery • pituitary adenoma • long-term results

P ITUITARY adenomas associated with acromegaly, hyperprolactinoma, Cushing’s disease, and Nelson’s syndrome have the capability of extending outside the sella turcica to produce serious intracranial problems. The hormonal effects of these lesions are generally detected when the adenomas are small. In contrast, clinically nonfunctioning adenomas often extend beyond the sella before producing symptoms that result in evaluation and detection. There are many recent reviews on the results of transsphenoidal surgical treatment of pituitary adenomas, but most of them deal with adenomas that cause hyperprolactinemia or Cushing’s disease, or acromegaly.

To date, little has been written about the effectiveness of surgical treatment of nonfunctioning macroadenomas. In our practice, transsphenoidal removal is currently accepted as the procedure of choice for the initial management of most clinically nonfunctioning pituitary adenomas, even when they are quite large in size and manifest suprasellar extension. The records of 100 consecutive patients with clinically nonfunctioning pituitary adenomas who had undergone a transsphenoidal operation between August, 1975, and June, 1980, were reviewed to evaluate the effectiveness of this procedure.

Clinical Material and Methods

Histology and Immunocytochemistry

Paraffin blocks of adenomas and, in some cases, nontumoral adenohypophyseal tissue from all 100 subjects were retrieved from the Mayo Clinic Tissue Registry. The formalin-fixed specimens consisted in part of frozen and unfrozen tissues. Microsections, cut at 5 μ, were then stained by the hematoxylin and eosin, periodic acid-Schiff (PAS), and the Gomori reticulin methods. Within null-cell adenomas, particular attention was focused upon the extent of oncocytic transformation (that is, cytoplasmic mitochondrial accumulation) as evidenced by eosinophilia, granularity, and increased cell size.

Commercially available antisera were used to stain microsections by the peroxidase-antiperoxidase method of Sternberger, et al., for prolactin (PRL), follicle-stimulating hormone, and luteinizing hormone. In view of the absence of relevant clinical features, immunostaining for growth hormone (GH), adrenocorticotropic...
hormone (ACTH), and thyroid-stimulating hormone (TSH) was not routinely performed. In cases with PRL immunoreactivity, GH and TSH immunostaining was performed to identify plurihormonal adenomas. Since the vast majority of corticotrophic adenomas, either functional or silent, are PAS-positive, stains for ACTH were selectively applied only to tumors showing PAS-reactivity.

Appropriately fixed tissues for electron microscopy were not available, and thus no ultrastructural studies were performed in any case.

**Clinical Aspects**

The ages of the 100 patients with nonfunctioning adenomas ranged from 14.5 to 78 years (median 57 years). There were 74 males and 26 females (Table 1). This sex distribution is in contrast to that of patients with prolactinomas, which until about 10 years ago frequently were considered to be nonfunctioning tumors. To eliminate patients with prolactinomas from this review, we excluded all patients with prolactin values greater than 50 ng/ml. We recognized that this measure may also have excluded some patients with nonfunctioning adenomas with elevations above 50 ng/ml prolactin due to compression of the pituitary stalk.

Unlike the patients with hormonally active pituitary adenomas, the patients with nonfunctioning adenomas presented primarily with symptoms secondary to the lesion itself (Table 2). The most common presenting complaint was loss of vision, which occurred in most of the 72 patients who had visual abnormalities. Many of these patients were not aware of their visual loss until it was demonstrated on a routine eye examination; this finding resulted in their referral to the Mayo Clinic. Symptoms that were considered to be due to hypopituitarism occurred in 61 patients; this disorder was subsequently confirmed with laboratory tests. Of these 61 patients, 36 complained of disturbances of sexual function, 32 had symptoms related to hypothyroidism, and 17 had symptoms of inadequate production of adrenal steroids. Fifteen patients were found to have parahypopituitarism. At the time of the initial evaluation, 36 patients complained of headache. Ten patients presented with cranial nerve disturbances that resulted in further evaluation and diagnosis of the pituitary tumors. Of these 10 patients, five had third nerve palsies, one had facial pain, two had decreased hearing, and one had loss of the sense of smell. The hearing deficits and loss of the sense of smell were not believed to be related to the pituitary adenoma. Five patients had a rapid onset of symptoms with neurological findings that suggested pituitary apoplexy. None of the patients had diabetes insipidus.

We were impressed with the degree of visual loss that was frequently found in these patients. The insidious growth of the tumors seemed responsible for the slowly progressive visual and hormonal disturbances that were frequently severe at the time of the initial evaluation. Examination of the 72 patients with symptoms of visual loss demonstrated that eight had quadrantic defects that were essentially unilateral and 58 had various degrees of bitemporal hemianopsia. Two of these patients had unilateral blindness with a field cut in the other eye. Three patients with diplopia had deficits of the third cranial nerve.

As radiographic evaluation of pituitary tumors and the resolution of computerized tomography (CT) have evolved, our confidence and experience with the interpretation of CT scans have improved. Some of the early patients in this review underwent pneumoencephalography, and most had undergone sellar tomography or angiography. Currently, we believe that CT with and without contrast enhancement and a lateral skull roentgenogram are adequate in most instances. Angiography is reserved for patients with extensive suprasellar extension, for patients in whom the diagnosis is in doubt, and for patients in whom a vascular lesion such as an intrasellar aneurysm is of concern. Frequently, digital subtraction angiography will provide adequate additional information and render conventional arteriography unnecessary. Although further advances and understanding will undoubtedly increase the information gained with magnetic resonance imaging of pituitary adenomas, we have not found that this procedure, using first-generation scanning, significantly alters the diagnosis and the treatment of such lesions.
Results of transsphenoidal excision of pituitary adenoma

### Pathological Findings

The immunocytochemical reactivity of all 100 tumors is summarized in Table 3. Eighty-two adenomas were found to be PAS-negative and basically nonimmunoreactive. Because such tumors, in our experience, regularly exhibit lack of ultrastructural differentiation, they are reasonably considered null-cell adenomas. Since immunoreactivity is negatively affected by freezing artifacts, particularly that of glycoprotein hormones, the low proportion of gonadotropic adenomas in this series (4%, as compared to an anticipated 15% to 20%) may be due to loss of immunoreactivity resulting in an apparent increase in the number of null-cell adenomas. In 14 of these lesions, less than 5% of cells were found to be immunoreactive for glycoprotein hormones, and far fewer yet for prolactin. Among the null-cell adenomas, oncocytic transformation was absent in 49%, variable in 30%, and fully developed in 21% of the tumors. No correlation was observed between oncocytic change and patient age, tumor size, or frequency of recurrence.

Of particular interest among the 100 clinically nonfunctional or hormonally silent tumors under study was the finding of nine prolactinomas, four gonadotropic adenomas, two silent corticotrophic adenomas, and one plurihormonal adenoma. The latter tumor demonstrated immunoreactivity for PRL as well as TSH. Two tumors were necrotic, thus precluding assessment.

### Clinical Findings

The follow-up period for the 100 patients ranged from 48 to 100 months (median 73.4 months). Ten patients died during this period, two during the first 30 days after operation (Table 4). The deaths were caused by intraoperative hemorrhage in one case and delayed postoperative hemorrhage in the other.

Interestingly, all 36 patients who presented with headache at the time of the initial evaluation noted relief after surgery. Of the 72 patients who presented with visual loss, 53 noted improvement, 15 remained stable, three patients had additional visual loss after the procedure, and one died. Two of these patients had received radiation therapy prior to the transsphenoidal operation. Two patients acquired hydrocephalus secondary to subarachnoid blood and required a cerebrospinal fluid (CSF) shunting procedure.

Paraparesis, possibly secondary to vasospasm and cerebral ischemia, occurred postoperatively in one pa-

### Table 3

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. of Cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>null-cell adenoma</td>
<td>82</td>
</tr>
<tr>
<td>prolactinoma</td>
<td>9</td>
</tr>
<tr>
<td>silent corticotrophic adenoma</td>
<td>2</td>
</tr>
<tr>
<td>gonadotropic adenoma</td>
<td>4</td>
</tr>
<tr>
<td>plurihormonal adenoma (PRL-TSH)†</td>
<td>1</td>
</tr>
<tr>
<td>nonassessable (necrosis)</td>
<td>2</td>
</tr>
</tbody>
</table>

* The high proportion of null-cell adenomas and the inordinately low number of gonadotropic tumors may be due to frozen-section artifact affecting immunoreactivity.
† PRL = prolactin; TSH = thyroid-stimulating hormone.

### Table 4

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>operative death (30 days)</td>
<td>2</td>
</tr>
<tr>
<td>intraoperative hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>delayed postoperative hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>heart disease</td>
<td>1</td>
</tr>
<tr>
<td>recurrence of pituitary tumor</td>
<td>1*</td>
</tr>
<tr>
<td>lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>lung cancer</td>
<td>1</td>
</tr>
<tr>
<td>liver failure</td>
<td>1</td>
</tr>
<tr>
<td>unknown (nonpituitary)</td>
<td>1</td>
</tr>
<tr>
<td>stroke 3 yrs postop</td>
<td>1</td>
</tr>
<tr>
<td>postop pulmonary emboli</td>
<td>1†</td>
</tr>
<tr>
<td>total cases</td>
<td>10</td>
</tr>
</tbody>
</table>

* This patient had progressive brain-stem compression after surgery, radiation therapy, and bromocriptine administration.
† This patient suffered a pulmonary embolism after cholecystectomy, 18 months after a second transsphenoidal procedure.
Effects of Radiation Therapy

An effort was made to evaluate the effects of radiation therapy; however, the number of patients in the various groups was small, making it impossible to gain data that had statistical significance. A total of 58 patients received radiation therapy. Eight of these patients received radiation therapy prior to being evaluated and treated at the Mayo Clinic. Of the remaining 50 patients who received radiation therapy after transsphenoidal surgery at the Mayo Clinic, nine were demonstrated to have radiographic evidence of pituitary tumor recurrence. Only three of these patients, however, had a symptomatic recurrence, two of which required repeat transsphenoidal surgery. The remaining patient was treated with bromocriptine.

Forty-two patients did not receive radiation therapy after their initial transsphenoidal surgery at the Mayo Clinic. Five had radiographic evidence of recurrence, and three were symptomatic, again requiring treatment. Twelve percent of patients who did not receive radiation therapy and 18% of those who did showed radiographic evidence of tumor recurrence. It is important, however, to realize that radiation therapy was only recommended when it was thought that an inadequate tumor removal had been accomplished during surgery because of cavernous sinus invasion, invasion of the dura, massive size of the adenoma, or residual tumor apparent on CT scanning in the postoperative period. Actually, radiation therapy probably does have a beneficial effect since the difference in radiographic recurrence rate was rather minimal and the number of symptomatic recurrences was the same in the two groups. These data do suggest, however, that radiation therapy in itself does not prevent recurrence, even when the tumor is significantly debulked. The data also suggest that we cannot count absolutely on clinical impression at the time of surgery or even on follow-up CT scans to confirm total tumor removal since five of 42 patients who were thought to have total removal did develop recurrent pituitary adenomas. A review of the 50 patients who received radiation therapy after transsphenoidal surgery did not reveal any apparent complications from such therapy in the follow-up period, suggesting that the morbidity associated with postoperative radiation therapy is probably quite small. No conclusion can be stated concerning 60Co versus linear accelerator treatment. We have seen several cases of biopsy-proven radiation necrosis involving the hypothalamus and optic apparatus in patients who have received as little as 5500 rads of radiation therapy, but current data and reviews of our patients as well as other clinical series suggest that such a complication is quite rare.

Discussion

Surgical Technique

Transsphenoidal surgical techniques have been well described, however, because so many patients in this series had large tumors with suprasellar extension, some technical comments are appropriate. The x-ray image-intensifier was used in every case, and all patients with significant suprasellar extension had a lumbar needle or catheter in place so that air could be injected and CSF removed during the procedure. Wide exposure of the sella from one cavernous sinus to the other, and from the clivus to the floor of the anterior fossa was considered essential. Once the intrasellar portion of the tumor was excised and any lateral extensions into the cavernous sinuses were removed, 5 to 10 cc of air was injected into the lumbar subarachnoid space. The patient was positioned so that the air would enter the head and outline the interpeduncular and chiasmatic cisterns. When the air injection was successful, the posterior and superior surfaces of the intracranial portion of the tumor could be visualized with the image-intensifier. Additionally, the increase in intracranial pressure

<table>
<thead>
<tr>
<th>TABLE 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs and symptoms of recurrence of pituitary adenoma in 16 patients</td>
</tr>
<tr>
<td>Signs &amp; Symptoms*</td>
</tr>
<tr>
<td>visual loss</td>
</tr>
<tr>
<td>apoplexy</td>
</tr>
<tr>
<td>dementia</td>
</tr>
<tr>
<td>headache</td>
</tr>
<tr>
<td>cranial nerve loss</td>
</tr>
<tr>
<td>asymptomatic (demonstrated on routine follow-up CT scans)</td>
</tr>
</tbody>
</table>

* These symptoms developed 15 months to 4 years after initial surgery. CT = computerized tomography.
Results of transsphenoidal excision of pituitary adenoma

produced by the air drove soft suprasellar tumor extensions into the sella, allowing for safe removal of some very large tumors (Fig. 1). In some cases, once gross tumor had been removed, the diaphragma sellae or tumor capsule was expanded by removal of CSF, allowing atmospheric pressure to fill the capsule with air from below. A dental mirror was sometimes used to search for pockets of unresected tumor. The greatest deterrent to successful removal of the intracranial portions of these tumors was a CSF leak early in the dissection, and it was found desirable to work within tumor tissue as long as possible so as to avoid inadvertent rupture of the diaphragm. Topical alcohol as a means for eradicating residual tumor was not employed in any of these cases.

The techniques utilized for closure were similar whether or not a CSF leak had occurred. The empty sella was filled with homograft or autograft muscle or fat. Muscle was generally preferred because of its hemostatic properties. The philosophy was generally one of obliterating dead space and reconstructing anatomical structures when possible. The sella floor was reconstructed with a tailored plate of nasal bone or cartilage. Special effort was taken to insert the plate epidurally if a CSF leak had occurred. The sphenoid sinus was packed with muscle or fat only when a large CSF leak had been created. On occasion, firm inaccessible suprasellar tumor was left in place and no CSF leak or significant bleeding resulted; in such cases, the sella was left empty so that tumor could gradually extrude into the sella. Fascia was not found helpful in this closure technique. When there was inadequate nasal cartilage or bone available, bank bone or plates fashioned from methyl methacrylate were used (Fig. 1).

Outcome

Of the 61 patients with inadequate preoperative pituitary function, 10 had postoperative improvement and did not require replacement hormonal therapy. The recovery of pituitary function after the removal of nonfunctioning pituitary adenomas has also been noted by others.1

Although 16 patients had apparent residual or recurrent pituitary adenoma, only six had recurrent symptoms during the follow-up period. Seven of the 100 patients died from disease other than pituitary tumor. Fewer patients died as a result of the pituitary operation or pituitary disease than from other causes. There were two operative deaths, and one patient died subsequently of recurrent tumor. Although total removal of pituitary adenomas with the transsphenoidal technique is not always possible, prolonged symptom-free intervals can frequently be achieved. Earlier work by MacCarty, et al.,24 suggests that radiation therapy decreases the recurrence rate, but we did not attempt to confirm this hypothesis because all patients with known or suspected residual adenoma were advised to have radiation therapy.

Despite current or future surgical advances, total removal of an adenoma will probably not be possible in some patients. However, the symptomatic recurrence rate of only 6% in our study indicates that further treatment may not be needed in all patients with residual adenoma. Certainly, progressive clinical and/or radiographic evidence of tumor growth can be demonstrated many years after initial treatment.24 Ten of the initial 100 patients in this review have asymptomatic radiographically apparent tumors, and others may later have radiographic or clinical evidence of tumor. We therefore recommend prolonged follow-up monitoring, even in the postoperative patient who appears free of pituitary adenoma.

Pathological Considerations

As expected, the majority of clinically nonfunctional or hormonally silent pituitary adenomas comprising this series were of the null-cell type, defined as clinically nonfunctional and essentially immunocytochemically nonreactive tumors. Such adenomas show characteristically poor ultrastructural differentiation. Microscopically, most (49%) of these tumors were typical chromophob adenomas. Mitochondrial accumulation in others resulted in increased cell size and acidophilia, indicating oncocytic transformation. Such change was variable in 30% and fully developed in 21%; no significant correlation with patient’s age, tumor size, or frequency of recurrence was observed. Limited differentiation, as evidenced by focal glycoprotein or prolactin immunoreactivity, is known to occur in null-cell adenomas and was observed in this series with a frequency of 17%. Such focal expression of hormone production is nevertheless consistent with the diagnosis of null-cell adenoma but, as previously noted, some of these might be gonadotropic tumors in which the effects of a freezing artifact mask full immunoreactivity.
The finding of prolactinomas in the group under study was not surprising; most occurred in male patients in whom the hormonal effects of hyperprolactinemia frequently go unnoticed. Their presence illustrates that, despite the usual correlation observed between prolactin levels and tumor size,22 serum prolactin levels need not be proportional to tumor bulk. In addition, significant overlap is observed in the elevation of prolactin levels attributed to the effects of pituitary stalk compression and that due to tumoral secretion. Our experience indicates that prolactin levels in excess of 200 mg/ml are regularly associated with a prolactin-producing adenoma.

Corticotrophic adenomas that are unassociated with clinical hyperfunction have only lately been characterized.12-14 Two examples were found in this series, one of which recurred. Such “silent corticotrophic adenomas” show the histochemical and immunocytochemical features associated with ACTH-producing tumors but are unaccompanied by elevated serum levels or clinical evidence of Cushing's disease. Unlike functional corticotrophic adenomas, the silent tumors are often large and reportedly show an increased tendency to spontaneous infarction as well as recurrence.

Four gonadotropic tumors were encountered but none recurred. The clinicopathological profile of these tumors has only recently been reported.13,35 Such adenomas characteristically occur in older patients and in the setting of gonadal failure. The most frequently noted symptoms are chiasmal compression34 and hypopituitarism; hyperfunction has not been recognized. Our preliminary experience with 40 gonadotropic adenomas suggests that, despite their frequently large size, they tend to compress and displace rather than grossly invade surrounding structures, and show little propensity to recur.

A single plurihormonal adenoma was observed in our study. The tumor subsequently recurred. Such tumors constitute approximately 10% to 15% of all pituitary adenomas in our institutional experience.31 Most (83%) of these tumors are associated with GH production and acromegaly, although coexisting lactotrophic and glycoprotein components are commonly seen.7 The effects of prolactin hypersecretion are apparent in only 20% of patients, whereas clinical evidence of glycoprotein hypersecretion is rare.

Acknowledgment

We express our appreciation to Mrs. Rose Comero of the laboratory of immunocytochemistry for excellent technical assistance.

References

Results of transsphenoidal excision of pituitary adenoma


Manuscript received August 10, 1984. Accepted in final form January 13, 1986. This work was supported in part by a generous contribution from Mr. and Mrs. James L. Wooters.