

EXTENSIVE PERSONAL EXPERIENCE

Surgical Management of Pituitary Tumors

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Having performed 3000 transsphenoidal procedures during the past 27 years, almost all of them for pituitary adenomas, I have been asked to give a surgical perspective on this small but important aspect of endocrine practice. In preparing this retrospective, I was freed from the customary journalistic format to present a personal perspective on surgical management that may prove helpful to endocrinologists in making decisions about the treatment of patients for whom surgery is a consideration.

The procedure

Transsphenoidal surgery has become an operation with remarkably little morbidity and exceptionally low mortality rates. Hospital stays of 2 days are standard, and selectively patients are being discharged even earlier. Patients whose jobs are not physically demanding can usually return to work within 1 to 2 weeks after surgery. To be sure, complications, both minor and major, occur even in the most experienced hands. As one example postoperative loss of pituitary function, whether categorized as a side effect or a complication, is a serious concern in a patient of any age, but most critically in children and young adults. Considering the benign behavior of most pituitary adenomas, the preservation and possible improvement of anterior pituitary function assumes a priority equal to that of avoiding injury to critical parasellar structures.

I subscribe to the principle of specialized care, and if it makes sense for interested internists to acquire special knowledge and experience in endocrinology, it seems reasonable to apply the same rationale to specialization in pituitary surgery. Particularly in neurosurgery practice makes perfect, and I advocate concentrating, rather than diffusing, surgical referrals—not in the sense of creating “centers”, but by encouraging one of several neurosurgeons in larger communities to become the local expert in pituitary surgery. There is no question about it: such a plan for referrals for pituitary surgery can provide improved outcomes for your patients. Has managed care, including capitated care, complicated the referral process? Unquestionably it has, but I hardly need to remind you that inexpert pituitary surgery

can be *very* expensive, in both the short term and the long term. Care of high quality is rarely cost-ineffective, particularly in the care of children and patients with Cushing's disease. Endocrinologists have a critical role in the diagnoses, preoperative preparation, and postoperative management of *all* patients with pituitary adenomas. The short- and long-term followup of every patient treated by surgery is best placed in the hands of an endocrinologist because critical decisions regarding recurrence of endocrine-active adenomas and the subtleties of anterior pituitary insufficiency require continuous monitoring by an expert for optimal outcomes.

Pathology

I am an advocate of immunostaining. At the University of California, San Francisco (UCSF) we do immunostaining routinely on all pituitary adenomas, even though it provides critically important information in only a minority of cases. Without immunostaining, for example, nodular corticotrophic hyperplasia might go undetected; and in the case of a large nonsecreting adenoma associated with hyperprolactinemia as a nonspecific effect of the compression and distortion of dopaminergic vascular pathways, the adenoma might be mistaken for a prolactin (PRL)-secreting adenoma and could be managed incorrectly. Only immunostaining differentiates an endocrine-inactive adenoma from a prolactinoma, each of which is managed quite differently.

In Table 1 is shown the distribution of tumor cell types in my own series of adenomas. Tumors are classified as either endocrine-active or endocrine-inactive based on their clinical presentation. For several reasons, the distribution of cell types does not reflect the true proportion of cell types in the universe of pituitary adenomas. As this is a series of tumors removed surgically, it does not include recognized but asymptomatic (“incidental” or “silent”) adenomas, or PRL-secreting adenomas that are managed satisfactorily by medical means and therefore not referred for surgery. Persistent or recurrent adenomas operated on after failed initial surgical procedures are not distinguished in the table, although the relative proportions of tumor types are no different for the secondary than for the primary procedures. Most adenomas of mixed endocrine-active cell types involved PRL and another cell type—either adrenocorticotrophin (ACTH), growth hormone (GH), or thyrotrophin (TSH); and in each instance the tumor was classified according to the other cell type, rather than as a PRL-secreting adenoma. Tumor type

Received January 8, 1997. Revision received May 6, 1997. Accepted May 21, 1997.

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TABLE 1. Pituitary adenomas: transsphenoidal resection in 2732 operations (1968–1996)

Adenoma and hormone secreted	Number	Percent
Endocrine-active (total)	1924	70
PRL	1021	37
ACTH	461	17
GH	422	15
TSH	20	1
Endocrine-inactive (total)	808	30
Total	2732	100

PRL, prolactin; ACTH, adrenocorticotrophin; GH, growth hormone; TSH, thyrotrophin.

for the adenomas in the other categories was determined by the presenting endocrinopathy. Finally, because of an institutional interest in Cushing's disease and a large pediatric endocrinology group at UCSF, the proportion of ACTH-secreting adenomas in the series, particularly those in children, is misleadingly high.

Categorized under endocrine-inactive adenomas are those adenomas that were recognized by their clinical presentation as a mass compressing either the anterior pituitary gland or extrasellar structures, presentation only with headache being one characteristic of the latter group. Although immunostaining revealed that many tumors contained one or several cell types, as determined by the presence of secretory granules or their appropriate ultrastructural characteristics, in none was a secretory syndrome associated with the mass effect. In contrast to immunostaining, in my experience routine α -subunit determination has been expensive and valueless in practice.

Prolactin-secreting adenomas

The prolactinoma is the only pituitary adenoma for which medical management in the long term is fully satisfactory, and for that reason the proportion of patients with prolactinomas referred for surgical consultation varies widely in different geographic regions. I assume that the proportion of patients referred for surgical consideration in Northern California represents an approximation of general practice. The referred group in my practice includes patients who have unacceptable side effects caused by medication, patients with dopamine-insensitive adenomas, and those patients who, after becoming informed, for personal reasons select surgical over medical management. In a significant proportion of patients referred to me for surgical consultation, I have advised medical over surgical management based on gender, age, and the probability of a surgical cure—"cure" in the sense of long-term freedom from recurrence.

In Table 2 are shown the indications I follow in recommending surgical removal of a microadenoma, and in Table 3 are shown the indications for removal of a macroadenoma. These indications for both small and large adenomas reflect my experience as well as my biases. Based on the basal PRL value and a high-resolution magnetic resonance MR image I can predict the likelihood of a surgical cure. If cure is not possible because of extrasellar spread, almost always on the basis of cavernous sinus invasion, surgery is not advised unless the patient fails to respond to medical management. When there is no likelihood of a surgical cure, surgery has the

TABLE 2. Surgical indications for prolactin-secreting microadenomas

Personal choice
Intolerant of medication at an effective dose
Desire for pregnancy ^a
Inadequate response (resistance) to medication
Primary amenorrhea
Prolactin value of 200 μ g/L
Male sex
Extrasellar extension (suprasellar or intrasphenoid) ^b

^a Rarely do microadenomas become symptomatic in the course of pregnancy. However, the microadenoma may expand during pregnancy without symptoms, most patients are still young, the likelihood of cure will never be better, and in my referral area a number of endocrinologists and gynecologists refer patients in this category to consider surgery as an alternative to medical treatment.

^b This is rare, but a microadenoma that originates on the surface of the anterior lobe may extend beyond the sella, and the likelihood of a surgical cure is greater with small tumors if for any reason medical management is rejected because of intolerance or personal choice.

TABLE 3. Surgical indications for prolactin-secreting macroadenomas

Personal choice (pattern of growth does not preclude surgical cure)
Unsuccessful trial of medication
a. with potential for cure
b. without potential for cure but bulk reduction advised to lower the effective dose of medication
Desire for pregnancy when an earlier pregnancy was complicated by symptomatic expansion of tumor

focused objective of reducing the adenoma's mass, either to reduce the production of PRL to a level that can be further reduced into a desirable range by a tolerated dose of a dopamine agonist or to relieve symptoms of compression and reduce the bulk of the adenoma before irradiation. Because prolactinomas continue to secrete PRL for several years after being rendered sterile by radiation therapy, irradiation is a poor and much delayed means of treating the hyperprolactinemic syndrome.

Unless a PRL-secreting adenoma is cystic, partly necrotic, or contains a significant collection of blood, the levels of PRL in the blood accurately reflect the tumor's size. Furthermore, the preoperative basal PRL value provides an accurate prediction of outcome, the probability of surgical cure having a directly inverse relationship to basal PRL value. An even more accurate prediction of outcome is provided by the immediately postoperative PRL value, obtained 1–2 days after surgery: an unmeasurable (<2 μ g/L) value predicts a cure with more than 90% probability, and higher values within the normal range are inversely related to probability of cure (1). Postoperative values even slightly above the upper limit of the normal range indicate incomplete removal of the adenoma.

Dopamine agonists, such as Parlodel (Sandoz Pharmaceuticals, Hanover, NJ), inhibit tumor-cell replication in the great majority of prolactinomas, and for that reason patients should be treated indefinitely with Parlodel. Often a dose as low as 1.25 mg, taken at bedtime, is sufficient to maintain or restore normal PRL levels and prevent tumor regrowth if the residual volume of adenoma is small or if the adenoma is

highly dopamine-sensitive. In all cases involving incompletely removed or recurrent PRL-secreting tumors, long-term administration of a dopamine agonist is the first line of treatment. Irradiation is reserved for those few patients who have adenomas refractory to medical therapy and for the larger number of individuals who cannot tolerate the medication.

Growth hormone-secreting (somatotrophic) adenomas

For almost three decades, the preferred primary treatment for the patient with acromegaly has been surgery. In occasional cases of acromegaly, uncontrolled diabetes, hypertension, or congestive heart failure may counsel against anesthesia, and in such cases preoperative medical preparation, including somatostatin, may be advisable. Still, today (with the exception of such cases) the initial and usually definitive treatment for acromegaly is transsphenoidal surgery. As a general rule, younger patients have larger tumors and higher basal growth hormone (GH) values, whereas older patients with acromegaly are more likely to have smaller tumors and lower, or even normal, random GH values.

Technically, surgery for acromegaly is often difficult. Because of the greater distance from the patient's lip to the sphenoid sinus, a longer speculum is required in many cases. The anesthesiologist must be forewarned of the difficulty often encountered in introducing an endotracheal tube because the enlarged tongue, uvula, and epiglottis of patients with acromegaly and their thickened vocal cords may catch the anesthesiologist unawares, resulting in crisis if pharmacological apnea rapidly produces hypoxia when intubation proves to be difficult.

Many patients with acromegaly have chronic sinusitis, and as a consequence the nasal and sinus mucosa is thickened and difficult to manage. However, the surgeon's biggest concern is the cavernous segment of the carotid artery. Typically, the dolichoectatic artery deviates medially and at times may be found, literally, protruding into the sella and compressing the sellar contents. The size and course of both carotid arteries can be determined exactly on MR coronal images, which is a compelling argument for obtaining an MR image even if doing so requires general anesthesia—the exception being a patient with a cardiac pacemaker.

Following selective transsphenoidal adenomectomy, more than 80% of patients with acromegaly have a sustained remission. Incompletely removed adenomas should be treated. Although some patients will do well with medical management using octreotide, most will be treated postoperatively with irradiation.

Corticotrophic adenomas (Cushing's disease)

In the short term, Cushing's disease is the most serious and life-endangering condition caused by any pituitary adenoma; for the surgeon, these tumors present the most difficult challenge of all pituitary adenomas. As I begin each operation for Cushing's disease, I have to assume that the operation will be difficult from beginning to end, and seldom am I pleasantly surprised by a truly "simple" case.

The patient with Cushing's disease has friable tissue, soft bone, and capillary fragility. Moreover, in many cases, obe-

sity and other factors conspire to produce venous hypertension, a major complicating factor during the transsphenoidal exploration of a normal-size sella surrounded, literally, by a moat of turgid, confluent dural venous sinuses. Neuroanesthesiologists at UCSF have developed a protocol for coping with elevated venous hypertension, and in the majority of cases the venous pressure can be reduced to normal or near-normal levels. However, these pharmacologic maneuvers are not always effective, and maintaining a lowered venous pressure requires sustained effort. In some cases, the surgeon must deal with persistently elevated venous pressure or, very rarely, abandon the procedure altogether. Even after extensive experience, I am wary, even apprehensive, as I prepare to operate on any patient who has Cushing's disease, and this is especially true if the patient is a young child.

In adults with suspected Cushing's disease, unless MR imaging indicates a tumor larger than 5 mm in diameter, we proceed to preliminary sampling of the cavernous sinuses. This means that the majority of such patients, more than 75%, undergo venous sampling and concurrent cavernous sinus venography. The tumors of Cushing's disease are tiny, the typical adenoma having a diameter of considerably less than 5 mm. Their minute size, coupled with the generally accepted likelihood of a false-positive MR image in 15% of the normal population, argues convincingly for preoperative venous sampling in almost all cases.

Venous sampling is invaluable in surgical decision-making. It helps to determine which patients to operate on, how to conduct the intrasellar exploration, and what to do in the case of a negative exploration. I have several caveats. The cavernous sinuses, rather than the downstream inferior petrosal sinuses, should be sampled bilaterally after the venographic anatomy is defined, and venograms of both cavernous sinuses should be obtained at the same time (2, 3). If venous drainage from the sella is dominantly unilateral, then simultaneously obtained left-right values may not be reliable in indicating lateralization. A cavernous sinus venogram should be obtained because a filling defect in a cavernous sinus may disclose the presence of an intracavernous adenoma (4). A 2:1 or larger cephalic-to-peripheral ACTH gradient establishes the diagnosis of Cushing's disease, and in our experience, the additional testing with corticotropin-releasing factor adds nothing to the value of samples taken from the cavernous sinus. If a patient with no anomalous venous drainage patterns exhibits a lateralizing ACTH gradient of 2:1 or greater, then removal of the appropriate half of the anterior pituitary gland will be curative in 80% of cases in which hemihypophysectomy is performed. Pediatric endocrinologists at UCSF are not enthusiastic about venous sampling because children rarely have an ectopic source of ACTH, venous sampling is technically difficult in children, and the risk of incurring morbidity from either local or general anesthesia is not entirely insignificant.

In contrast, I anticipate a difficult exploration whenever I treat a child, and I welcome a guide to the adenoma's probable location. Assuming a normal venographic anatomy, I would like to offer the option of hemihypophysectomy in the event of a negative exploration. The complexity of interpreting the results of venous sampling underscores the need for caution in performing hemihypophysectomy under any cir-

cumstances. Nonetheless, under the right circumstances, hemihypophysectomy is appropriate and, in most cases, will be successful. My clinical observations support the view that one third, or even slightly less, of a normal anterior pituitary gland provides normal anterior pituitary function.

The adenoma of Cushing's disease has distinctive gross characteristics. It is dirty-white and soft, bordering on semi-liquid, and it is often freckled by petechial hemorrhage. Because it may be small, the adenoma can go undetected entirely or can suddenly disappear into the tip of a sucker. The adenoma often has a diameter of 2 mm or less. It can reach the surface of the anterior lobe, can be exophytic into the subarachnoid space, can invade or even lie entirely within the cavernous sinus, as it did in one recent case, and, rarely, it can originate in the posterior lobe. Furthermore, in a small number of cases, Cushing's disease is the consequence of non-neoplastic hyperplasia. In none of the other endocrine-active tumors is expert knowledge of the gross and microscopic pathology so critical.

The surgical exploration must be meticulous and must include the posterior lobe. If total hypophysectomy is indicated after a negative exploration (that is, in an adult after nonlateralized venous sampling), then the sella must be entered, the stalk carefully inspected for involvement of the pars tuberalis, and the pituitary stalk sectioned as close as possible to the anterior lobe to avoid permanent diabetes insipidus. When hemihypophysectomy is indicated after a negative exploration (that is, in a child or adult who has a clearly lateralizing venous gradient and a normal venous anatomy and who has given an informed consent), the stalk must not be injured. Before removing the half of the anterior lobe suspected of harboring the adenoma, I explore it once again and, in addition, explore thoroughly the "normal" half of the anterior lobe that is not to be removed. I have operated on several patients in whom the *normal* half of the anterior lobe had previously been removed elsewhere based on an assumed infallibility of inferior petrosal venous sampling.

Cushing's disease is not a common disease; by one estimate, there are approximately 200 newly recognized cases annually. If left untreated, the disease is fatal. With no other tumor is the surgeon's experience more critical in determining outcome, and for this reason I suggest that inexperienced pituitary surgeons must gain experience with less complex tumor types, initially referring patients with Cushing's disease—particularly pediatric patients—to an experienced colleague. In my view, these rare and difficult cases should be concentrated in the capable hands of experienced pituitary surgeons throughout the United States. Requests for referral to an "out-of-plan" surgeon may be denied because of concern for cost, but a comparison of the long-term costs of a curative operation to those accrued from a failed first attempt creates a compelling argument for referral to an experienced surgeon for economic considerations alone, even without invoking the equally valid issue of appropriate patient care.

Endocrine inactive adenomas

In this category are adenomas that produce no clinically recognizable secretory product. At the time of diagnosis, the great majority of cases present with impaired vision and

some expression of hypopituitarism, typically gonadotropic insufficiency, with or without associated headache. Because of the increasingly prevalent use of high-resolution MR imaging, a new category of incidental and asymptomatic—presumed—pituitary adenomas requires the formulation of a new management algorithm, which I will consider separately.

With infrequent exceptions, symptomatic endocrine-inactive adenomas are large, even when headache is the only presenting symptom. Neither suprasellar extension nor focal perforation of the sellar floor, by itself, precludes complete removal. Nearly all symptomatic, endocrine-inactive macroadenomas have extended beyond the confines of an expanded sella turcica, the most common pattern of extrasellar growth being directly upward into the suprasellar space. With infrequent exceptions, the only patterns of growth that preclude total removal are lateral extension into the cavernous sinus or middle fossa and diffuse destruction of the sellar floor with extension of tumor into the sphenoid sinus. Invasion of the dura separating the sella from the cavernous sinus, even without extension into the sinus itself, renders the tumor surgically unresectable unless the invasion is focal, in which case the involved dura can sometimes be removed. A large tumor often displaces the intact dural wall of the cavernous sinus very far laterally without actually invading the dura, and unless coronal MR images display extreme lateral extension, the wall of the sinus may be stretched rather than invaded. The caveat: preoperative radiographic prediction of invasion into the cavernous sinus may be, and often is, incorrect.

For many years, my surgical objective in treating large endocrine-inactive adenomas was decompression of the optic nerves and chiasm with the assumption that irradiation was required afterwards to prevent regrowth. I did not attempt a total removal of large tumors, very possibly as a carryover from the established practice when these tumors were treated by craniotomy. However, as I gained experience and discovered that it was possible to achieve total removal of intrasellar macroadenomas while preserving compressed anterior lobe tissue, I changed the surgical objective from decompression to total removal. In the majority of large adenomas, a clean surgical plane separates the surface of the tumor from the compressed normal structures. By finding and developing this plane early in the process of removal, a surprisingly large proportion of large tumors can be removed completely. Subsequent follow-up of these adenomas with serial MR images at 6-month intervals for the first 2 years and then yearly has shown a 5% rate of recurrence after 5 years. If tumors that invade the cavernous sinus are excluded, I believe that as many as 40–50% of endocrine-inactive adenomas can be cured by surgery alone, and for this reason the surgeon should go into the operation with complete removal, rather than decompression, as the goal. Loss of anterior pituitary function that existed before surgery has been an infrequent complication; more often, function that was lost preoperatively later returned spontaneously. To borrow from the lexicon of the Olympics, the bar has been raised for pituitary surgeons.

TABLE 4. Defining features of an incidental pituitary adenoma

Asymptomatic
Normal anterior pituitary function
Absence of calcification
Confinement to the sella turcica

Incidental (coincidental) pituitary adenomas

Although I have kept no record of the number of patients with presumed incidental pituitary adenomas whom I have evaluated since the introduction of high-resolution MR images, I estimate that they constitute one out of five patients referred to me with the diagnosis of pituitary adenoma. Radiographically, some presumed adenomas are pure cysts rather than cystic adenomas, but if a cyst has attained a diameter of 1 cm, it should be managed in the same manner as an adenoma because both the pure cyst of this size and an adenoma, whether smaller or larger than 1 cm, have potential for further growth.

The defining features of a presumed incidental pituitary adenoma are these: (1) it is asymptomatic; (2) there is normal anterior pituitary function, including a normal GH response to provocative testing; (3) calcification is absent; and (4) the lesion is confined to the sella (Table 4). Of the anterior pituitary cell types, somatotrophs are the most vulnerable to compression, followed by gonadotrophs as a distant second. Although GH has a legitimate physiologic role throughout life, GH secretion is essential for the normal development of children. If GH secretion is normal, all other anterior pituitary functions are almost certainly normal as well. Because most craniopharyngiomas are calcified, and because there is a compelling argument for early intervention, the presence of calcium should be excluded by computed tomography scanning before the surgeon assumes that a mixed solid and cystic mass is an incidental adenoma.

Any incidental adenoma or cyst meeting the criteria just defined should be left alone and the patient advised to have follow-up examinations by a physician who accepts responsibility for periodic clinical, laboratory, and radiographic assessments based on the patient's age, the size of the adenoma, and other concerns. As a rule, younger patients require more frequent evaluation, and in that regard opinions vary as to frequency in each particular case.

What are the indications for surgical intervention? The indications presented in Table 5 are not absolute, and a decision to operate that is appropriate for an adolescent may be inappropriate for an elderly patient. Moreover, an adenoma that has doubled in size within 1 year, although still asymptomatic, should be viewed differently from an adenoma that has shown slight but unquestioned growth (expansion) over the course of 5 years. The listed indications for operation are only guidelines to be used in conjunction with clinical judgment. A pure cyst that, by its size, has qualified

TABLE 5. Relative indications for surgical intervention

Impairment of anterior pituitary function
Extrasellar extension
Attained greatest diameter >2 cm
Headache associated with expansion, persistent and reasonably attributable to the tumor
Rapid growth
Symptomatic or asymptomatic impairment of vision documented by formal eye examination

for inclusion with incidental adenomas has a likely potential for further growth; and, in contrast to the common and innocuous small cysts seen so often in the pars intermedia, the cyst that is 1 cm or larger is, in my opinion, certain to have further expansion at some unpredictable rate of growth.

Closing thoughts

I have acquired a deep respect for pituitary adenomas. Although rarely fatal because of their unrestrained growth, they can have a profound effect on the quality of life, and in many cases lead to secondary complications caused by endocrine dysfunction that affect not only quality but also length of life. Quite apart from cosmetic considerations, patients with active acromegaly are unhealthy, and their life span is shortened significantly. Unless treated successfully by either medical or surgical means, prolactinomas have consequences that are profound for physical and psychological health as well as fertility. The patient with Cushing's disease becomes disabled rapidly by a range of cortisol-produced complications, and a shortened life expectancy is a certain consequence of uncontrolled hypercortisolism. Endocrine-inactive adenomas threaten vision and pituitary function and, even though they can be cured by irradiation (particularly when the volume of tumor is small), irradiation of the normal anterior pituitary gland (and hypothalamus) can and often does produce hypopituitarism. Technologic advances during the past 2 decades have produced more effective therapeutic tools than were available at any time in the past, but even so, optimal management of any pituitary adenoma requires thoroughness in the evaluation process, the thoughtful and expert use of medical and surgical interventions, and in many cases a bit of good luck!

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