

Advances in Surgery for Pituitary Tumors

a report by

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Although benign in nature, pituitary tumors continue to offer many opportunities for improvement in therapy. Goals of treatment include complete removal or ablation of tumor cells, maintenance of normal pituitary function, normalization of elevated hormone levels in endocrine-active tumors, and minimizing adverse effects from therapy. There have been many recent advances related to the surgical treatment of pituitary tumors and the purpose of this article is to review some of the more significant ones.

Behavior of Pituitary Tumors

One of the most notable features of pituitary adenomas is their ubiquity in population studies compared with the relatively small number of tumors that actually present with clinical problems. Pituitary adenomas have been consistently reported in up to 25% of people in autopsy studies dating back to 1936.¹ More recent studies have attempted to clarify the relative prevalence of ‘incidentalomas’ compared with clinically relevant tumors. A meta-analysis performed in 2004² found an incidence of 16.7% with autopsies reporting 14.4% and radiologic studies finding a rate of 22.5%. Prolactinomas represented 25–41% of incidentalomas in studies that included immunohistochemical staining.^{3,4} A recent population study from Belgium⁵ found a prevalence of clinically relevant pituitary adenomas of 94 per 100,000. Of this group, 66% were prolactinomas, 14.7% were not endocrine-active, 13.2% had acromegaly, 5.9% had Cushing’s disease, and 20.6% had hypopituitarism. These same authors provided a concise set of recommendations for management of incidentalomas, including initial evaluation and periodic follow-up with magnetic resonance imaging (MRI) and endocrine studies.⁶

One recent paper reported new findings on the cellular biology of the normal pituitary gland that may ultimately have implications for tumorigenesis of adenomas.⁷ The investigators used a thoughtfully crafted series of transgenic mice that coupled the gene for nestin (a marker of adult stem cells) to a reporter gene (green fluorescent protein). They found that

at birth the anterior pituitary gland is composed of cells that were created by embryonic stem cells. However, throughout post-natal life, adult stem cells contributed new pituitary cells of all major sub-types to the gland. This means that the adult gland represents a mosaic of cells that have similar phenotypes (i.e. lactotrophs, somatotrophs, etc.) but have very different origins (i.e. embryonic or adult progenitor cells). They also provided preliminary evidence that adult stem cells may be involved in tumorigenesis in the pituitary in a mouse model, the retinoblastoma (Rb-1)+/- mouse. This will, no doubt, stimulate considerable interest in the study of the cellular originators of human pituitary tumors.

Diagnosis of Pituitary Tumors

Accurate surgical planning and prognostication for pituitary tumors rely heavily on pre-operative imaging studies, primarily MRI. Invasion of the cavernous sinus is a recognized indicator of increased aggressiveness of the tumor and reduced probability of complete surgical removal. However, in many cases it can be difficult to differentiate between invasion of the cavernous sinus by the tumor and simple compression of the sinus, even with high-resolution MRI. Yoneoka and colleagues⁸ used a new MRI technique, 3D anisotropy contrast (3DAC) MRI, to address this problem. They found that 3DAC MRI identified the oculomotor and ophthalmic/maxillary nerves in the cavernous sinus in 100% of controls and the trochlear and abducent nerves in 76 and 72% of cases, respectively. They compared imaging of 33 patients with pituitary macroadenomas with 25 control subjects. They used tumor encasement of at least half the circumference of one of the intracavernous cranial nerves as a criterion for sinus invasion. This was validated by direct intra-operative observations at the time of tumor removal. They found 100% correlation between the imaging-based predictions and the operative findings. Although preliminary, these findings suggest that 3DAC MRI may prove to be a useful addition to pre-surgical work-up in patients with pituitary macroadenomas.

Surgical Techniques and Peri-operative Management

Although pituitary adenomas are most commonly benign and slow-growing, they remain a considerable source of morbidity and mortality over a long time-frame. Uncertainties exist regarding long-term post-operative cure and control rates for pituitary tumors, with some centers recommending post-operative radiation therapy in all patients. A recent retrospective study from the University of California, San Francisco (UCSF)⁹ has provided excellent long-term outcome data from patients with non-functioning pituitary adenomas treated with surgery and, in some cases, adjuvant radiation therapy. They followed 663 patients treated by a single surgeon from 1975 to 1995. They compared outcomes for patients with surgery alone and those with surgery followed by fractionated radiation therapy. They found overall recurrence-free probabilities



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of 0.87 at 10 years and 0.81 at 15 years. They found that radiation therapy did not provide any improvement in recurrence-free status if a gross total resection of the tumor had been achieved, but it did improve outcome if a sub-total resection had been performed. They found that patients with gross total resections and those with sub-total resections followed by radiation therapy had similar long-term control rates. However, when comparing long-term mortality rates with those expected from the general population, they found that the patients with sub-total resections and those who had undergone radiation therapy had increased long-term mortality rates and those with gross total resection had mortality rates similar to the general population. This led to the recommendation that a gross total resection should be the goal of all surgeries where it is feasible and radiation therapy should be reserved for those patients with known residual or recurrent disease. This study also documented the importance of long-term follow-up with pituitary adenomas, as recurrences could occur five to 10 years after treatment.

Although prolactinomas are the most common sub-type of pituitary tumor in population-based studies, they account for a minority of patients in surgical series. This is because of the excellent control rates achieved with the use of the dopamine agonists bromocriptine and cabergoline. Two recent studies have added new information on surgical outcomes in patients with prolactinomas. Kreutzer and colleagues¹⁰ reported on their experience in 212 patients who underwent resection of prolactinomas from 1990 to 2005. These included patients who underwent surgery for 'non-classic indications,' i.e. cystic tumors and patients who simply preferred surgery over prolonged medical therapy. They found an overall remission rate of 42% for all tumors. However, patients with microadenomas and cystic tumors fared much better. This report confirms that prolactinomas can be successfully treated with surgery in a large number of patients and that those with small tumors and cystic tumors have a higher probability of long-term tumor and endocrine control. An interesting study from UCSF¹¹ took advantage of their large surgical experience that extends back to a time before medical therapy for prolactinomas was well-established as the first-line choice of therapy for these tumors. They compared patients who underwent surgery for prolactinoma as the initial treatment with patients who had a course of dopamine agonist therapy prior to surgery. They found that short- and long-term endocrine control rates were better in patients who had medical therapy prior to surgery. This argues against the observation reported by some surgeons that pre-surgical medical therapy makes prolactinomas harder to remove.

In a related issue, investigators continue to address the concern for possible deleterious effects of the ergot-derived dopamine agonist, cabergoline, on heart valve abnormalities in patients with prolactinomas. Two studies demonstrated an increased risk in patients taking pergolide or cabergoline for Parkinson's disease.^{12,13} Both drugs were associated with an increased risk for heart valve regurgitation. This is similar to heart valve abnormalities seen with other ergot alkaloids and carcinoid tumors and appears to be related to activation of the serotonin receptor type 2B (5-HT_{2B}). However, the doses of cabergoline used in the Parkinson's studies were much higher than those typically used in the treatment of prolactinomas. Three recent cross-sectional studies have attempted to address the issue of safety of cabergoline in the treatment of prolactinomas. Two studies found no increased prevalence of clinically relevant heart disease in patients treated with cabergoline.^{14,15} One study found an increased prevalence of moderate tricuspid regurgitation on echocardiography in patients being treated with cabergoline compared with newly diagnosed prolactinoma patients and control subjects.¹⁶ Currently, most

centers are continuing to use cabergoline to treat prolactinomas, but many are advocating an increased use of surveillance echocardiography in these patients and the safe upper limit of cabergoline dosage in relatively refractory prolactinomas remains an open issue.

Minimally invasive approaches to pituitary tumors continue to generate widespread enthusiasm in the surgical community. The endonasal, trans-sphenoidal approach offers the advantage of no visible incision, limited disruption of soft tissue and bony structures, no need for post-operative nasal packing, and shorter hospital stays. The minimally invasive endonasal approach can be used either with direct vision through a surgical microscope or as a purely endoscopic procedure. Both methods have their proponents. Several new clinical series have continued to document the safety and utility of these minimally invasive approaches to pituitary tumors. Sanai and colleagues¹⁷ reported results using the direct, endonasal approach (using the operating microscope) in 64 patients with challenging pituitary tumors. These included large macroadenomas (>3cm diameter), tumors with cavernous sinus invasion, and craniopharyngiomas. They reported complete removal in 49% and near-gross total removal in 9%. Of those patients who presented with visual deficits, 81% showed improvement post-operatively. Zhang and colleagues¹⁸ reported results using the purely endoscopic, endonasal approach in 78 patients with invasive pituitary adenomas (including 11 microadenomas). They achieved complete removal in 79.5% of patients and improvement in visual symptoms in 96.4% of cases. Dehdashti and colleagues¹⁹ reported their outcomes in 200 consecutive patients with removal of pituitary adenomas using the purely endoscopic, endonasal technique. They reported gross total resection in 91% of cases overall. This improved to 96–98% if tumors that invaded the cavernous sinus were excluded. Visual improvement occurred in 89% of patients. These reports lend additional support to the use of the minimally invasive approach to pituitary tumors in the majority of cases.

Several recent papers addressed issues of peri-operative management for patients with pituitary adenomas. Many patients with adenomas will have impaired pituitary function pre-operatively and a small percentage will develop impairment secondary to surgical manipulation. Therefore, peri-operative administration of corticosteroids is common practice at most surgical centers. However, the dosages and duration of this therapy vary and there is little hard data to address these issues. Kristoff and colleagues²⁰ prospectively studied three groups of patients for 12 weeks after surgery: adenoma patients with impaired pituitary function, adenoma patients with intact pituitary function, and patients undergoing lumbar laminectomy. They treated patients with impaired pre-operative pituitary function with a regimen of intravenous (IV) and oral hydrocortisone that started with 100mg on the day of surgery and tapered off over six to 10 days after surgery. They followed 24-hour urinary free cortisol levels for two weeks in all three groups. They found that cortisol levels increased much higher and for much longer in pituitary tumor patients than in laminectomy patients. They found no difference in cortisol levels between the adenoma patients with hydrocortisone replacement and those with intact pituitary function. This suggests that the replacement regimen used at the University of Bonn (similar to that used by many centers worldwide) is probably sufficient, although they suggested increasing replacement on the day of surgery from 100mg to 150mg/day based on a non-significant difference between the two groups.

Leakage of cerebrospinal fluid (CSF) is the most common complication of surgery for pituitary tumors. In most cases it can be managed with packing of

the surgical site and temporary CSF diversion using a lumbar drain. However, CSF fistulae can, rarely, lead to more serious problems such as life-threatening meningitis and hydrocephalus. Han and colleagues²¹ reviewed a large series of 529 patients after removal of pituitary macroadenomas. They found an intra-operative leak rate of 14.2% and a post-operative rate of 4.4%. Almost 20% of the post-operative CSF leaks presented with meningitis. Repeat surgery, tenacity (consistency) of the tumor, and an indistinct tumor margin were associated with an increased risk for intra-operative CSF leak. Intra-operative leaks were managed effectively in 83% of patients with initial treatment. Of post-operative leaks, 60% were effectively treated with a lumbar drain alone and 40% required additional surgery. This report gives additional information on the incidence and expected outcomes from this relatively common complication of pituitary surgery.

Central diabetes insipidus (DI) is another complication of pituitary surgery that requires prompt diagnosis and treatment. Sigounas and colleagues²² studied DI in 119 patients who underwent endoscopic removal of pituitary-region tumors. They found that permanent DI occurred in 2.7% of cases and transient DI occurred in 13.6%. Risk factors for DI included a pathology of Rathke's cleft cyst, intra-operative CSF leak, and prior non-endoscopic surgery.

Human Tissue Studies

Many investigators have sought to predict tumor behavior based on labeling characteristics of the tumor specimen from surgery. The Ki-67 labeling index (LI) has been useful in predicting tumor growth and recurrence rates in a number of tumors, but results in pituitary adenomas have not been consistent throughout the literature. Gejman and colleagues²³ studied Ki-67 LI in 24 patients who required surgery for recurrence within five years of the original surgery and compared them with 31 adenomas that did not progress. They found that a Ki-67 LI above 1.3% predicted recurrence within five years of surgery. Fusco and colleagues²⁴ studied Ki-67 LI in 68 patients with acromegaly. They found that the LI was higher in tumors with cavernous sinus invasion, lower in patients who were cured of their tumor after surgery, and lower in patients who responded to medical therapy (somatostatin analogs) compared with those who did not respond.

Additional studies have focused on growth hormone (GH)-secreting tumors and their response to medical therapy. Plockinger and colleagues²⁵ studied the expression of somatostatin receptor subtypes in 34 patients with acromegaly; 20 of these patients had medical therapy with octreotide (a somatostatin analog that acts primarily at the sst2A receptor) prior to surgery. All patients who responded (>50% reduction in GH secretion) to octreotide expressed sst2A receptors while none of the non-responders expressed it. In addition, sst1 and sst5 were expressed in 85 and 70% of all tumors, respectively. This raises the possibility that somatostatin analogs that target the sst1 and sst5 receptors may be effective in a larger proportion of acromegaly patients. In addition, Fougner and colleagues²⁶ showed that low levels of the protein non-phosphorylated Raf kinase inhibitory protein in GH-secreting tumors correlated with a poor response to octreotide. They suggest that this may be due to effects on the mitogen-activated protein kinase kinase (MEK)–extracellular regulated kinase (ERK) signaling pathway that are complementary to the effects of the sst2 receptor. Vazquez-Martinez and colleagues²⁷ also found that expression of Rab18, a protein involved in regulation of intracellular membrane transport and secretory activity in neuroendocrine cells, is inversely correlated with GH levels and GH secretion in tumor cells from patients with acromegaly.

Endocrine-active Pituitary Tumors

Endocrine-active pituitary tumors pose significant additional challenges to healthcare providers above the consideration of tumor growth and mass effect, with Cushing's disease representing the most urgent medical issues and most difficult problems in diagnosis and treatment. In 2007, a panel of worldwide experts met in Budapest, Hungary to review the literature and provide a current consensus statement on the diagnosis and management of adrenocorticotrophic hormone (ACTH)-dependent Cushing's syndrome.²⁸

Their recommendations support many practices in effect in major endocrine surgery centers. Direct, surgical removal of the ACTH-producing tumor is the preferred initial mode of therapy and carries the highest chances of cure. They recommend early post-operative cortisol levels (<2ng/dl is desired) to help predict the chances of long-term remission after pituitary surgery. Management options for recurrent tumors include repeat direct surgery on the tumor, hypophysectomy, radiation therapy, and adrenalectomy. Patients must be treated for secondary adrenal insufficiency after curative pituitary surgery in most cases. Successful management of these complex tumors demands an individualized, multidisciplinary approach led by the endocrinologist and surgeon involved.

Hoffman and colleagues²⁹ reported on a large series of 426 primary surgeries for Cushing's disease performed by a single surgeon from 1971 to 2004. The median follow-up on the patients was 66 months. After surgery alone, the authors found an early remission rate of 68.5%. After repeat surgeries were included, the long-term remission rate was 62.4% for surgical therapy alone. Patients with microadenomas fared better than those with macroadenomas and cases where adenomas were found did better than those where no adenoma was identified. These data highlight the utility of surgery in the hands of an experienced pituitary surgeon but also the need for additional forms of therapy in cases that cannot be cured by surgery alone.

Among pituitary adenomas, those that produce thyroid-stimulating hormone (TSH) are the least common, representing <2% in most series. Clarke et al.³⁰ reported on 21 patients with known TSH-immunoreactive adenomas that were treated between 1987 and 2003. Endocrine-active tumors, based on serum TSH levels, were present in 14 of the 21 patients. Ten presented with clinical hyperthyroidism and seven of these patients had undergone ablative procedures of the thyroid prior to diagnosis of the pituitary adenoma. Macroadenomas accounted for 85% of these tumors. Tumor remission rate after initial surgery was 50%. Immunohistochemical staining for a second pituitary hormone was relatively common, although the second hormone was clinically active in only one patient with acromegaly. This report highlights the rarity of these tumors and a relative delay to diagnosis (based on tumor size) compared with other endocrine-active tumors.

Summary

Surgical treatment for pituitary tumors continues to evolve based on improved diagnostic techniques, refinements in surgical technique and technologies, better understanding of tumor behavior, better documentation of treatment outcomes, and improved guidelines for peri-operative management and long-term follow-up. All of these developments move physicians further toward their ultimate goal of permanent cure with minimal side effects in all patients. ■

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Editor's Recommendations

Impaired Developmental Switch of Short-term Plasticity in Pyramidal Cells of Dysplastic Cortex

Chen HX, Xiang H, Roper SN, et al.

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Human cortical dysplasia (CD) has a strong clinical association with intractable epilepsy. It is believed that neuronal networks of CD are hyperexcitable, which may initiate seizures. The mechanisms are poorly understood. The authors have studied the alterations of synaptic properties in a rat model of CD *in utero* irradiation. Pregnant rats on E17 were exposed to 225 cGy of external gamma irradiation and offspring were used for experiments. Coronal somatosensory brain slices were obtained from 13–60-day-old rats. Visualized whole-cell recordings were performed on pyramidal neurons in layer V of control neocortex and the middle region of dysplastic cortex. Short-term plasticity (STP) of evoked excitatory post-synaptic currents (EPSCs) was induced by five-pulse (20 or 50Hz) train stimulations. STP of EPSCs in pyramidal cells of the normal cortex induced by five-pulse train stimulation (20 or 50Hz) switched from depression at P13–15 to facilitation at P28–35 and P55–60. STP in CD at P28–35 and P55–60 still showed depression. The failure rate of synaptic responses to the first pulse of the stimulation tested at P28–35 was significantly lower in CD than in controls. The depression of STP in CD at P28–35 was not altered either by blocking the de-sensitization of glutamate receptors or by blocking postsynaptic Ca²⁺ rise. It was not affected by an antagonist of mGluR2/3, LY341495. Our results indicate that the pre-synaptic release probability of excitatory synapses in CD

pyramidal cells at P28–35 and P55–60 remains abnormally high and reduced tonic activity of pre-synaptic mGluR2/3 may contribute to this. ■

Headache Associated with Pituitary Tumors

Gondim JA, et al.

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This study analyzed the presence of headache in pituitary tumors and their characteristics, and the relationship between pituitary tumor size, biological type, local extension, and intrasellar pressure (ISP). This is a prospective study of 64 consecutive patients presenting with primary pituitary masses at the Neuroendocrinological Department of the General Hospital of Fortaleza from October 2005 to December 2006. The authors analyzed sex, age, headache (laterality, site, severity, quality, frequency, duration, associated symptoms, time of onset, trigger, alleviating factors, and familial history), and tumor characteristics (type, size, quiasmatic compression, cavernous sinus invasion, sella turcica destruction, cystic or solid mass, and ISP). The authors observed a statistically significant factor between pituitary tumor and tumor size, optic compression, sellar destruction, cavernous sinus invasion, and ISP. Biochemical-neuroendocrine factors, mainly in prolactinomas, seem to be an important factor in the determination of headache. The presence of headache in pituitary tumor is related to a combination of factors, including ISP, tumor extension, relationship with the sellar structures, patient predisposition, familial history, and functional disturbance within the hypothalamo-pituitary axis. ■