Medical Versus Surgical Management of Prolactinomas

Michael C. Oh, MD, PhD, Sandeep Kunwar, MD,
Lewis Blevins, MD, Manish K. Aghi, MD, PhD*

KEYWORDS

• Prolactinomas • Pituitary adenoma • Dopamine agonist • Bromocriptine • Cabergoline
• Transsphenoidal surgery

KEY POINTS

- Prolactinomas are the most common endocrine active adenomas, comprising 40% of pituitary tumors.
- Prolactinomas present a unique challenge for clinicians given the relatively comparable efficacy of medical management versus transsphenoidal surgery.
- A full endocrine laboratory panel should be obtained, especially for macroprolactinomas, as stalk compression can cause hypopituitarism.
- Small, asymptomatic prolactinomas may be observed with close hormonal and radiographic monitoring, whereas symptomatic prolactinomas require treatment.
- Dopamine agonists have become the standard treatment for symptomatic prolactinomas, including macroprolactinomas causing mass-effect symptoms such as visual loss.
- Although most patients with prolactinomas respond to medical therapy, 10% to 20% do not respond to dopamine agonist therapy in terms of prolactin normalization, and may require surgery.
- Transsphenoidal surgery is recommended if (1) the tumor is cystic, (2) inadequate prolactin reduction or tumor growth occurs despite high doses of dopamine agonists, (3) a female patient is planning pregnancy, (4) there is intratumoral hemorrhage with mass effect or apoplexy, (5) the patient presents with rapid visual loss or rapid visual loss occurs on dopamine agonist therapy, or (6) the patient opts for surgical resection rather than medical management.

INTRODUCTION

Pituitary tumors represent 10% to 15% of primary intracranial neoplasms,[1] of which more than 90% are benign pituitary adenomas with World Health Organization grade I.[1–3] Among endocrine active adenomas (EAAs), prolactinomas are the most common, comprising 40% of pituitary tumors.[4,5] One study, for example, determined that among 46 pituitary macroadenomas found incidentally, 15% were prolactinomas based on laboratory evaluation.[6] Given that autopsy and imaging studies suggest that pituitary tumors are up to 700 times more prevalent (16.7%, or 1 out of 6 people in the general population) than suggested by registry studies,[7,8] prolactinomas can be a large component of practice for pituitary neurosurgeons and neuroendocrinologists.

Prolactinomas present a unique challenge for clinicians given the relatively comparable efficacy of medical management versus transsphenoidal surgery.[9,10] In fact, currently prolactinomas are the only brain tumors for which remission, defined as biochemical and radiographic remission in an endocrine active tumor, can be achieved by medical

Department of Neurological Surgery, California Center for Pituitary Disorders, University of California, 400 Parnassus Avenue, A-808, San Francisco, CA, 94143, USA
* Corresponding author. Department of Neurological Surgery, University of California, San Francisco, 505 Parnassus Avenue, M770, Box 0112, San Francisco, CA 94143.
E-mail address: AghiM@neurosurg.ucsf.edu

Neurosurg Clin N Am 23 (2012) 669–678
http://dx.doi.org/10.1016/j.nec.2012.06.010
1042-3680/12/$ – see front matter

therapy alone. After initial studies proving the efficacy of dopamine agonists as medical therapy for prolactinomas,[11] these medications came to be viewed by many as the first-line therapy for prolactinomas. Over the years, however, several indications have arisen for surgery to treat prolactinomas. The surgical approach to prolactinomas is typically via a transseptal transsphenoidal corridor achieved through microscopic or endoscopic exposure. This article reviews the recent advancements in medical and surgical management of prolactinomas.

CLINICAL FINDINGS OF PROLACTINOMAS

Symptoms Associated with Prolactinomas

Prolactinomas are the most common EAAs, comprising 40% of pituitary tumors.[4,5] Symptoms associated with prolactinomas are due to 2 factors: (1) the endocrine effects of prolactin oversecretion and (2) the mass effect on the surrounding structures. Endocrine symptoms include decreased libido, galactorrhea, gynecomastia, amenorrhea in females, and infertility. Because amenorrhea is readily detected in women and decreased libido is often not reported by men, women more often present with microprolactinomas whereas men often present with macroprolactinomas. The prevalence of prolactinomas is generally higher is women as well,[12,13] possibly because endocrine symptoms are more easily detected in women than in men. Asymptomatic microprolactinomas grow slowly in general and may not require treatment, as only 9 of 139 (7%) women in 6 studies with microprolactinomas had tumor growth during untreated follow-up averaging 8 years.[4]

Patients with large macroprolactinomas, however, may present with symptoms of mass effect, including bitemporal hemianopsia caused by suprasellar extension with compression of the optic chiasm (**Fig. 1**), headache potentially attributable to stretching of the nearby dura or diaphragm sella, hypopituitarism caused by compression of portal vessels, the pituitary stalk, or the pituitary gland, and cranial neuropathies resulting from parasellar extension with cavernous sinus invasion. Hypopituitarism, most often manifesting as hypogonadism, may be present in 43% of patients with macroadenomas.[14] Though acutely reversible, prolonged compression of the optic chiasm can lead to optic-nerve atrophy, permanent visual-field deficits, and decreased visual acuity. Cranial neuropathies may include ptosis, ophthalmoplegia, and diplopia from compression of the cranial nerves III, VI, and IV, in the order of frequency.[15]

Radiological Findings

The radiographic features of prolactinomas are identical to those of other pituitary adenomas, and are best detected on gadolinium-enhanced magnetic resonance imaging (MRI). Prolactinomas may be isointense or slightly hypointense compared with the pituitary gland on T1-weighted images. While pituitary adenomas such as prolactinomas enhance with gadolinium on T1-weighted images, their enhancement is typically less than that of the pituitary gland or the stalk (**Fig. 2**). A convex outline along the pituitary gland or deviation of the pituitary stalk away from the adenoma may or may not be present.

Diagnostic Investigations

A full endocrine laboratory panel should be obtained, especially for macroprolactinomas, as stalk compression can cause hypopituitarism. For example, large nonfunctioning pituitary adenomas (NFPAs) may mimic the clinical picture of macroprolactinomas by the stalk effect, whereby compressing the portal vessels can inhibit delivery of dopamine from the hypothalamus to pituitary lactotrophs.[12] Dopamine inhibits prolactin release from the pituitary gland and, thus, the stalk effect can lead to excessive release of prolactin, causing large NFPAs to sometimes present with laboratory hyperprolactinemia that is sometimes clinically symptomatic.

In general, the degree of prolactin elevation correlates with tumor size. Most patients with prolactin greater than 150 mg/L have prolactinomas, whereas macroprolactinomas can have levels well above 250 mg/L. In some giant prolactinomas, prolactin levels may be extremely high, saturating the immunoradiometric assays and leading to falsely low levels. Performing assays with diluted serum samples can prevent this "hook effect."

Differential Diagnosis

The differential diagnosis in a patient with elevated serum prolactin and a pituitary tumor on MRI is prolactinoma versus NFPA with stalk effect. Although serum prolactin may improve or normalize in stalk-effect patients treated medically, the associated NFPA will usually not regress and the associated mass effect will not improve in the way it would with a prolactinoma treated medically. There is a linear correlation between adenoma size and a serum prolactin below which the stalk effect should be suspected and above which prolactinoma should be suspected,[16] but this correlation is not perfect, particularly with cystic adenomas

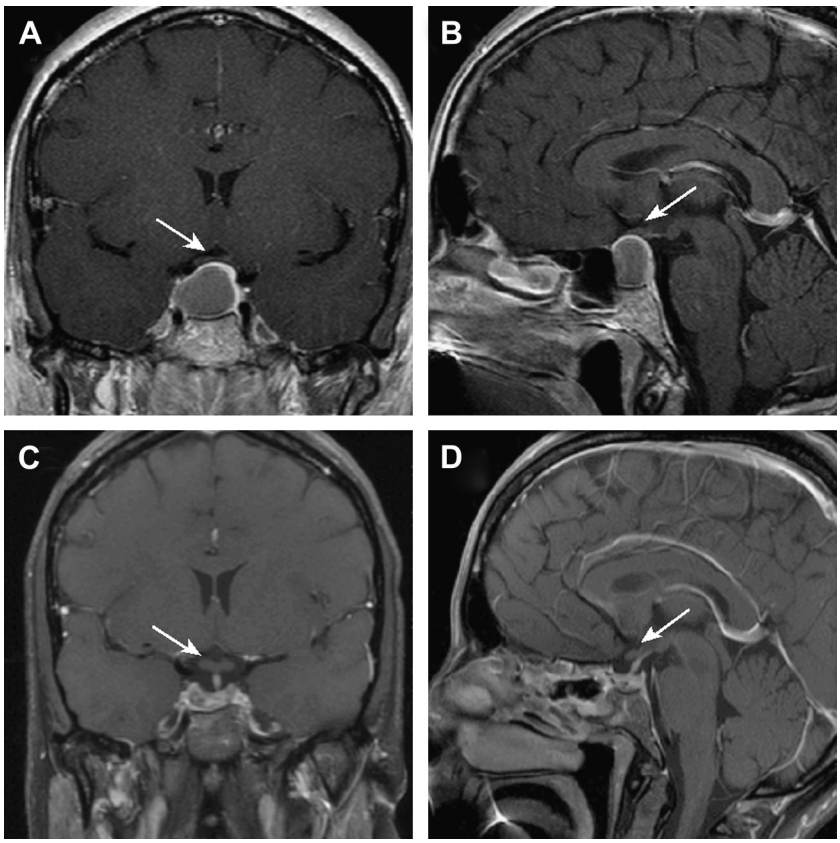

Fig. 1. A 38-year-old woman presenting with amenorrhea. Laboratory workup revealed elevated prolactin at 85 ng/mL, suggesting that the tumor was a cystic microprolactinoma rather than a cystic nonfunctioning pituitary adenoma with stalk effect. Gadolinium-enhanced T1-weighted images (*A*, *B*) confirmed a cystic lesion with suprasellar extension and compression of the optic chiasm (*arrows*). Although with bromocriptine her prolactin level normalized to 14.1 ng/mL, the tumor size did not respond to medical treatment. Normalization of serum prolactin to medical treatment suggested that this lesion is indeed a prolactinoma. She underwent transsphenoidal resection of the tumor with decompression of the cystic component (*C*, *D*), which resulted in decompression of the optic chiasm (*arrows*). Surgical pathology confirmed the lesion as prolactinoma.

(see **Fig. 1**). Other different diagnoses include other EAAs (adenomas releasing adrenocorticotropin or growth hormones and, rarely, gonadotropins or thyroid-stimulating hormones), hypophysitis, Rathke cleft cyst, craniopharyngioma, meningioma, and metastases.

MANAGEMENT OF PROLACTINOMAS

With increasing prevalence of pituitary incidentalomas from more frequent imaging for other reasons, such as headaches, trauma, and vertigo, studies delineating the natural progression history of microprolactinomas will become more important for management stratification. The evidence to date suggests that asymptomatic microprolactinomas grow slowly and may not warrant treatment. Only 9 of 139 (7%) women in 6 studies with microprolactinomas had tumor growth during untreated follow-up averaging 8 years.[4] In another study observing 30 women with hyperprolactinemia for an average of 5.2 years, one-third (10 of 30) of patients had a decrease in prolactin levels during the observation period.[17] Thus, small, asymptomatic prolactinomas may be observed with close hormonal and radiographic monitoring, whereas symptomatic prolactinomas require treatment.

Dopamine Agonist Therapy

Prolactinomas are tumors of lactotrophs, whose production of prolactin is normally inhibited by dopamine from the hypothalamus and enhanced by estrogen. Understanding the regulation of lactotrophs by dopamine has led to the development of drugs to treat prolactinomas. Prolactinoma cells

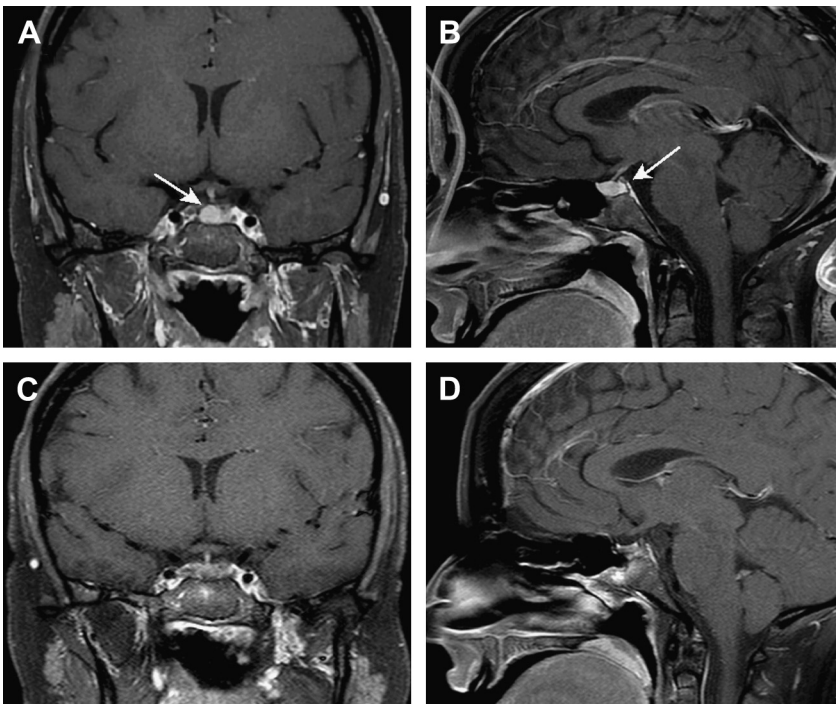

Fig. 2. A 29 year-old woman presenting with galactorrhea, found to have a microadenoma on MRI. Despite medical treatment, the tumor size increased. (*A*, *B*) Gadolinium-enhanced T1-weighted images show a 7-mm enhancing lesion (*arrows*). She underwent transsphenoidal resection with complete removal of the lesion (*C*, *D*), with normalization of prolactin levels by way of dopamine agonists.

express dopamine D2 receptors which, when activated, cause cell death, decrease cellular metabolism, and decrease prolactin gene synthesis, thereby inhibiting prolactin production and secretion. Furthermore, prolactinoma cell size decreases as well as a result of decreased cytoplasmic, nuclear, and nucleolar areas, with involution of endoplasmic reticulum and Golgi complex,[18,19] which may be responsible for reduction in tumor size in response to dopamine agonists. Thus, dopamine agonists have been used to treat prolactinomas with great success over the last 4 decades.

Indeed, over the last 25 years dopamine agonists have become the standard treatment for symptomatic prolactinomas, including macroprolactinomas causing mass-effect symptoms such as visual loss. In 1985, a prospective multicenter trial showed that the dopamine agonist bromocriptine, an ergoline derivative that activates dopamine D1 and D2 receptors, normalized prolactin levels in 18 of 27 patients.[11] Tumors decreased in size as early as 6 weeks after administration. Tumor size decreased by more than 50% in 13 patients (46%), 50% in 5 patients (18%), and 10% to 25% in 9 patients (36%).[11] Of note, visual fields improved in 9 of 10 patients who had deficits, confirming that medical treatment can treat tumor mass effect as well. These results with medical therapy resemble those achieved with surgery,[9,10] and a meta-analysis of 34 series showed that 73.7% of microadenomas and 32.4% of macroadenomas had normal prolactin levels 1 to 12 weeks following surgery.[20] Although a randomized trial directly comparing medical with surgical treatment has not been performed, based on the results of these studies demonstrating comparable efficacy of surgery versus medical therapy, dopamine agonist therapy has replaced surgery as the first-line therapy for prolactinomas, including macroprolactinomas with symptomatic mass effect (**Fig. 3**).

Another dopamine agonist that has recently supplanted bromocriptine is cabergoline, a more potent and longer-acting dopamine D2 receptor agonist than bromocriptine. Cabergoline only requires once- or twice-weekly oral administration, and has a very low side-effect profile. A direct comparison of cabergoline with bromocriptine in a randomized multicenter trial involving 459 women showed that cabergoline is more effective and better tolerated than bromocriptine.[21] Normal prolactin levels were achieved in 59% of women treated with bromocriptine, whereas cabergoline restored normal prolactin in 83%.[21] Amenorrhea

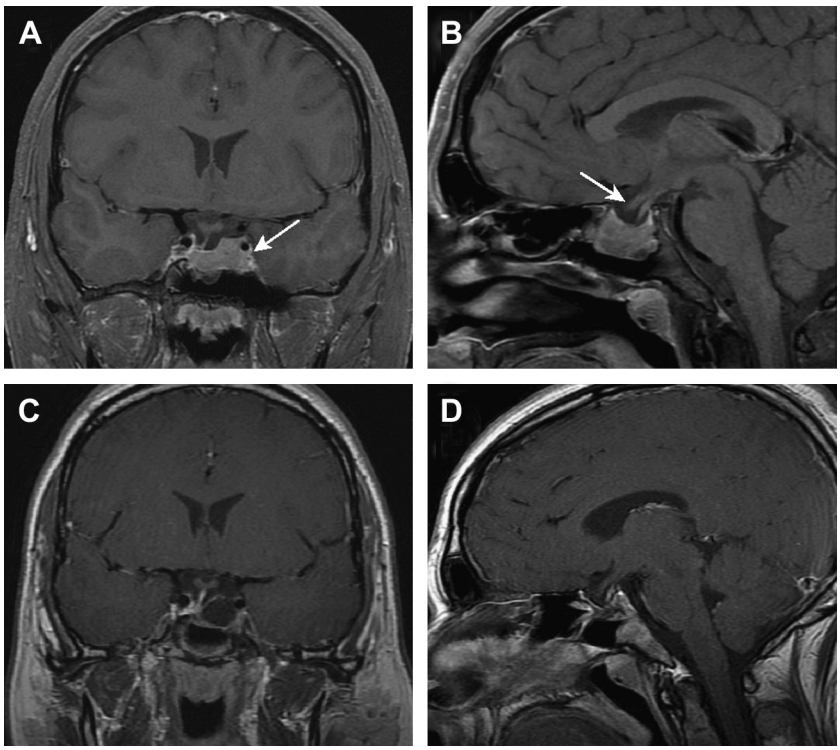

Fig. 3. A 30-year-old man presenting with left ocular headaches and decreased libido. Further workup revealed elevated prolactin well above 1000 ng/mL with a 3-cm macroprolactinoma on MRI. He was started on cabergoline with a consequent 50% reduction in tumor size. Gadolinium-enhanced T1-weighted images showed invasion into the left cavernous sinus (*A*, *arrow*), and a partially empty sella with slight downward herniation of the optic chiasm (*B*, *arrow*). He remained stable on medical treatment until he presented with spontaneous cerebrospinal fluid rhinorrhea. He underwent transsphenoidal tumor resection with septal repair for the rhinorrhea (*C*, *D*). He improved symptomatically but his prolactin level remained elevated, at 130 ng/mL.

persisted in 7% of women taking cabergoline versus 16% for bromocriptine, and 3% stopped cabergoline because of drug intolerance versus 12% for bromocriptine.[21] These findings were confirmed by another multicenter, randomized double-blind study involving 120 women, in which prolactin normalization occurred in 93% of patients taking cabergoline and 48% of patients taking bromocriptine.[22] As a consequence of these 2 randomized trials, cabergoline has replaced bromocriptine as the dopamine agonist of choice for prolactinomas, with surgery reserved for prolactinomas resistant to medical therapy.

Furthermore, a recent prospective study showed that higher cabergoline doses can restore prolactin to normal levels irrespective of previous treatment with other dopamine agonists.[23] Even patients previously resistant to other dopamine agonists responded to cabergoline, with 35% of patients in remission within a year.[23] Cabergoline is also more effective than bromocriptine in its ability to be withdrawn without prolactin elevation after prolactin has normalized, the ultimate goal with medically managed prolactinomas. Although no randomized comparison has been done, numerous series have reported 0% to 44% rates of maintaining normal prolactin 2 to 48 months after bromocriptine withdrawal, compared with 10% to 69% rates of maintaining normal prolactin 3 to 60 months after cabergoline withdrawal.[24]

Other dopamine agonists with clinical benefit exist, such as pergolide mesylate and quinagolide (CV 205-502). Neither of these drugs is available in the United States, however, and pergolide was voluntarily removed from the US market in 2007 because of concerns over increased incidence of serious restrictive cardiac valvular disease with high doses of pergolide used in patients with Parkinson disease.[25]

Prognosis

Overall, approximately 80% to 90% of patients with microprolactinomas and 70% of patients with macroprolactinomas can achieve normalized prolactin level, reduced tumor size, and restoration

of gonadal function with bromocriptine.[26] Results are even better with cabergoline, with 95% and 80% of patients normalizing prolactin levels in microprolactinomas and macroprolactinomas, respectively.[26] Tumor volume can decrease dramatically, even in macroprolactinomas, with rapid improvements in headache and visual field, with complete tumor shrinkage with cabergoline in about one-third of patients with macroprolactinomas.[24] Thus the short-term and long-term prognosis for prolactinoma patients is good when managed with medial therapy alone.

Dopamine Agonist–Resistant Prolactinomas

Although most patients with prolactinomas respond to medical therapy, data suggest that 10% to 20% do not respond to dopamine agonist therapy in terms of prolactin normalization, or are intolerant of the medication owing to nausea and postural hypotension.[27–29] Moreover, an even higher percentage of patients do not respond to dopamine agonists through reduction in tumor size. Although no clear consensus exists, dopamine agonist–resistant prolactinomas (DARPs) have been defined as prolactinomas that fail to normalize prolactin levels despite greater than 15 mg of daily bromocriptine for at least a 3-month period,[30–32] while cabergoline resistance is present when prolactin levels fail to normalize despite greater than 1.5 to 2.0 mg of weekly cabergoline.[33,34] The exact definition for dopamine agonist resistance has been difficult to establish, as it is unclear which criteria, such as prolactin level normalization, tumor volume reduction, or reestablishment of hormonal function without complete normalization of prolactin level (ie, reestablishment of menses or pregnancy in women), should be used. Nonetheless, DARPs make up a considerable portion of prolactinomas, with different clinical behavior and management.

Although they are more commonly macroprolactinomas,[33] DARPs can be microprolactinomas as well. DARPs also do not metastasize and are not associated with pituitary carcinomas. Thus DARPs are benign pituitary tumors with distinct biochemical and cellular makeup that favor a larger, more invasive, and more proliferative tumor in comparison with dopamine-responsive prolactinomas.[29]

The main therapy for DARPs after failing initial dopamine agonist therapy consists of more intense medical therapies. First, the dose of current dopamine agonist being used may be increased, as long as there is a response shown in prolactin level to higher doses of dopamine agonist. Moreover, patients currently unresponsive to bromocriptine may respond to cabergoline. Prolactin normalized in 95% of patients previously untreated or intolerant to bromocriptine with cabergoline at 6 months, while 58% of patients previously resistant to cabergoline at a lower dose responded at higher doses of cabergoline.[23] More importantly, by 12 months of treatment nearly all of the patients (99.3%) in the group resistant to bromocriptine responded to high doses of cabergoline, although a much higher dose of cabergoline was required compared with other groups (mean cabergoline dose of 2 mg/wk in previously untreated; 0.9 mg/wk in intolerant to bromocriptine; and 5.2 mg/wk in bromocriptine-resistant groups).[23] Most patients (83%), however, are managed sufficiently with low doses of cabergoline (0.5–1.5 mg/wk).[33] About 11% of remaining patients achieved normal prolactin levels with higher doses of cabergoline (up to 7 mg/wk, but most by 3.5 mg/wk) while the remaining 6% remained resistant to cabergoline.[33] Thus, overall most patients (94%) can be controlled with cabergoline doses of less than 3.5 mg per week. For the remaining 6% who are resistant to high doses of dopamine agonists, surgery and radiation therapy are available. Alternative medical therapies, mainly using temozolomide, an alkylating agent used in glioblastoma multiforme, have been reported in a small number of case studies.[35–37]

SURGICAL TREATMENT OF PROLACTINOMAS

Transsphenoidal surgery is recommended for prolactinomas if (1) the tumor is cystic, as cysts will not shrink with dopamine agonist therapy (see **Fig. 1**); (2) inadequate prolactin reduction or tumor growth occurs despite high doses of dopamine agonist (DARPs); (3) a female patient is planning pregnancy, which may be difficult to achieve on dopamine agonists; (4) there is intratumoral hemorrhage with mass effect or apoplexy,[38] which will not resolve with dopamine agonist therapy; (5) the patient presents with rapid visual loss or rapid visual loss occurs on dopamine agonist therapy; or (6) the patient opts for surgical resection rather than medical management after discussion of risks, benefits, and alternatives to both treatments with a neurosurgeon and endocrinologist. Even in the absence of these conditions, a patient with a newly diagnosed prolactinoma should be made aware that surgery and medicine are two treatment alternatives, and should understand the risks and benefits of each before committing to an initial treatment choice. The goal of surgical resection of prolactinomas is to completely remove all surgically accessible portions of the tumor.

A retrospective study evaluated surgical outcomes of patients who required surgery because of intolerance to dopamine agonist therapy or because patients had DARPs.[39] Among patients who were intolerant to dopamine agonist therapy, 67% had normalization of prolactin levels following surgery, whereas only 36% of patients with DARPs achieved prolactin normalization after surgery. This result is likely due to the fact that more macroprolactinomas were present in the groups with DARPs (74%). In fact, patients with microprolactinomas had good outcomes following surgery, as 84% of patients with microprolactinomas achieved normal prolactin levels following surgery. This finding is corroborated by other studies that achieved 73% to 90% remission rates following transsphenoidal surgery for microprolactinomas.[40–42]

Another debate concerns whether prolactinomas causing intractable headaches should be considered for surgical resection. Headache is present in 33% to 72% of patients with pituitary tumor[14,43,44] and 48% of patients with primary and metastatic brain tumor,[45] similar to the 47% prevalence of headache in the general population.[46] A retrospective study reviewed 41 patients with pituitary microadenomas to determine whether headache improved following transsphenoidal surgery.[47] This study showed that 85% of patients had headache improvement while 58% had complete resolution. EAA patients had similar improvement in headache. Given the relatively low morbidity of transsphenoidal surgery and the potential to improve headache, surgery may be appropriate for microprolactinoma patients with intractable headaches.

Microscopic Versus Endoscopic Approaches

For the past few decades, surgery for pituitary tumors involved using a microscope with an endonasal speculum via a transseptal transsphenoidal approach with fluoroscopy or neuronavigation used for intraoperative localization, although transcranial approaches were used in 10% of cases for large pituitary tumors with significant extrasellar components.[48] Over the last decade endoscopic pituitary surgery has gained popularity, based on proposed advantages over microscope-based surgery, including angled scopes improving visualization and resection of tumor in the suprasellar, infrasellar, and parasellar (lateral to the sella) spaces.[49] For example, a 36-patient series reported a 72% gross total resection rate of pituitary tumors invading the cavernous sinus using the endoscopic approach.[49] The endoscopic approach has also been reported to offer better preservation of sinonasal function, reduced length of stay in hospital, decreased pain postoperatively, less blood loss, and less lumbar drain usage.[50] The microscope, however, allows a 3-dimensional view of the surgical field, whereas an endoscope with a monitor may provide inferior resolution. Furthermore, postoperative pain, complications, blood loss, and length of hospital stay are already quite low with the microscopic-based surgery.[50]

Arguments for or against the endoscopic versus microscope-based approaches have not been tested by randomized studies. A meta-analysis of 9 studies showed that pituitary tumors can be removed endoscopically, with good short-term outcomes and low complication rates.[51] Complete tumor removal was achieved in 78%, with 81% to 84% remission rates for EAAs. Visual-field deficits improved in 62% to 100% of patients with deficits. A retrospective cohort study found that endoscopic and microscopic pituitary tumor resection produced similar operative results and complication rates.[50] Thus, endoscopy may allow an experienced neurosurgeon to completely resect tumors invading the cavernous sinus that were previously incompletely resectable, but for noninvasive adenomas. For now the choice between endoscopic and microscope-based surgery falls on surgeon preference, institutional experience, and available resources. It is hoped that long-term studies in the future with a large sample size will compare endoscopic with microscope-based pituitary surgery, and will allow an informed choice between the two methods while accounting for patient-specific and tumor-specific factors.

RADIATION TREATMENT OF PROLACTINOMAS

Radiation, in the form of either fractionated radiation therapy delivered in multiple treatments or stereotactic radiosurgery given in single or few treatments, is rarely used for prolactinomas, given the efficacies of medical and surgical treatments. Moreover, given the high incidence of significant side effects, including hypopituitarism from damage to the stalk, increased risk of strokes and secondary brain tumors, and damage to the optic nerve,[12] radiation therapy or radiosurgery are usually reserved for recurrences following surgery or medical treatment, or if a patient is a poor surgical candidate because of other medical comorbidities. Radiation therapy or radiosurgery may be an option for malignant pituitary carcinomas[12] or DARPs that have failed to respond to higher doses of multiple dopamine agonists.

Previous studies have shown that fractionated stereotactic radiotherapy (FSRT) and Gamma Knife stereotactic radiosurgery (SRS) are both

effective means to control recurrent pituitary adenomas, including prolactinomas, after surgery or medical treatment.[52] Tumor control rates with FSRT for pituitary adenomas can be as high as 95%, but with 1% to 3% risk of damage to the optic nerve and 50% to 100% risk of hypopituitarism.[52–54] In comparison, the risk of hypopituitarism seems to be lower with SRS than with FSRT, ranging from 0% to 36%,[55] whereas the risk of visual deficits may be slightly higher with SRS.[56] With SRS, radiographic prolactinoma control rate, in one study, was 100%, whereas biochemical remission defined by a prolactin level of less than 13 ng/mL in men and less than 27 ng/mL in women was 64%.[57] Although the definition of biochemical remission varies, previous studies have reported 13% to 83% remission rates for patients with prolactinomas who were intolerant or unresponsive to dopamine agonist therapy following SRS.[38,57] Thus, SRS is considered the first-line radiotherapy for pituitary adenomas when both surgery and medical therapies fail. FSRT is considered for large tumors (>3.5 cm) or for tumors less than 5 mm from the optic chiasm.[52]

SUMMARY

Prolactinomas are unique, being the only brain tumor for which remission can typically be achieved through medical management. However, surgery has a clear role in the management of prolactinomas, and patients are ultimately best served when neurosurgeons and neuroendocrinologists work together to inform patients of risks and benefits, allowing patients to make personalized choices in their health care. Further research is also needed to improve current management for the rare subset of prolactinomas resistant to dopamine agonists.

REFERENCES

1. Monson JP. The epidemiology of endocrine tumours. Endocr Relat Cancer 2000;7(1):29–36.
2. CBTRUS. 2009-2010 CBTRUS Statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2004-2006. 2010. Available at: http://www.cbtrus.org. Accessed April 4, 2010.
3. DeLellis RA, Lloyd RV, Heitz PU, et al. World Health Organization classification of tumours: tumours of endocrine organs. Lyon (France): IARC; 2004.
4. Colao A. Pituitary tumours: the prolactinoma. Best Pract Res Clin Endocrinol Metab 2009;23(5):575–96.
5. Gillam MP, Molitch ME, Lombardi G, et al. Advances in the treatment of prolactinomas. Endocr Rev 2006;27(5):485–534.
6. Fainstein Day P, Guitelman M, Artese R, et al. Retrospective multicentric study of pituitary incidentalomas. Pituitary 2004;7(3):145–8.
7. Daly AF, Burlacu MC, Livadariu E, et al. The epidemiology and management of pituitary incidentalomas. Horm Res 2007;68(Suppl 5):195–8.
8. Ezzat S, Asa SL, Couldwell WT, et al. The prevalence of pituitary adenomas: a systematic review. Cancer 2004;101(3):613–9.
9. Losa M, Mortini P, Barzaghi R, et al. Surgical treatment of prolactin-secreting pituitary adenomas: early results and long-term outcome. J Clin Endocrinol Metab 2002;87(7):3180–6.
10. Tyrrell JB, Lamborn KR, Hannegan LT, et al. Transsphenoidal microsurgical therapy of prolactinomas: initial outcomes and long-term results. Neurosurgery 1999;44(2):254–61 [discussion: 261–3].
11. Molitch ME, Elton RL, Blackwell RE, et al. Bromocriptine as primary therapy for prolactin-secreting macroadenomas: results of a prospective multicenter study. J Clin Endocrinol Metab 1985;60(4):698–705.
12. Casanueva FF, Molitch ME, Schlechte JA, et al. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol (Oxf) 2006;65(2):265–73.
13. Daly AF, Rixhon M, Adam C, et al. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. J Clin Endocrinol Metab 2006;91(12):4769–75.
14. Ferrante E, Ferraroni M, Castrignanò T, et al. Nonfunctioning pituitary adenoma database: a useful resource to improve the clinical management of pituitary tumors. Eur J Endocrinol 2006;155(6):823–9.
15. Kim SH, Lee KC. Cranial nerve palsies accompanying pituitary tumour. J Clin Neurosci 2007;14(12):1158–62.
16. Klijn JG, Lamberts SW, de Jong FH, et al. The importance of pituitary tumour size in patients with hyperprolactinaemia in relation to hormonal variables and extrasellar extension of tumour. Clin Endocrinol (Oxf) 1980;12(4):341–55.
17. Schlechte J, Dolan K, Sherman B, et al. The natural history of untreated hyperprolactinemia: a prospective analysis. J Clin Endocrinol Metab 1989;68(2):412–8.
18. Bassetti M, Spada A, Pezzo G, et al. Bromocriptine treatment reduces the cell size in human macroprolactinomas: a morphometric study. J Clin Endocrinol Metab 1984;58(2):268–73.
19. Tindall GT, Kovacs K, Horvath E, et al. Human prolactin-producing adenomas and bromocriptine: a histological, immunocytochemical, ultrastructural, and morphometric study. J Clin Endocrinol Metab 1982;55(6):1178–83.
20. Molitch ME. Medical management of prolactin-secreting pituitary adenomas. Pituitary 2002;5(2):55–65.

21. Webster J, Piscitelli G, Polli A, et al. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. N Engl J Med 1994;331(14):904–9.
22. Pascal-Vigneron V, Weryha G, Bosc M, et al. Hyperprolactinemic amenorrhea: treatment with cabergoline versus bromocriptine. Results of a national multicenter randomized double-blind study. Presse Med 1995;24(16):753–7 [in French].
23. Ono M, Miki N, Kawamata T, et al. Prospective study of high-dose cabergoline treatment of prolactinomas in 150 patients. J Clin Endocrinol Metab 2008;93(12):4721–7.
24. Colao A, Pivonello R, Di Somma C, et al. Medical therapy of pituitary adenomas: effects on tumor shrinkage. Rev Endocr Metab Disord 2009;10(2):111–23.
25. Van Camp G, Flamez A, Cosyns B, et al. Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. Lancet 2004; 363(9416):1179–83.
26. Colao A, di Sarno A, Pivonello R, et al. Dopamine receptor agonists for treating prolactinomas. Expert Opin Investig Drugs 2002;11(6):787–800.
27. Molitch ME. Dopamine resistance of prolactinomas. Pituitary 2003;6(1):19–27.
28. Molitch ME. Pharmacologic resistance in prolactinoma patients. Pituitary 2005;8(1):43–52.
29. Oh MC, Aghi MK. Dopamine agonist-resistant prolactinomas. J Neurosurg 2011;114(5):1369–79.
30. Brue T, Pellegrini I, et al. Prolactinomas and resistance to dopamine agonists. Horm Res 1992;38(1–2):84–9.
31. Morange I, Barlier A, Pellegrini I, et al. Prolactinomas resistant to bromocriptine: long-term efficacy of quinagolide and outcome of pregnancy. Eur J Endocrinol 1996;135(4):413–20.
32. Pellegrini I, Rasolonjanahary R, Gunz G, et al. Resistance to bromocriptine in prolactinomas. J Clin Endocrinol Metab 1989;69(3):500–9.
33. Delgrange E, Daems T, Verhelst J, et al. Characterization of resistance to the prolactin-lowering effects of cabergoline in macroprolactinomas: a study in 122 patients. Eur J Endocrinol 2009;160(5):747–52.
34. Di Sarno A, Landi ML, Cappabianca P, et al. Resistance to cabergoline as compared with bromocriptine in hyperprolactinemia: prevalence, clinical definition, and therapeutic strategy. J Clin Endocrinol Metab 2001;86(11):5256–61.
35. Hagen C, Schroeder HD, Hansen S, et al. Temozolomide treatment of a pituitary carcinoma and two pituitary macroadenomas resistant to conventional therapy. Eur J Endocrinol 2009;161(4):631–7.
36. Neff LM, Weil M, Cole A, et al. Temozolomide in the treatment of an invasive prolactinoma resistant to dopamine agonists. Pituitary 2007;10(1):81–6.
37. Sheehan J, Rainey J, Nguyen J, et al. Temozolomide-induced inhibition of pituitary adenoma cells. J Neurosurg 2011;114(2):354–8.
38. Castinetti F, Regis J, Dufour H, et al. Role of stereotactic radiosurgery in the management of pituitary adenomas. Nat Rev Endocrinol 2009;6(4):214–23.
39. Hamilton DK, Vance ML, Boulos PT, et al. Surgical outcomes in hyporesponsive prolactinomas: analysis of patients with resistance or intolerance to dopamine agonists. Pituitary 2005;8(1):53–60.
40. Faria MA Jr, Tindall GT. Transsphenoidal microsurgery for prolactin-secreting pituitary adenomas. J Neurosurg 1982;56(1):33–43.
41. Hardy J, Beauregard H, Robert F, et al. Prolactin-secreting pituitary adenomas: transsphenoidal microsurgical treatment. Clin Neurosurg 1980;27:38–47.
42. Thomson JA, Davies DL, McLaren EH, et al. Ten year follow up of microprolactinoma treated by transsphenoidal surgery. BMJ 1994;309(6966):1409–10.
43. Abe T, Matsumoto K, Kuwazawa J, et al. Headache associated with pituitary adenomas. Headache 1998;38(10):782–6.
44. Scheithauer BW, Jaap AJ, Horvath E, et al. Clinically silent corticotroph tumors of the pituitary gland. Neurosurgery 2000;47(3):723–9 [discussion: 729–30].
45. Forsyth PA, Posner JB. Headaches in patients with brain tumors: a study of 111 patients. Neurology 1993;43(9):1678–83.
46. Jensen R, Stovner LJ. Epidemiology and comorbidity of headache. Lancet Neurol 2008;7(4):354–61.
47. Fleseriu M, Yedinak C, Campbell C, et al. Significant headache improvement after transsphenoidal surgery in patients with small sellar lesions. J Neurosurg 2009; 110(2):354–8.
48. Buchfelder M, Schlaffer S. Surgical treatment of pituitary tumours. Best Pract Res Clin Endocrinol Metab 2009;23(5):677–92.
49. Kitano M, Taneda M, Shimono T, et al. Extended transsphenoidal approach for surgical management of pituitary adenomas invading the cavernous sinus. J Neurosurg 2008;108(1):26–36.
50. Higgins TS, Courtemanche C, Karakla D, et al. Analysis of transnasal endoscopic versus transseptal microscopic approach for excision of pituitary tumors. Am J Rhinol 2008;22(6):649–52.
51. Tabaee A, Anand VK, Barrón Y, et al. Endoscopic pituitary surgery: a systematic review and meta-analysis. J Neurosurg 2009;111(3):545–54.
52. Sun DQ, Cheng JJ, Frazier JL, et al. Treatment of pituitary adenomas using radiosurgery and radiotherapy: a single center experience and review of literature. Neurosurg Rev 2011;34:181–9.
53. Kokubo M, Sasai K, Shibamoto Y, et al. Long-term results of radiation therapy for pituitary adenoma. J Neurooncol 2000;47(1):79–84.
54. Zierhut D, Flentje M, Adolph J, et al. External radiotherapy of pituitary adenomas. Int J Radiat Oncol Biol Phys 1995;33(2):307–14.
55. Sheehan JP, Jagannathan J, Pouratian N, et al. Stereotactic radiosurgery for pituitary adenomas: a review of

the literature and our experience. Front Horm Res 2006;34:185–205.
56. Sheehan JP, Niranjan A, Sheehan JM, et al. Stereotactic radiosurgery for pituitary adenomas: an intermediate review of its safety, efficacy, and role in the neurosurgical treatment armamentarium. J Neurosurg 2005;102(4):678–91.
57. Tanaka S, Link MJ, Brown PD, et al. Gamma knife radiosurgery for patients with prolactin-secreting pituitary adenomas. World Neurosurg 2010;74(1):147–52.