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Role of surgery in the treatment of microprolactinomas

William T. Couldwell, MD, PhD[a,*], Richard L. Rovit, MD, MSc[b], Martin H. Weiss, MD[c]

[a]*Department of Neurosurgery, University of Utah, Suite 3B409, 30 North 1900 East, Salt Lake City, UT 84132-2303, USA*
[b]*Department of Neurosurgery, St. Vincent Hospital Medical Center, 153 W. 11th St., New York, NY 10011-8397, USA*
[c]*Department of Neurosurgery, University of Southern California, LAC/USC Medical Center, Box 786, 1200 N. State Street, Room #5046, Los Angeles, CA 90033, USA*

Prolactinomas are a common cause of reproductive and sexual dysfunction and account for a large proportion of pituitary adenomas. The objectives for treatment of hyperprolactinemia due to microprolactinomas are to suppress excessive hormone secretion, preserve residual pituitary function, and prevent disease recurrence. These objectives may be achieved in most patients harboring microprolactinomas by medical treatment with effective dopamine agonists or microsurgical or endoscopic adenomectomy by an experienced surgeon. The choice of pituitary surgery should be made in consideration of the volume and location of the adenoma, age of the patient, the desire for restoration of fertility, and the efficacy and tolerability of dopamine agonists. The presence of a symptomatic microprolactinoma, especially in a young patient, should remain an indication for micro- or endoscopic tumor removal. This article reviews the emergence of radiosurgery as a treatment for microprolactinomas.

Prolactinomas are a common cause of reproductive and sexual dysfunction. These tumors account for 40% to 50% of pituitary adenomas [1]. Before the symptoms of hyperprolactinemia are attributed to the presence of a prolactinoma, other causes should be excluded with a careful history (including current medications), physical examination, routine chemistries, and a thyrotropin level. If a prolactin (PRL)-secreting adenoma is suspected, MRI with intravenous contrast will delineate the size and extent of the tumor.

The general objectives of the treatment of hyperprolactinemia are to suppress excessive hormone secretion and its clinical consequences, remove tumor mass, preserve residual pituitary function, and prevent disease recurrence or progression. In the treatment of microadenomas (tumors <10 mm in size), removal of tumor mass is of secondary importance because the size of the tumor is not likely to produce symptoms by mass effect. Although pharmacotherapy should be the first consideration for treatment of macroprolactinomas, the optimal treatment of patients with microprolactinomas remains controversial [2–9].

Medical treatment

Prolactinomas are frequently treated with dopamine agonists (DAs). DAs bind to type 2 dopamine (D_2) receptors on the lactotroph membrane, inhibit PRL synthesis and release, and reduce tumor volume [10]. The widest experience has been accumulated with bromocriptine, which is considered the reference standard in clinical pharmacology with other DAs. These medications are effective; in microprolactinomas, suppression of PRL levels and tumor shrinkage are achieved in more than 80% of patients with bromocriptine at doses of 2.5 to 5 mg per day. In 5% to 10% of patients, the appearance of

* Corresponding author.
E-mail address: william.couldwell@hsc.utah.edu (W.T. Couldwell).

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side effects (eg, nausea, dizziness, and postural hypotension) is a limiting factor in the continuation of treatment. Cabergoline, a selective and long-lasting D_2-receptor agonist given at weekly doses of 0.5 to 2 mg (usually administered twice weekly, although weekly dosing also has been shown to be effective), both normalizes PRL levels and induces tumor shrinkage. The success rate of cabergoline appears to be superior to that of bromocriptine, with less frequent and less severe side effects [11]. This favorable profile enables escalation of doses to achieve normal serum PRL levels in approximately 85% of patients with microadenomas and, more importantly, in a proportion of bromocriptine-resistant patients [12]. Thus, many authors have advocated DAs as primary therapy for both micro- and macroprolactinomas [3]; however, these agents have disadvantages, which include the likely and inconvenient need for life-long therapy, which may become a financial burden for some patients. Furthermore, a minority (10%–25%) of patients are partially or totally resistant to bromocriptine. It may be difficult to distinguish resistance from intolerance to doses of bromocriptine high enough to control PRL secretion by the tumor.

Surgical treatment

The choice of pituitary surgery for prolactinomas should be based on the volume and location of the adenoma, the age of the patient, and the efficacy and tolerability of the dopamine agonists. In general, the cogency of a neurosurgical approach is inversely related to adenoma volume and serum PRL levels. Local microinvasion of the dura or cavernous sinus or the presence of fibrosis related to prior radiation treatment may affect surgical outcome. Surgery should not be considered unless a complete removal with chemical cure of the prolactinoma is an expected outcome. In macroprolactinomas, the success rate for chemical cure by surgery alone is usually less than 50%, and adjunctive medical therapy is needed in the majority of cases. The availability and efficacy of DA therapy have limited the indications for surgery in macroprolactinomas to debulking large tumors before pregnancy, [13] restoration of visual function not immediately responsive to medical treatment, and alleviation of other neurological symptoms in giant adenomas that do not shrink adequately with medical therapy [10]; however, surgical therapy should certainly be considered for those patients with microadenomas amenable to complete resection. The realization that medical therapy will require lifelong treatment in most cases (a particularly significant factor in young patients) and consideration of the very low morbidity and mortality rates associated with contemporary transsphenoidal resection [14] in experienced hands should factor into the decision-making process. Furthermore, the continued evolution of endoscopic approaches for tumor resection, which are somewhat less invasive, may reduce the morbidity rate of the surgical approach even further.

In a recently published review of the surgical management of 121 female patients treated surgically for prolactinomas between 1976 and 1992 by an experienced surgeon, 89% of women who experienced initial remission continued to experience clinical remission; 85% exhibited normal PRL values, and 5% demonstrated mild, asymptomatic, recurrent hyperprolactinemia (PRL values <34 ng/ml) [15]. Lower postoperative PRL values were predictive of long-term remission. In conclusion, successful outcomes and long-term remission were achieved in patients with microadenomas and noninvasive macroadenomas.

In patients with hyperprolactinemia due to a pituitary microprolactinoma, transsphenoidal surgery by an experienced pituitary surgeon should be considered a potentially curative procedure. The financial cost of treatment over a 10-year period is similar in uncomplicated cases to that of long-term DA therapy [16]. Taken together, the presence of a symptomatic microprolactinoma, especially in a young patient, should remain an indication for microscopic or endoscopic tumor removal or medical therapy.

Stereotactic radiosurgery

Stereotactic radiosurgery is becoming increasingly popular as a treatment of pituitary adenomas [17–21]. Indeed, radiosurgery presents an intuitively rational treatment modality for these localized tumors. Current MRI enables resolution and dose planning with accuracy. There is recently published literature that reviews the experience with treatment of functional pituitary tumors with radiosurgery, both as primary and secondary treatment after failed microsurgery. In a recent review of 20 patients who had residual prolactinomas after unsuccessful transsphenoidal surgery, or who had failed medical therapy, and were then

subjected to gamma knife radiosurgery (GKRS) [19], five were treated successfully, with their PRL levels reaching normal values, and 11 experienced improvement. The treatment failed in four patients who were receiving DA at the time of GKRS, suggesting some radioprotective effect of DA therapy. In a cohort of 164 patients with PRL-secreting tumors in China who were treated with primary radiosurgery [21], tumor growth was controlled in all but two of the patients. Chemical cure was achieved in 67 cases (41%), with a mean follow-up of 33.2 months. Among this group, nine infertile women became pregnant 2 to13 months after treatment; all gave birth to normal children. In 31 (29%) of 108 patients followed for greater than 2 years, no improvement in serum PRL was noted. In a recent series of 13 patients in Korea with microprolactinomas treated primarily with GKRS, serum PRL was normalized in three, decreased in eight, and unchanged in two over a median 12-month follow-up [18].

In recent reports, tumor marginal radiation dosages varied from 9 to 35 Gy; dosimetry has yet to be standardized to optimize tumor control and limit side effects. It does appear from initial reports that the time to normalization of hormonal levels may be reduced by a high maximal dose (at least 55Gy) and broad coverage of the target volume within the prescription dose, thereby increasing integral dose [17]. These preliminary results indicate that GKRS as a primary treatment for prolactinomas is effective in controlling tumor growth and may reduce PRL levels in a significant number of patients. The apparent success of growth control may be a lesser victory considering the low propensity for growth in PRL-secreting microadenomas without treatment [22]. A liability of such treatment is continued risk of the development of late hypopituitarism; longer follow-up is necessary to assess the likelihood of this complication.

References

[1] Terada T, Kovacs K, Stefaneanu L, Horvath E. Incidence, pathology, and recurrence of pituitary adenomas: study of 647 unselected surgical cases. Endocr Pathol 1995;6:301–10.

[2] Ciric I, Rosenblatt S, Kerr W Jr, Lamarca F, Pierce D, Baumgartner C. Perspective in pituitary adenomas: an end of the century review of tumorigenesis, diagnosis and treatment. Clin Neurosurg 2000;47: 99–111.

[3] Colao A, Annunziato L, Lombardi G. Treatment of prolactinomas. Ann Med 1998;30:452–9.

[4] Gokalp HZ, Deda H, Attar A, Ugur HC, Arasil E, Egemen N. The neurosurgical management of prolactinomas. J Neurosurg Sci 2000;44:128–32.

[5] Liuzi A, Oppizzi G. Microprolactinomas: why requiem for surgery? J Endocrinol Invest 1996;19: 196–8.

[6] Molitch ME. Medical treatment of prolactinoma. Endocrinol Metab Clin N Am 1999;28:142–69.

[7] Ozgen T, Oruckaptan HH, Ozcan OE, Acikgoz B. Prolactin secreting pituitary adenomas: analysis of 429 surgically treated patients, effect of adjuvant treatment modalities and review of the literature. Acta Neurochir (Wien) 1999;141:1287–94.

[8] Rees DA, Davies JS, Scanlon MF. Microprolactinoma: medical or surgical treatment as first line approach? The case for medical therapy. J Endocrinol Invest 2000;23:122–4.

[9] Zacur HA. Indications for surgery in the treatment of hyperprolactinemia. J Reprod Med 1999;44 (Suppl 12):1127–31.

[10] Faglia G. Prolactinomas and hyperprolactinemic syndrome. In: DeGroot LJ, Jameson JL, editors. Endocrinology. 4th edition. Philadelphia: WB Saunders; 2001. p. 329–42.

[11] Di Sarno A, Landi ML, Marzullo P, et al. The effect of quinagolide and cabergoline, two selective dopamine receptor type 2 agonists, in the treatment of prolactinomas. Clin Endocrinol (Oxf) 2000;53: 53–60.

[12] DelGrange E, Maiter D, Donckier J. Effects of the dopamine agonist cabergoline in patients with prolactinoma intolerant or resistant to bromocriptine. Eur J Endocrinol 1996;134:454–6.

[13] Molitch ME. Management of prolactinomas during pregnancy. J Reprod Med 1999;44(Suppl 12): 1121–6.

[14] Liu J, Das K, Weiss MH, Laws ER, Couldwell WT. The history and evolution of transsphenoidal surgery. J Neurosurg 2001;95:1083–96.

[15] Tyrell JB, Lamborn KR, Hannegan LT, Applebury CB, Wilson CB. Transsphenoidal microsurgical therapy of prolactinomas: initial outcomes and long-term results. Neurosurgery 1999;44:254–61.

[16] Turner HE, Adams CB, Wass JA. Transsphenoidal surgery for microprolactinoma: an acceptable alternative to dopamine agonists? Eur J Endocrinol 1999;140:43–7.

[17] Kim SH, Huh R, Chang JW, et al. Gamma knife radiosurgery for functioning pituitary adenomas. Stereotact Funct Neurosurg 1999;72(Suppl 1): 101–10.

[18] Kim MS, Lee SI, Sim JH. Gamma knife radiosurgery for functioning pituitary microadenoma. Stereotact Funct Neurosurg 1999;72(Suppl 1):119–24.

[19] Landolt AM, Lomax N. Gamma knife radiosurgery for prolactinomas. J Neurosurg 2000;93(Suppl 3): 13–8.

[20] Morange-Ramos I, Regis J, Dufour H, Andrieu JM, Grisoli F, Jaquet P, et al. Short-term

endocrinological results after gamma knife surgery of pituitary adenomas. Stereotact Funct Neurosurg 1998;70:127–38.

[21] Pan L, Zhang N, Wang EM, Wang BJ, Dai JZ, Cai PW. Gamma knife radiosurgery as a primary treatment for prolactinomas. J Neurosurg 2000; 93(Suppl 3):10–3.

[22] Nishioka H, Ito H, Haraoka J, Hirano A. Growth potential of female prolactinomas. Surg Neurol 2001;55:213–7.