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Long-term management and outcome for pituitary tumors

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Most reports in the literature on outcomes in pituitary tumors deal with immediate postoperative results as to the extent of removal of a macroadenoma, the improvement in vision, the endocrine cure in hypersecreting microadenoma and in regard to operative morbidity and mortality [1–3]. Our personal experience is based on case material of close to 1500 pituitary adenomas operated on over a period of 35 years and on a score of other pituitary tumor patients who were treated medically at our institution. We have followed our patients for as long as temporally and spatially possible and for as long as they deemed it necessary themselves. Some patients have been followed for as long as 30 years. The average follow-up of our patients is 8 years.

Prolactinomas

Our experience demonstrates that most patients with prolactinomas have good outcomes regardless of the type of management. In fact, we have withheld treatment in a number of our patients with suspected microprolactinomas who were evaluated at our institution. The treatment was withheld for many reasons, including age, intercurrent medical illnesses, and patient preference. Many of these patients had their suspected prolactinomas discovered on an incidental basis as the result of unrelated imaging of the brain and pituitary region, and many of these patients have preferred no treatment after being informed as to the natural course of a suspected prolactin-secreting pituitary microadenoma. Long-term follow-up of these patients has shown no appreciable growth in more than 90% of patients. Consequently, when a decision is made not to proceed with surgery or medical therapy, follow-up imaging is still necessary for a period of at least 5 years.

Medical treatment of prolactinomas with the dopamine agonists bromocriptine or cabergoline is associated with excellent results [4–6]. This includes normalization of the menses, cessation of galactorrhea, and normalization of the serum prolactin level in patients with microprolactinomas and medium-sized tumors as well as a significant reduction in the tumor size and serum prolactin level in macroprolactinomas, especially in the invasive group. We have a subset of 14 patients with giant invasive prolactinomas treated with dopamine agonists who have done extremely well in terms of an improvement in their symptoms caused by the compression of the suprasellar structures, a decrease in the tumor size on imaging studies, and a serum prolactin level reduction [7]. Surgery can be treacherous in these patients in that invasive prolactinomas are surgically not easily palliated. These tumors are ofttimes rather hard and rubbery; they tend to destroy the skull base anatomy and surround the neurovascular structures in the cavernous sinus to the extent that they are not only not resectable but difficult to remove in a meaningful way without serious complications.

Indications for transsphenoidal microsurgery for removal of a prolactin-secreting pituitary microadenoma include failure of medical management with dopamine agonists (continued enlargement of a microprolactinoma or continued elevation of the serum prolactin level); patient intolerance to dopamine agonists as a result of side effects; and patient preference after a thorough explanation as to the medical and surgical treatment

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options and their implications, side effects, and possible complications. Indeed, most microprolactinomas are surgically curable [8]. A postoperative serum prolactin level of less than 5 ng/mL (preferably less than 2 ng/mL) portends an excellent long-term prognosis for cure. In contrast, a serum prolactin elevation of greater than 10 ng/ mL is frequently associated with recurrences that can occur within a period of 6 months to 2 years. Noninvasive macroprolactinomas are also curable with surgery. This is especially true if they are first shrunken with medical therapy using dopamine agonists for a period of approximately 6 to 12 weeks before surgery. If they are not cured, postoperative use of dopamine agonists for an indefinite period is indicated. It is possible to maintain these patients in good health and with no evidence of tumor progression for decades with such combined treatment.

Growth hormone-secreting adenomas

The only predictable long-term outcomes in patients with acromegaly are those that are associated with a surgical cure [9–11]. The criteria for a surgical cure are a postoperative serum growth hormone (GH) level of less than 2.0 ng/ mL, suppression of the GH level to less than 1 ng/ mL after an oral glucose tolerance test (OGTT), and normalization of the insulin growth factor-1 (IGF-1). When these criteria for cure are met, the long-term outcomes are excellent and the incidence of recurrence is small (less than 5%) [12–14]. In contrast, there is ample evidence in the literature that serum GH levels of greater than 2.5 ng/mL are associated with active acromegaly, because of which the patient's life expectancy may be shortened [15–17]. It has been our experience that the surgical cure as defined by these strict criteria [35] is not necessarily dependent on the preoperative tumor size or GH level as previously described in the literature. For example, we have had patients with a preoperative GH level of greater than 100 ng/mL and a tumor size of 2 cm who were cured, mostly because their tumors were enclosed and noninvasive. Indeed, it is the predilection of GH-secreting pituitary adenomas to invade the surrounding dura, especially in the cavernous sinus region, that precludes cure. The long-term follow-up results in these patients can improve when surgical treatment is combined with medical therapy using the somatostatin analogues Octreotide and Sandostatin-LAR [18–21]. There is some controversy as to whether preoperative use of the somatostatin analogues promotes improved surgical results [10,22,23]. It has been our experience that preoperative medical therapy can facilitate the surgical removal of both GH-secreting microadenomas as well as macroadenomas, although there is no statistical evidence that the surgical outcomes are better when somatostatin analogues are used before surgery. In our practice, the decision to proceed with preoperative medical therapy is made on a case-by-case basis. One of the prime indications in this regard is a GH-induced cardiomyopathy, which may preclude safe general anesthesia and surgery. The improvement in the ejection fraction noted after treatment with somatostatin analogues is quite dramatic in most patients.

It has been shown in the literature that fractionated teletherapy is ineffective in normalizing the serum GH levels according to the surgical criteria for cure [24]. Consequently, fractionated teletherapy is not effective in eradicating acromegaly. In contrast, radiosurgery has been shown to be effective in eradicating acromegaly in approximately 50% of patients so treated [25–27]. Long-term good outcome of treatment in patients with acromegaly depends largely on how early in the disease process the diagnosis is made and on how early the treatment is instituted. The prognosis is by far better for a normal life expectancy and high quality of life when the diagnosis is made early and treatment is instituted accordingly. In contrast, many patients with advanced acromegaly who harbor invasive tumors cannot be cured in spite of the combination of treatments available today; consequently, their life expectancy is shortened.

There is a subset of acromegalic patients who have had a long-standing history of acromegalic changes, some of whom are first diagnosed when they became septo- or octogenarians, and whose imaging studies show evidence of a relatively small tumor. These patients have been symbiotic with their acromegaly and probably do not require treatment. If treatment is instituted, no significant improvement should be realistically expected. Thus, the natural course of an acromegalic patient is not always predictable; some patients have a rapidly progressive florid acromegaly, and others go on along in life with some but not devastating changes and do not seem to have a shortened life expectancy. Because it is difficult to predict which patients will go on and have a progressive acromegaly, it is best to treat every acromegaly initially when it is first diagnosed,

especially in younger patients, and even more so when cure is anticipated after surgery.

There have been numerous reports in the literature on the various proliferative and molecular biology indexes that would help to determine which of the acromegalic tumors would tend to be more aggressive in terms of future biologic behavior. These indexes, such as the KI-67 and others, have not proven to be a statistically significant and reliable prognostic factor in this regard, however [9,28–33].

Cushing's disease

Patients with Cushing's disease who undergo transsphenoidal microsurgical removal of their corticotropin-secreting microadenoma usually do well in the long run if the immediate postoperative plasma cortisol drops down to below the level of 2 μg/dL within 24 to 48 hours after surgery. The recurrence rate is then approximately 5%. If a recurrence occurs, follow-up MRI should be obtained in search of a recurrent microadenoma. If none is found, petrosal sinus sampling tests can be performed in search of a central to peripheral venous corticotropin gradient. With and without that study, re-exploration of the pituitary for a recurrent microadenoma is usually not as successful as the initial operation in accomplishing a cure. Other treatment options include chemical and surgical adrenalectomy.

It is a more complex issue in terms of long-term management when a patient presents with the clinical picture and laboratory data consistent with Cushing's disease and a microadenoma is not found at initial anterior pituitary exploration. The present criteria for the diagnosis of Cushing's disease include evidence of hypercortisolism as demonstrated by a 24-hour urinary free cortisol determination and a 24-hour hourly plasma cortisol determination that show the plasma cortisol to be higher than 5 μg/dL in the early morning hours (around midnight to 2:00 am), determination of concordance of corticotropin and plasma cortisol secretion based on a 24-hour hourly corticotropin and plasma cortisol determination, evidence of corticotropin and plasma cortisol suppression with high but not low doses of dexamethasone, and, finally, evidence of a brisk rise in corticotropin concentration on corticotropin-releasing hormone (CRH) stimulation obtained in conjunction with the petrosal sinus sampling test. Absence of any of these criteria, especially an inadequate response to CRH stimulation, raises the suspicion that the patient may have an ectopic source of corticotropin secretion. Indeed, it has been our experience that the absence of any of these criteria in conjunction with negative MRI findings for a microadenoma portends a relatively uncertain prognosis in terms of finding a microadenoma at surgery.

To be sure, some of those criteria (eg, corticotropin response to CRH stimulation) carry more weight in terms of diagnostic accuracy. Consequently, we have explored the pituitary in patients who may not have responded accordingly on the suppression test but did have a vigorous corticotropin response to CRH stimulation on the petrosal sinus sampling test. Overall, the incidence of negative explorations in patients with negative MRI findings may be as high as 5% to 15%. It is therefore of the utmost importance that each and every patient be evaluated thoroughly along the above-described lines, with some of the endocrine testing repeated if the results are not clearcut and diagnostic. In patients in whom there is preponderant endocrine evidence for Cushing's disease, a pituitary exploration is carried out. Given a negative exploration of the pituitary, one has several options. These include a complete hypophysectomy versus removal of the central portion of the gland, which harbors most of the corticotropin-secreting pituitary cells. Considering that this arrangement within the anterior pituitary is not unique, an anterior hypophysectomy in a female patient who is beyond childbearing age is probably indicated. Such issues have to be discussed with the patient and family as well as by the treating physicians at length before surgery. Even so, we have had three patients whose anterior pituitary was removed completely without histologic evidence of a microadenoma. In that case, a surgical or chemical adrenalectomy should be performed if the Cushing's disease is deemed threatening to the patient's overall health and longevity. Medical treatment is usually unsuccessful.

Nonsecreting pituitary macroadenomas

Pituitary adenomas can be classified according to the size and appearance of the sella and the size and ramification of the adenoma itself. If the sella is normal in size, it is classified as grade I. An enlarged and ballooned but enclosed sella is classified as grade II. Local erosion along the sella floor is classified as grade III. A complete sella erosion with loss of sella anatomy is classified

as grade IV. Pituitary adenomas with no suprasellar extension are labeled as stage 0. Those with suprasellar extension into the cisterns are labeled as stage A, those that extend to the anterior recesses of the third ventricle are labeled as stage B, and those that extend as high up as the foramen of Monro are labeled as stage C. Tumors with predominantly retrosellar extension behind the clivus or anteriorly along the planum are classified as stage D, and those invasive adenomas that predominantly involve the cavernous sinus are classified as stage E [34].

The goal of surgical therapy of macroadenomas is to remove the mass effect on the optic nerves and chiasm as well as on the cavernous sinus, accomplish gross total removal and thus preclude the necessity for postoperative radiation therapy, prevent a recurrence, and, finally, to preserve the residual normal anterior pituitary. The residual normal pituitary usually surrounds the pituitary adenoma as a thin layer of tissue, most frequently observed superiorly beneath the diaphragma sella. On the preoperative MRI study, the residual normal anterior pituitary is represented by a thin layer of high signal intensity surrounding a relatively hypointense adenoma. At operation, this layer can be saved by following a cleavage plane between the surface of the tumor and this usually distinct layer of tissue. The separation is facilitated by an initial internal decompression of the tumor that results in a slackening of the tumor and an opening of a cleavage plane between the adenoma surface, the so-called pseudocapsule, and the residual normal anterior pituitary. Given gross total removal of the macroadenoma, the recurrence rate is usually low. Postoperative radiation therapy is rarely necessary and is usually reserved for patients who have had inadequate partial removal for whatever reason or when there has been a recurrence. A recurrent nonsecreting pituitary adenoma can be reoperated on. If the recurrence occurred in a relatively short time after initial gross total removal, it is probably advisable to proceed with radiation therapy after the re-resection. Fractionated teletherapy using conformal fields is quite effective in eradicating the tumor; however, it also induces hypopituitarism in at least 50% of patients. Radiosurgery using the Gamma Knife or linear accelerator (LINAC)–based radiosurgery can also be employed in recurrences that are not too large with high effectiveness and probably less chance for anterior pituitary insufficiency. Whenever possible, however, a surgical re-resection should be the first choice of treatment for recurrent nonsecreting pituitary macroadenomas. A point of caution is that if the patient initially underwent a craniotomy for a pituitary adenoma, a recurrent tumor should probably also be approached via a craniotomy. The reason for this is that during a craniotomy, the arachnoid barrier between the tumor and the intra-arachnoid neurovascular structures is breached, resulting in adhesions between the neurovascular structures and the dome of the recurrent tumor. If the recurrent tumor is then approached transsphenoidally, the surgical manipulation could result in injury to the neurovascular structures.

Summary

As we enter the twenty-first century, neurosurgeons and endocrinologists are armed with a greater variety of treatment options for pituitary adenomas, both secreting and nonsecreting. These include an ever-increased availability of different drugs that can be used for suppression of hypersecretion of pituitary adenomas in conjunction with their shrinkage (at least for the duration of the treatment), surgical techniques that have greatly improved, and newer techniques, such as endoscopic microsurgery, that have been added to the surgeon's armamentarium. Radiation therapy techniques have also improved in terms of structuring the radiation field as well as in terms of dosimetry and delivery.

References

[1] Ciric I, Mikhael MD, Stafford T, Lawson L, Garces R. Transsphenoidal microsurgery of pituitary macroadenomas with long-term follow-up results. J Neurosurg 1983;59:395–401.

[2] Ciric I, Ragin A, Baumgartner C, Pierce D. Complications of transsphenoidal surgery: results of a national survey, review of the literature and personal experience. Neurosurgery 1997;40:225–37.

[3] Ross DA, Wilson CB. Results of transsphenoidal microsurgery for growth hormone-secreting pituitary adenoma in a series of 214 patients. J Neurosurg 1988;68:854–67.

[4] Biller BM, Molitch ME, Vance ML, et al. Treatment of prolactin-secreting macroadenomas with the once-weekly dopamine agonist cabergoline. J Clin Endocrinol Metab 1996;81:2338–43.

[5] Colao A, Di Sarno A, Sarnacchiaro F, et al. Prolactinomas resistant to standard dopamine agonists respond to chronic cabergoline treatment. J Clin Endocrinol Metab 1997;82:876–83.

[6] Ferrari CI, Abs R, Bevan JS, et al. Treatment of macroprolactinoma with cabergoline. A study of 85 patients. Clin Endocrinology 1997;46:409–13.
[7] Ciric I. Giant and invasive prolactin-secreting pituitary adenoma. In: Winchester DP, Brennan MF, Dodd GD, Jr, et al., editors. Tumor board case management. Philadelphia: Lippincott-Raven; 1997. p. 631–4.
[8] Feigenbaum SL, Downey DE, Wilson CB, Jaffe RB. Transsphenoidal pituitary resection for preoperative diagnosis of prolactin-secreting pituitary adenoma in women: long-term follow-up. 1996; 81:1711–9.
[9] Anniko MD, Wersall J. DNA studies for prediction of prognosis of pituitary adenomas. Adv Biosci 1988;69:45–52.
[10] Colao A, Ferone DR, Cappabianca P, et al. Effect of octreotide pretreatment on surgical outcome in acromegaly. J Clin Endocrinol Metab 1997;82: 3308–14.
[11] Swearingen B, Barker FG II, Katnelson L, et al. Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly [comment]. J Clin Endocrinol Metab 1998;83:3419–26.
[12] Davis DH, Laws ER, Jr., Ilstrup DM, et al. Results of surgical treatment for growth hormone-secreting pituitary adenomas. J Neurosurg 1993;79:70–5.
[13] Fahlbusch R, Honegger J, Buchfelder M. Evidence supporting surgery as treatment of choice for acromegaly. J Endocrinol 1997;155(Suppl):S53–5.
[14] Tindall GT, Oyesiku NM, Watts NB, Clark RV, Christy JH, Adams DA. Transsphenoidal adenomectomy for growth hormone-secreting pituitary adenomas in acromegaly: outcome analysis and determinants of failure. J Neurosurg 1993;78:205–15.
[15] Clayton RN. New developments in the management of acromegaly. Should we achieve absolute biochemical cure? J Endocrinol 1997;155(Suppl 1): S23–9.
[16] Holdaway IM, Rajasoorya C. Epidemiology of acromegaly. Pituitary 1999;2:29–41.
[17] Rajasoorya C, Holdaway IM, Wrightson P, Scott DJ, Ibbertson HK. Determinants of clinical outcome and survival in acromegaly. Clin Endocrinol 1994;41:95–102.
[18] Farooqi S, Bevan JS, Shepperd MC, Wass JAH. The therapeutic values of somatostatin and its analogues. Pituitary 1999;2:79–88.
[19] Gisslis JC, Noble S, Goa KL. Octreotide long-acting release (LAR). Drugs 1997;53:681–99.
[20] Lancranjan I, Atkinson AB. Sandostain LAR in acromegalic patients. Results of a European multicare study with Sandostain LAR in acromegalic patients. Pituitary 1999;1:105–14.
[21] Newman CB. Medical therapy for acromegaly. Endocrinol Metab Clin North Am 1999;28:171–90.
[22] Lucas-Morante T, Garcia-Uria J, Estrada J, et al. Treatment of invasive growth hormone pituitary adenomas with long-acting somastatin analog SMS 201–995 before transsphenoidal surgery. J Neurosurgery 1994;81:10–4.
[23] Stevenaert A, Beckers A. Presurgical octreotide treatment in acromegaly. Acta Endocrinol 1993; 129(Suppl 1):18–20.
[24] Jaffe CA. Reevaluation of conventional pituitary irradiation in the therapy of acromegaly. Pituitary 1999;2:55–62.
[25] Jackson IMD, Norene G. Role of gamma knife radiosurgery in acromegaly. Pituitary 1999;2:71–8.
[26] Landolt AM, Haller DR, Lomax N, et al. Stereotactic radiosurgery for recurrent surgically treated acromegaly: comparison with fractionate radiotherapy. J Neurosurg 1998;88:1002–8.
[27] Morange-Ramos I, Regis J, Defour H, et al. Gamma-knife surgery for secreting pituitary adenomas. Acta Neurochir (Wien) 1998;140:437–43.
[28] Amar AP, Hinton DR, Krieger MD, Weiss MH. Invasive pituitary adenomas: significance of proliferation parameters. Pituitary 1992;2:117–22.
[29] Ezzat S, Smyth HS, Raymar L, Asa SL. Heterogeneous in vivo and in vitro expression of basic fibroblast growth factor by human pituitary adenomas. J Clin Endocrinol Metab 1995;80:878–84.
[30] LeRiche VK, Asa SL, Ezzat S. Epidermal growth factor and its receptor (EGFR) in human pituitary adenomas: EFG-R correlates with tumor aggressiveness. J Clin Endocrinol Metab 1995;81:656–62.
[31] Thepar K, Scheithauer BW, Kovacs K, Pernicone PJ, Laws ER, Jr. p53 expression in pituitary adenomas and carcinomas: correlations with invasiveness and tumor growth fractions. Neurosurgery 1996;38:763–70.
[32] Zhang X, Horwitz GA, Heaney A, Prezant TR, Melmed S. Pituitary adenomas: marker for functional tumor invasiveness. J Clin Endocrinol Metab 1999;84:761–7.
[33] Zhang X, Horwitz GA, Prezant TR, et al. Structure, expression and function of human pituitary tumors transforming gene (PTTG). Mol Endocrinol 1999;13:156–66.
[34] Hardy J, Vezina JL. Transsphenoidal neurosurgery of intracranial neoplasms. In: Thompson RA, Green JR, editors. Advances in Neurology. New York: Raven Press; 1976. p. 261–74.
[35] Sheaves R, Jenkins P, Blackburn P, et al. Outcome of transsphenoidal surgery for acromegaly using strict criteria for surgical cure. Clin Endocrinol 1996;45:407–13.