J Neurosurg 97:307–314, 2002

Predictive value of serum prolactin levels measured immediately after transsphenoidal surgery

Arun P. Amar, M.D., William T. Couldwell, M.D., Ph.D., Joseph C. T. Chen, M.D., Ph.D., and Martin H. Weiss, M.D.

Department of Neurosurgery, Keck School of Medicine, University of Southern California, Los Angeles, California; and Department of Neurosurgery, University of Utah School of Medicine, Salt Lake City, Utah

Object. Prolactin-secreting pituitary adenomas may be managed by surgery, medication, radiotherapy, or observation. The authors reviewed a consecutive series of patients who were followed for at least 5 years after surgery to assess the prognostic significance of preoperative factors (tumor size and prolactin level) and an immediate postoperative factor (prolactin level obtained the morning after surgery) on long-term hormonal outcome, thereby clarifying the indications for surgical removal of tumor, the definition of successful treatment outcomes, and the nature of "recurrent" tumors.

Methods. Between 1979 and 1991, 241 patients with prolactinomas underwent transsphenoidal resection. Nineteen patients were lost to follow-up review, whereas the remaining 222 patients underwent measurement of their prolactin levels on postoperative Day 1 (POD 1), at 6 and 12 weeks, and every 6 months thereafter for a minimum of 5 years. On POD 1, prolactin levels in 133 patients (Group 1) were lower than 10 ng/ml, in 43 patients (Group 2) between 10 and 20 ng/ml, and in 46 patients (Group 3) higher than 20 ng/ml. At 6 and 12 weeks, normal prolactin levels ($\leq$ 20 ng/ml) were measured in 132 (99%) of the 133 patients in Group 1 but only in 32 (74%) of the 43 patients in Group 2. By 5 years postoperatively, normal levels of prolactin were still measured in 130 patients (98%) in Group 1 compared with only five patients (12%) in Group 2. No patient with a prolactin level lower than 3 ng/ml on POD 1 was found to have an elevated hormone level at 5 years. The likelihood of a long-term chemical cure was greater for patients with microadenomas (91% cure rate) than for those with macroadenomas (33%). Preoperative prolactin levels also correlated with hormonal outcome.

Conclusions. Prolactin levels lower than 10 ng/ml on POD 1 predict a long-term chemical cure in patients with microadenomas (100% cure rate) and those with macroadenomas (93% cure rate). In contrast, a cure is not likely to be obtained in patients with normal levels ranging between 10 and 20 ng/ml on POD 1 if they harbor macroadenomas (0% cure rate). A recurrence reported several years after surgery probably represents the presence of persistent tumor that was not originally removed. If the initial operation was performed by an experienced surgeon, however, reoperation is not likely to yield a chemical cure.

Key Words • pituitary adenoma • prolactin • prolactinoma • transsphenoidal approach

Prolactin-secreting adenomas (prolactinomas) are the most common type of functional pituitary tumor. Despite their frequency, many aspects of their management remain controversial, including indications for operative removal, the definition of successful treatment outcomes, and therapy of recurrent tumors.[3] These uncertainties arise from several features that are unique to the biology and growth of these tumors. 1) Prolactinomas produce demonstrable symptoms relatively early in their development and are often detected at smaller stages than other types of pituitary tumors, particularly in female patients.[63] 2) Despite the high prevalence of these tumors, the clinical manifestations of hyperprolactinemia are not as life-threatening as those of excessive adrenocorticotrophic hormone or growth hormone secretion in Cushing disease and acromegaly, respectively.[21,22,32,59,63] Nonetheless, the endocrinological consequences of excessive prolactin secretion (such as hypogonadism, infertility, and osteoporosis) require treatment, preferably by addressing the underlying cause. 3) The natural history of prolactinomas often is indolent, and neither tumor size nor prolactin levels change significantly over time in most cases. Data from six series of patients with microadenomas who refused treatment, including two of our own studies, indicate that the risk of progression to macroademona is less than 7% over a 2- to 6-year interval of observation.[29,32,42,50,61] 4) Unlike other types of pituitary tumors, many prolactinomas may be safely and effectively managed by a regimen of pharmacological agents alone. The efficacy of bromocriptine in reducing serum prolactin levels, diminishing tumor size, and inhibiting tumor growth, is well established.[7,35,47,58,60,65] The recent availability of cabergoline, a synthetic agonist with a high specificity and affinity for the D2 dopaminergic receptor, represents an advance over bromocriptine in its efficacy, tolerability, and compliance.[6,11,14,33,39,57]

In an effort to resolve some of the disease management

Abbreviation used in this study: POD 1 = postoperative Day 1.

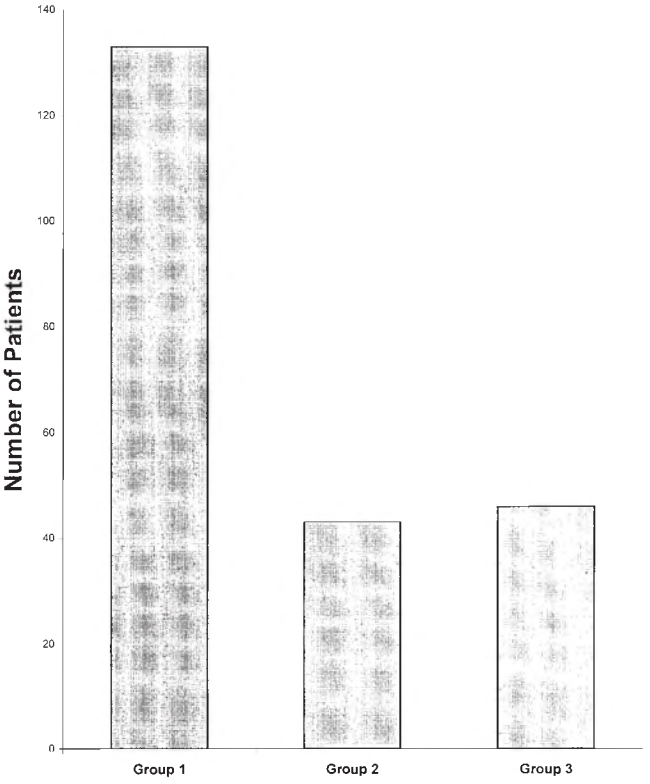

FIG. 1. Bar graph demonstrating stratification of 222 patients according to fasting prolactin levels on the morning after surgery. Group 1 consisted of 133 patients (60%) with serum prolactin levels lower than 10 ng/ml, Group 2 included 43 patients (19%) with levels between 10 and 20 ng/ml, which is still considered normal, and Group 3 was composed of the remaining 46 patients (21%) in whom prolactin levels were greater than 20 ng/ml on POD 1.

controversies surrounding prolactinomas, we retrospectively reviewed our experience with patients harboring these tumors whose cases were followed at least 5 years postoperatively to assess the prognostic value of serum prolactin levels obtained the morning after surgery. The ability to predict long-term outcomes in patients with prolactin-secreting pituitary adenomas immediately following transsphenoidal resection is important for determining the vigilance with which residual or recurrent tumor is sought and for allaying the concerns of patients who want to know whether their disease has been cured.[19] Furthermore, this analysis of immediate and long-term endocrinological response helps to clarify the issues of patient selection (indications for surgery), the definition of successful treatment outcomes, and the nature of "recurrent" tumors.

Clinical Material and Methods

Since 1968, the senior surgeon (M.H.W.) has performed more than 2500 transsphenoidal operations, including more than 500 resections of prolactin-secreting pituitary adenomas. From this latter group, we retrospectively selected a series of consecutive patients whose cases were followed for a minimum of 5 years after the procedure so that we could correlate their long-term outcomes with two preoperative factors (tumor size and prolactin level) and hormone levels determined in the immediate postoperative period. This study met the requirements of the Institutional Review Board of the University of Southern California.

Patient Population

Between July 1979 and May 1991, 241 patients underwent transsphenoidal surgery for prolactin-secreting tumors. Nineteen of these patients were lost to follow-up review, whereas the remaining 222 patients have been observed for a mean of 14 years (range 6–18 years).

There were 191 female and 31 male patients in this group, ranging in age from 15 to 63 years (mean 29 years). Although prolactinomas are discovered at autopsy with equal frequency in women and men, the gender differential in our study reflects disparities in the way such tumors are detected in vivo and referred for surgical evaluation. The demographic characteristics of this population are qualitatively similar to those from other large series of prolactin-secreting tumors.[3,63]

Clinical presentations of the disease in all patients included primary amenorrhea in 12 female patients (5%), none of whom had associated galactorrhea. Secondary amenorrhea developed in an additional 160 female patients (72%), 82 of whom were found to suffer from galactorrhea as well. Seventeen male patients (8%) presented with decreased libido, impotence, or sterility; galactorrhea accompanied the symptoms in six of these patients. Visual loss, ranging in duration from 2 to 24 months, was the initial complaint in another 19 female patients (9%) and 14 male patients (6%).

The patients were almost equally divided between those harboring microadenomas (107 patients) and those with macroadenomas (115 patients). Preoperative prolactin levels ranged from 89 to 6460 ng/ml and were distributed as follows: less than 200 ng/ml in 110 patients; 201 to 600 ng/ml in 80 patients; and greater than 601 ng/ml in 32 patients (normal $\leq$ 20 ng/ml). In no patient was there a concomitant elevation of serum levels of growth hormone or insulin-like growth factor 1, and no tumor reacted positively for growth hormone with immunostaining.

Perioperative Management

Although most patients underwent initial attempts at pharmacological management with bromocriptine, surgery was mandated by bromocriptine failure or intolerance, progressive visual loss, or the desire for fertility. All patients were treated before the availability of cabergoline, which was approved for use by the United States Food and Drug Administration in 1997.

All patients underwent transsphenoidal microsurgical adenomectomy via a unilateral, transseptal approach.[12] Pathological confirmation of prolactinoma was obtained in all cases. The surgical objectives were gross-total tumor resection with preservation of normal gland, although in cases in which there was extensive invasion of the cavernous sinus, complete tumor removal was not always feasible. Hypophysectomy was not performed in any case. Dehydrated alcohol was applied to the tumor bed if the integrity of the arachnoid was maintained. Patients were not maintained on a regimen of glucocorticoids during the postoperative period unless they suffered from adrenal insufficiency preoperatively.

Postoperative Evaluation and Patterns of Clinical Response

In all patients fasting morning prolactin levels were determined by withdrawing serum on POD 1 and random serum levels were again sampled at 6 weeks, 12 weeks, and every 6 months thereafter for a minimum of 5 years. Based on these serial evaluations, three patterns of response could be observed. Some patients experienced immediate hormonal normalization that was maintained over time ("chemical cures"). Others experienced immediate normalization, followed by a relapse of hyperprolactinemia after a variable period of time ("endocrinological recurrences"). The remaining demonstrated improved, but persistently elevated levels of prolactin, even in the initial postoperative period ("immediate endocrinological failures").

All patients who experienced endocrinological recurrence or immediate endocrinological failure underwent at least one follow-up imaging study after the elevated prolactin level was detected.

Results

Endocrinological Response on POD 1

The 222 patients were stratified into three groups according to their fasting prolactin levels on the morning after surgery (Fig. 1). Group 1 consisted of 133 patients (60%) in whom serum prolactin levels were lower than 10 ng/ml. Group 2 included 43 patients (19%) in whom prolactin levels were between 10 and 20 ng/ml, which are still considered normal values in our laboratory. Group 3 was composed of the remaining 46 patients (21%) in whom prolactin levels were higher than 20 ng/ml on POD 1. The long-term outcomes of these three groups will be considered separately.

Long-Term Outcomes in Groups 1 and 2

Of the 222 patients in this study, 176 (79%) were assigned to Group 1 or 2 because hormone testing revealed normal prolactin levels on POD 1. All these patients improved clinically. Galactorrhea resolved in all patients who suffered from this symptom preoperatively, and 151 (88%) of the 172 women presenting with amenorrhea resumed normal menses. In addition, 72 (75%) of 96 women who wanted to achieve pregnancy did so.

At 6 and 12 weeks postoperatively, normal prolactin levels were maintained in 132 (99%) of the 133 patients in Group 1 and, and, by 5 years, prolactin levels were still 20 ng/ml or lower in 130 patients (98%) (Fig. 2). No patient in whom the prolactin level was lower than 3 ng/ml on POD 1 was found to have an elevated level after 5 years.

In contrast, normal prolactin levels were found in only 32 (74%) of the 43 patients in Group 2 at 6 and 12 weeks, and after 5 years, in only five patients (12%) was a chemical cure maintained (Fig. 2).

Among the 176 patients in whom normal prolactin levels were measured on POD 1, 41 (23%) experienced endocrinological recurrence; three of these patients were from Group 1 and 38 were from Group 2. Two of the recurrences developed in women after successful gestations; both were Group 2 patients who resumed normal menses and became pregnant within 6 months after the operation.

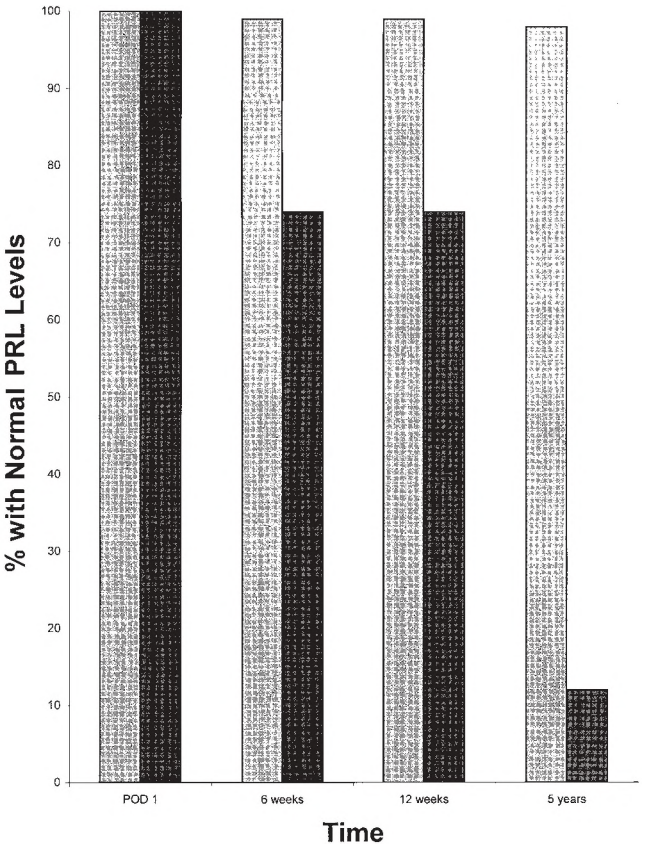

FIG. 2. Bar graph showing long-term endocrinological responses in patients in Groups 1 *(gray bars)* and 2 *(black bars)*.

All patients who experienced relapse had harbored macroadenomas preoperatively, whereas none of the patients with microadenomas suffered recurrence. The mean duration to relapse was 9 months postoperatively, and all recurrences developed within 33 months after surgery. No patient in whom a normal prolactin level was measured at 5 years experienced a relapse subsequently.

All patients who experienced a relapse underwent at least one follow-up magnetic resonance imaging study, but only two were found to have imaging evidence of residual or recurrent tumor. One of these patients underwent reoperation, but failed to achieve a chemical cure for the disease even after the second procedure. In no instance did a recurrence manifest in a prolactin level exceeding 55 ng/ml. All 41 patients resumed treatment with bromocriptine, although in no case has a normal serum prolactin level been achieved. No patient has received postoperative radiotherapy or other adjuvant therapies.

Long-Term Outcome in Group 3

Among the 46 patients in whom immediate endocrinological failure occurred, the mean prolactin level on POD 1 was 780 ng/ml (range 33–2480 ng/ml). Most of these patients who had presented with amenorrhea and galactorrhea remained symptomatic, but 81% of those with visual impairment improved. Two patients underwent reoperation, but a chemical cure was not achieved, despite the second procedure. All patients were treated with bromocriptine,

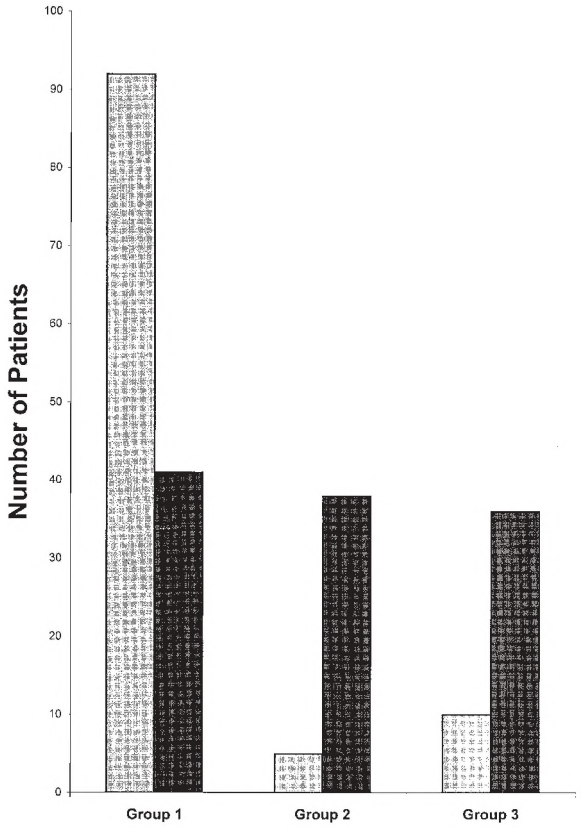

FIG. 3. Bar graph demonstrating the effect of tumor size on immediate postoperative endocrinological outcomes. Most of the 107 patients with microadenomas were in Group 1 *(gray bars)*, whereas the distribution across groups in the 115 patients with macroadenomas *(black bars)* was nearly uniform.

but in no cases has a normal serum prolactin level been achieved. No patient has required postoperative radiation therapy.

Relationship Between Tumor Size and Outcome

Tumor size was found to correlate with both immediate (Fig. 3) and long-term (Table 1) endocrinological outcomes. Among the 107 patients with microadenomas, normal prolactin levels were measured on POD 1 in 97 (91%), 92 patients in Group 1 and five patients in Group 2. At five years postoperatively, a chemical cure was maintained in all 97 patients (100%), and no patients with a microadenoma has experienced endocrinological recurrence.

In contrast, of the 115 patients with macroadenomas, the distribution among the three groups on POD 1 was more uniform: 41 patients were from Group 1, 38 from Group 2, and 36 from Group 3. Thus, normal prolactin levels were found immediately after surgery in only 79 patients (69%) with macroadenomas, and immediate endocrinological failure was observed in 36 patients (31%). At 5 years, only 38 (48%) of these 79 patients in whom normal prolactin levels were measured postoperatively continued to benefit from a chemical cure, whereas the other 41 patients (52%) experienced recurrence. These 38 patients all belonged to Group 1. Therefore, 38 (93%) of the 41 patients with macroadenomas in Group 1 experienced chemical cures, whereas none

TABLE 1

Effect of tumor size in long-term endocrinological outcome in 222 patients who underwent surgery for prolactinomas

Group	5-Yr Cure Rate (%)	
	Patients W/ Microadenoma	Patients W/ Macroadenoma
1	92 of 92 (100)	38 of 41 (93)
2	5 of 5 (100)	0 of 38 (0)
3	0 of 10 (0)	0 of 36 (0)
all patients	97 of 107 (91)	38 of 115 (33)

of the 38 patients in Group 2 achieved a cure (100% recurrence rate).

Relationship Between Preoperative Prolactin Level and Outcome

The preoperative prolactin level also correlated with endocrinological outcome (Fig. 4). Among the 110 patients presenting with levels lower than 200 ng/ml, chemical cure was achieved in 95 (86%) at 5 years. Of the 80 patients in whom values of prolactin were between 201 and 600 ng/ml, a normal prolactin hormone level was maintained in 36 (45%) at 5 years, whereas after more than 5 years a chemical cure was maintained in only four (12.5%) of 32 patients with preoperative levels greater than 601 ng/ml. The highest preoperative prolactin level that resulted in long-term endocrinological control was 920 ng/ml.

Discussion

Treatment goals for patients with prolactinomas include the following: 1) reduction of the tumor mass; 2) correction of the hyperprolactinemic state; 3) restoration of visual or cranial nerve function; and 4) preservation of anterior pituitary function.[3] Microsurgical resection and pharmacotherapy are accepted means of accomplishing these objectives. Recently, gamma knife surgery also has been proposed as a primary treatment modality for prolactinomas.[37] Our analysis of the immediate and long-term endocrinological response after transsphenoidal adenomectomy has many implications for the manner in which these therapeutic goals are achieved. Specifically, it helps clarify the issues of patient selection for surgery, the definition of successful treatment outcomes, and the nature of recurrent tumors.

Role of Transsphenoidal Surgery

In general, a rough correlation exists between the size of the tumor determined by imaging and pathological studies and the serum prolactin level, except in cases in which local tumor invasion into adjacent venous sinuses produces a marked increase in serum prolactin that is out of proportion to tumor size.[19,32,63] The preoperative prolactin level is helpful in formulating management strategies, because the ability to extirpate the tumor successfully and achieve a chemical cure is reduced in cases of large or invasive lesions,[4,41,48,54,56] as our study has confirmed (Fig. 4).

Central limitations of bromocriptine therapy include the side effects of the medication, the requirement for lifelong administration, and the uncertainty of its safety during pregnancy. Approximately 20 to 30% of patients complain of

one or more adverse drug effects, including nausea, vomiting, constipation, postural hypotension, psychosis, and depression, and approximately 5 to 10% find that bromocriptine treatment is so intolerable that they therefore request surgery.[3,30,37,44] In most cases, the medication must be continued indefinitely, because cessation usually results in the return of symptomatic hyperprolactinemia and reexpansion of the tumor.[30,47,54] In addition, the United States Food and Drug Administration recommends discontinuing bromocriptine once pregnancy has been established, because of concerns about its safety for both mother and fetus.[1] The volume of the normal pituitary gland increases by approximately 70% during pregnancy,[24] however, and up to 35% of pregnant patients experience symptomatic enlargement of their tumor.[24,31,58] The superimposition of these two effects can lead to compression of optic structures during gestation if bromocriptine treatment is suspended. The teratogenic potential of cabergoline has not been extensively investigated and consequently, this drug is generally not considered to be a first-line therapy for the treatment of infertility associated with hyperprolactinemia.[31,39] Thus, the desire for pregnancy, particularly in patients harboring a macroadenoma, constitutes a relative indication for surgical resection.[64] In our series, 72 of the 96 women who wished to become pregnant did so after transsphenoidal adenomectomy.

Up to 40% of tumors fail to shrink in response to bromocriptine therapy.[18,38,47] Furthermore, there are rare cases in which patients initially respond to bromocriptine with a reduction in tumor size and normalization of serum prolactin, and subsequently experience recrudescence of the tumor even as medical therapy continues.[5,7,47] The tumor may undergo a process of dedifferentiation and become refractory to further dopamine agonist action, as evidenced by the in vitro resistance of cultured lactotrophs to high concentrations of bromocriptine.[8,38] Similarly, a discrepancy in the clinical response, as judged by tumor size and circulating prolactin levels, may develop. Despite a marked reduction in serum prolactin levels throughout the duration of bromocriptine therapy, for instance, some patients may experience continued tumor expansion and progressive symptoms from mass effect.[13,23,63] Conversely, others may suffer the adverse effects of persistent hyperprolactinemia, despite serial imaging studies that indicate continued regression in tumor size.[2] Bromocriptine resistance or dissociation between tumor growth and serum prolactin measurements constitute other indications for surgical resection.

Although it is intuitive to suggest that pretreatment with bromocriptine will shrink the tumor and facilitate surgical resection, there have been no conclusive reports of higher cure rates after such preoperative measures.[15,20] In fact, some surgeons believe that preoperative bromocriptine therapy produces adverse effects on the consistency of the adenoma, impeding tumor resection,[17,25,56,63] although that has not been our experience.[62] Bromocriptine might also increase the radioresistance of prolactinomas to gamma knife surgery.[26]

Our study confirms that transsphenoidal resection is a highly effective modality in the management of prolactin-secreting pituitary tumors among patients who are not considered candidates for medical therapy for the reasons outlined above. For microadenomas, the likelihood of long-term chemical cure exceeds 90% (Table 1). In patients with these tumors the operative mortality rate was 0%, and the

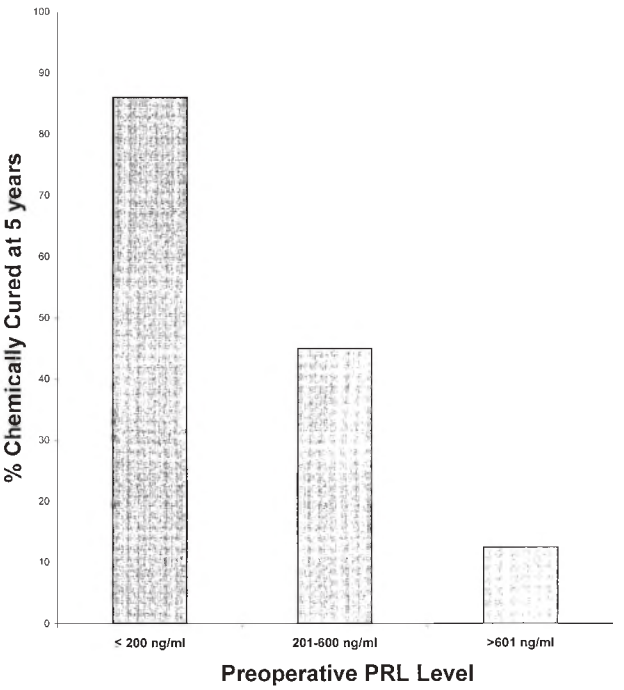

FIG. 4. Bar graph demonstrating the effect of preoperative prolactin level on long-term outcome. The 5-year cure rates were 86% for patients with preoperative prolactin levels lower than 200 ng/ml; 45% for patients with preoperative levels between 201 and 600 ng/ml; and 12.5% in patients with preoperative levels greater than 601 ng/ml.

associated morbidity rate was low. These results compare favorably with those of pharmacological management. In addition, the economic costs of surgical resection may be comparable with those of lifelong medical therapy.[49] The experience of other centers corroborates this high rate of surgical success among cases of microprolactinomas.[17–19,28,30,32,36,51,54–56,63] Thus, strong consideration should be given to surgical intervention in patients harboring smaller tumors without significant hyperprolactinemia.

In cases of larger tumors, however, surgical cures are much less common.[17,18,28,30,32,36,51,54,55,63] Using the classification scheme proposed by Hardy, the cure rates of Stage I, II, III, and IV tumors after transsphenoidal resection are 84, 50, 25, and 0%, respectively.[34] Tumors associated with preoperative prolactin levels greater than 200 ng/ml recur in more than 50% of cases after surgery alone, and the rate of recurrence of hyperprolactinemia after surgery for macroadenomas in patients with prolactin levels greater than 250 ng/ml exceeds 70%.[22] In the current series, only 38 (33%) of 115 patients with tumors larger than 1 cm achieved chemical cures, as opposed to 91% of those with tumors smaller than 1 cm (Table 1). Therefore, bromocriptine may be considered as the initial therapy for patients in whom surgical resection is deemed unlikely to result in a chemical cure.[27,53,65] For patients in whom surgery has failed, subsequent treatment with reduced doses of bromocriptine is often better tolerated and more effective than this treatment before surgery.[34,36,41] As our study has shown, reoperation is seldom necessary, and postoperative radiotherapy is usually not required.

Predictive Value of Immediate Postoperative Prolactin Levels

Patients should undergo a systematic routine assessment of endocrinological outcome postoperatively. Our study demonstrates that serum prolactin levels obtained the morning after surgery predict long-term results. Levels lower than 10 ng/ml on POD 1 predict cure (Table 1) in patients with microadenomas (100%) as well as in those with macroadenomas (93%). No patient in our study in whom the prolactin level was lower than 3 ng/ml on POD 1 was found to have an elevated level at 5 years postoperatively.

In contrast, patients with normal levels between 10 and 20 ng/ml on POD 1 remain at risk for endocrinological recurrence if the preoperative tumor size exceeds 10 mm (Table 1). All Group 2 patients with macroadenomas experienced recurrence by 5 years, whereas none of those with microadenomas suffered relapse. These data indicate that the traditional criteria used to determine successful adenoma resection in the immediate postoperative period (prolactin levels $\leq$ 20 ng/ml) may be too liberal.

In his early experience, Wilson[63] also found that immediate postoperative prolactin levels have prognostic value. Levels lower than 5 ng/ml virtually assured cure, whereas those greater than 15 ng/ml implied existence of residual tumor and the probability of regrowth. In a later study, Wilson and coworkers[16] found that the likelihood of cure was 84% for patients with postoperative levels lower than 5 ng/ml, but only 67% for those with levels higher than 20 ng/ml. Serri and Massoud and colleagues[30,46] have also suggested that the risk of recurrence is increased among patients with early postoperative prolactin levels in the upper limit of the normal range. In their series, prolactin levels measured 7 to 30 days after surgery were significantly lower in patients in whom normoprolactinemia was maintained long term (6.4 ng/ml) than in those who experienced relapse (11.7 ng/ml).[46] In the study by Schlechte and colleagues,[43] the mean serum prolactin level 6 weeks after surgery in patients in whom the disease was cured (7 ng/ml) was less than that in patients who later experienced recurrence (13 ng/ml), although this difference was not statistically significant. Postoperative prolactin levels near the upper limit of normal were also found to be prognostic of hyperprolactinemia recurrence in the study by Charpentier, et al.[10]

Nature of Endocrinological Recurrence

After surgery, postoperative measurements of prolactin levels are the most sensitive indices of the completeness of resection and the possibility of recurrence. As we have shown, the finding of a normal prolactin level of 10 to 20 ng/ml on POD 1 indicates the possibility that residual tumor remains. Thus, the results of our analysis of immediate and long-term endocrinological responses after transsphenoidal adenomectomy suggest that recurrences reported after several years most likely represent persistent tumor that was not originally removed.

In other series, relapse of hyperprolactinemia after initial hormonal normalization occurred frequently. Recurrence rates range from 17 to 50% for microadenomas and from 20 to 80% for macroadenomas, depending on the duration of follow-up review, experience of the surgeon, and other factors.[9,17–19,28,30,40,43–46,51,52,56] Differences in surgical technique may also underlie the variation in reported rates of relapse after apparently successful adenomectomy. For instance, based on the hypothesis that delayed recurrences in situ result from residual tumor cells at the periphery of an adenoma, some have proposed performing an enlarged rather than selective adenomectomy by removing a layer of normal pituitary gland at the outer edge of the tumor and the pituitary capsule in contact with the sellar meninges.[18,56] Using this technique in 26 patients with tumors smaller than 20 mm in diameter and prolactin levels lower than 200 ng/ml, Grisoli and associates[18] obtained normal prolactin levels in all cases after an average of 16 months. This length of follow-up review is short, however, and it remains to be proven whether this technique results in a lower incidence of delayed recurrence. In our series, chemical cure was achieved in 86% of the 110 patients presenting with prolactin levels lower than 200 ng/ml at 5 years (Fig. 4).

Relapses usually occur within the first few years after surgery, although they have been reported more than 10 years later.[30,51,52] Often, such recurrences are asymptomatic,[28,30,43,45,46] but even in patients without overt clinical manifestations, treatment is indicated to prevent osteoporosis and other endocrinological sequelae of hyperprolactinemia.

In most cases of relapse or immediate endocrinological failure, imaging of the sella turcica fails to reveal residual or recurrent adenoma.[28,30,43,45,46,52] Our study indicates that, if the original operation was performed by an experienced surgeon, reoperation is not likely to yield a chemical cure. This observation may reflect the fact that by following vigilant protocols for sampling postoperative prolactin levels, most tumor recurrences will be detected early. In our series, no recurrence produced a serum level greater than 55 ng/ml. Alternatively, this observation may imply that there are reasons for recurrent hyperprolactinemia other than regrowth of residual tumor remnants. These include a secondary empty sella, primary hypothyroidism, or a persistently disordered hypothalamic–pituitary axis characterized by reduced delivery of prolactin-inhibiting factors after surgery due to scarring at the tumor cavity.[28,30,46,52] The dynamic responses of lactotrophs to provocative stimuli such as thyrotrophin-releasing hormone or metoclopramide may help distinguish between these possibilities.[18,19,28,43,53,56]

Recently, Thomson and colleagues[52] analyzed outcomes of patients with recurrent hyperprolactinemia after initial hormonal normalization. Relapses occurred 2 to 10 years postoperatively in eight (18.2%) of 44 patients undergoing transsphenoidal removal of a microprolactinomas; however, the relapse was permanent in only two of these patients. Of the remaining six patients, four experienced spontaneous remission after 6 to 7 years of recurrence and only marginally elevated prolactin levels were measured in two others. The authors concluded that recurrence of hyperprolactinemia after transsphenoidal surgery is not necessarily a permanent feature and does not inevitably indicate operative failure.

Conclusions

Prolactin levels lower than 10 ng/ml on POD 1 predict long-term chemical cure in patients with microadenomas (100%) as well as in those with macroadenomas (93%). In contrast, a cure is not likely to be obtained in patients with normal levels of prolactin between 10 and 20 ng/ml on

POD 1 if these patients harbor macroadenomas (0% cure rate). Recurrences reported several years after surgery probably represent persistent tumor that was not originally removed. If the initial operation was performed by an experienced surgeon, however, reoperation is not likely to yield a chemical cure.

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Manuscript received November 12, 2001.
Accepted in final form April 29, 2002.
This work was supported by the Michael J. Connell Foundation and the A. J. Cox Family Foundation.

Address reprint requests to: Arun Paul Amar, M.D., 1200 North State Street, Suite 5046, Los Angeles, California 90033. email: amar @aya.yale.edu.